AudioDigest

ONCOLOGY
Board Review
2nd EDITION

Written Summaries

Wolters Kluwer

Lecture ONBR200101

Acute Myelogenous Leukemia and Myelodysplastic Syndromes

Daniel A. Pollyea, MD, MS

The goal of this program is to improve the awareness of pathophysiology and management of acute myelogenous leukemia and myelodysplastic syndrome. After hearing and assimilating this program, the clinician will be better able to:

1. *Understand the underlying pathophysiology of AML.*
2. *Discuss the various treatment options, including standard intensive chemotherapy and the role for newer, targeted therapies.*
3. *Recognize the proper role for emerging therapies and how they are changing outcomes in AML.*

Lecture ONBR200102

Chronic Lymphocytic Leukemia

Hamid Sayar, MD, MS

The goal of this program is to improve the awareness of current practice for diagnosis and management of chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and other types of leukemia. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the presentation and diagnosis of CLL.*
2. *Identify treatment considerations for initial therapy for patients with CLL.*
3. *Describe the presentation and diagnosis of ALL.*
4. *List treatment considerations for relapsed/refractory ALL.*

Lecture ONBR200103

Multiple Myeloma

Shaji Kumar, MD

The goal of this program is to improve the awareness of current practice for diagnosis and management of multiple myeloma. After hearing and assimilating this program, the clinician will be better able to:

1. *Describe the approach to multiple myeloma and related monoclonal gammopathies.*
2. *Outline the risk stratification of multiple myeloma.*
3. *Describe multiple myeloma initial treatment.*
4. *Summarize relapsed multiple myeloma treatment.*

Lecture ONBR200104

Stem Cell Transplantation

Corey Cutler, MD, MPH

The goal of this program is to improve the awareness of current practice for stem cell transplantation. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss indications for transplant.*
2. *Explain differences between autologous and allogeneic stem cell transplantation.*
3. *List considerations for matching donors and recipients.*
4. *Identify complications of transplantation.*

Lecture ONBR200105

Screening and Localized Breast Cancer

Chirag Shah, MD

The goal of this program is to improve the comprehension and management of breast cancer. Upon completion of this program, the clinician will be better able to:

1. *Describe risk factors for developing breast cancer.*
2. *Discuss screening recommendations for breast cancer.*
3. *Explain the staging of breast cancers.*
4. *Describe the surgical management of breast cancers.*

Lecture ONBR200106

Systemic Therapy for Localized and Locally Advanced Breast Cancer

Ruth O'Regan, MD

The goal of this program is to improve the awareness of and current practice for diagnosis and treatment of breast cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Understand the management and choice of therapy for patients with early-stage hormone receptor–positive breast cancer*
2. *Understand the role of adjuvant chemotherapy for patients with early-stage HER2-negative breast cancer*
3. *Recognize the role of preoperative systemic therapy in patients with early-stage breast cancer*
4. *Understand the role of systemic therapy in treating patients with HER2-positive breast cancer*

Lecture ONBR200107

Metastatic Breast Cancer

Ruth O'Regan, MD

The goal of this program is to improve the awareness of current practice in treatment choices for patients with metastatic breast cancer based on subtyping and to understand the role of systemic therapy in patients with metastatic breast cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss considerations for patients with hormone receptor-positive metastatic breast cancer and a PIK3CA mutation.*
2. *Identify the first-line treatment of choice for patients with HER2-positive metastatic breast cancer.*
3. *Discuss considerations for combination vs single-agent chemotherapy regimens for patients with HER2-negative breast cancer, triple-negative breast cancer, or hormone receptor-positive breast cancer who have exhausted endocrine therapy.*

Lecture ONBR200108

Pancreatic and Biliary Cancer

Lei Zheng, MD, PhD

The goal of this program is to improve the comprehension and management of pancreatic and biliary cancers. Upon completion of this program, the clinician will be better able to:

1. *Differentiate between resectable, borderline resectable, and unresectable locally advanced pancreatic cancer.*
2. *Describe the use of chemotherapy in the treatment of pancreatic cancer.*
3. *List the four major types of biliary cancer.*
4. *Describe the management of biliary cancers.*

Lecture ONBR200109

Colorectal Cancer Biology and Management of Localized and Locally Advanced Disease

James Church, MD

The goal of this program is to improve the comprehension of the biology of colorectal cancer and its management when localized and locally advanced. Upon completion of this program, the clinician will be better able to:

1. *Explain the way in which colorectal cancer develops at a molecular level, including the relevance of biology to clinical management.*
2. *Recognize the symptoms by which cancer presents in light of its diagnosis and stage.*
3. *Discuss principles underlying the treatment of colorectal cancer.*
4. *Understand the most effective and most efficient care of colorectal cancer according to stage and location of the cancer.*

Lecture ONBR200110

Metastatic Colorectal Carcinoma

Afsaneh Barzi, MD, PhD

The goal of this program is to improve the comprehension and management of metastatic colorectal cancer. Upon completion of this program, the clinician will be better able to:

1. *Explain the importance of staging in the setting of metastatic colorectal cancer.*
2. *Discuss the use of molecular testing in the setting of metastatic colorectal cancer.*
3. *Describe chemotherapy agents used to treat metastatic colorectal cancer.*
4. *List common toxicities associated with chemotherapy agents used in the treatment of metastatic colorectal cancer.*

Lecture ONBR200111

Lung Cancer: Part 1 — Disease Overview and Patient Workup

Martin J. Edelman, MD

The goal of this program is to improve the awareness of current practice for lung cancer diagnosis and staging. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the epidemiology of lung cancer in the United States.*
2. *Identify the appropriate radiographic screening modality and interval for patients with a history of cigarette smoking.*
3. *Describe the role of radiographic studies, tissue evaluation, and immunohistochemical markers in staging tumors of the lung.*

Lecture ONBR200112

Lung Cancer: Part 2 — Non–Small Cell Cancers

Martin J. Edelman, MD

The goal of this program is to improve the management of non-small cell lung cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Describe the role of oncology in stage I and II non-small cell lung cancer.*
2. *Summarize relevant chemotherapy and radiotherapy studies in treatment of stage III non-small cell lung cancer.*
3. *Discuss the development and impact of immunotherapy in the treatment of non-small cell lung cancer.*
4. *Describe toxicities caused by immunotherapy agents.*

Lecture ONBR200113

Lung Cancer: Part 3 — Small-Cell Cancer and Rare Thoracic Malignancies

Martin J. Edelman, MD

The goal of this program is to improve the awareness of current practice for the evaluation and management of small cell lung cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the staging for small cell lung cancer.*
2. *Differentiate between treatment strategies for limited stage disease and extensive stage disease.*
3. *Identify the immunotherapeutic agents approved for treatment of small cell lung cancer.*
4. *Discuss the diagnosis and management of mesothelioma and thymic tumors, which may be confused with small cell lung cancer.*

Lecture ONBR200114

Thymic Carcinoma, Mesothelioma, and Anaplastic Thyroid Cancer

Andrea Wolf, MD

The goal of this program is to improve the comprehension and management of thymic carcinoma, malignant pleural mesothelioma, and anaplastic thyroid cancer. Upon completion of this program, the clinician will be better able to:

1. *Distinguish thymic carcinoma from thymoma by histology.*
2. *Describe the staging of thymic carcinoma.*
3. *Discuss the treatment of malignant pleural mesothelioma.*
4. *Describe the prognosis of anaplastic thyroid cancer.*

Lecture ONBR200115

Kidney Cancer

Brian I. Rini, MD

The goal of this program is to improve the awareness of and current practice for management of kidney cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Understand the biology underlying renal cell carcinoma (RCC).*
2. *Appreciate recent data regarding the role of immunotherapy in metastatic RCC.*
3. *Understand novel regimens with combination of anti-VEGF and immunotherapy in RCC.*

Lecture ONBR200116

Localized and Locally Advanced Prostate Cancer

Peter C. Albertsen, MD

The goal of this program is to improve the comprehension and management of localized and locally advanced prostate cancer. Upon completion of this program, the clinician will be better able to:

1. *Describe the use of the Gleason score.*
2. *Discuss the primary treatments for localized and locally advanced prostate cancer.*
3. *Discuss the evidence for the efficacy of surgery, radiation, and antiandrogen therapy to treat prostate cancer.*
4. *Explain why the treatment of localized and locally advanced prostate cancer remains controversial, especially for tumors detected by prostate-specific antigen testing.*

Lecture ONBR200117

Advanced Prostate Cancer

Andrew Armstrong. MD

The goal of this program is to improve the comprehension and management of metastatic prostate cancer. Upon completion of this program, the clinician will be better able to:

1. *Discuss the prognosis of metastatic hormone-sensitive prostate cancer.*
2. *Describe the use of germline and somatic genetic testing in the setting of advanced prostate cancer.*
3. *List agents used in the treatment of metastatic castration-resistant prostate cancer.*
4. *Describe treatment of small cell or neuroendocrine prostate cancer.*

Lecture ONBR200118

Bladder Cancer and Upper Urinary Tract Cancers

Matthew I. Milowsky, MD

The goal of this program is to improve the comprehension of bladder and other urothelial cancers and their management, including novel therapeutic options. Upon completion of this program, the clinician will be better able to:

1. *Understand the pathology and molecular biology of urothelial carcinoma with important implications for treatment.*
2. *Recognize the importance of multidisciplinary care in the management of patients with localized urothelial carcinoma of the bladder including the role of perioperative chemotherapy and trimodality therapy.*
3. *Understand the evolving landscape of treatment options including immunotherapy and targeted therapy in patients with locally advanced and metastatic urothelial carcinoma.*

Lecture ONBR200119

Testicular Cancer

Timothy Gilligan, MD

The goal of this program is to improve the awareness of current practice for the evaluation and management of testicular cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Describe the epidemiology of and risk factors for testicular cancer.*
2. *Explain the biology and pathology of testicular germ cell tumors.*
3. *Discuss the role of serum tumor markers AFP, beta hCG, and LDH in the management of testicular cancer.*
4. *Identify the key diagnostic steps in the workup of a suspected testicular cancer.*
5. *Discuss the staging of testicular seminomas and nonseminomas and how staging relates to prognosis and choice of therapy.*
6. *Select treatment approaches based on tumor type, stage, and setting.*
7. *Identify treatment toxicities for which patients should be monitored.*

Lecture ONBR200120

Penile and Adrenal Cancers

Tanya Dorff, MD

The goal of this program is to improve the comprehension of penile and adrenal cancers, including staging and management. Upon completion of this program, the clinician will be better able to:

1. *Review the epidemiology and etiology of penile cancer, highlighting the role of HPV.*
2. *Describe local management of penile cancer, emphasizing consideration of organ preservation.*
3. *Identify the implications of T stage on the need for lymph node dissection in penile cancer, and the impact of lymph node involvement on the need for systemic therapy.*
4. *Review chemotherapy regimens associated with response in penile cancer.*
5. *Highlight what is known about molecular-targeted therapy and immunotherapy for patients with advanced refractory penile cancer.*
6. *Recognize the importance of metabolic and endocrine investigation prior to surgery for adrenal tumors.*
7. *Describe alpha and beta blockade management prior to adrenalectomy or embolization for pheochromocytoma.*
8. *Review the genetic syndromes associated with pheochromocytoma and adrenocortical carcinoma.*
9. *Understand the use of mitotane and chemotherapy in the adjuvant and advanced settings of adrenal cancers.*

Lecture ONBR200121

Ovarian Cancer

Jenna Z. Marcus, MD

The goal of this program is to improve the awareness of current practice for screening and prevention, diagnosis and staging, and treatment, outcomes, and survivorship issues of ovarian cancer. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the considerations for screening for ovarian cancer.*
2. *Identify risk factors for ovarian cancer.*
3. *Discuss markers for detection of ovarian cancer.*
4. *Identify treatment options for patients with platinum-sensitive, recurrent ovarian cancer.*

Lecture ONBR200122

Cervical Cancer

Mark Einstein, MD

The goal of this program is to improve the comprehension and management of cervical cancer. Upon completion of this program, the clinician will be better able to:

1. *Explain the etiology of cervical cancer.*
2. *Discuss the current strategy for the prevention of cervical cancer.*
3. *Describe the management of each stage of cervical cancer.*
4. *Discuss common long-term survivorship issues in patients with cervical cancer.*

Lecture ONBR200123

Uterine Cancer

Shannon N. Westin, MD, MPH

The goal of this program is to improve the comprehension and management of uterine cancer. Upon completion of this program, the clinician will be better able to:

1. *List common risk factors for uterine cancer.*
2. *Explain the workup of suspected uterine cancer.*
3. *Describe the clinical stages of uterine cancer.*
4. *Differentiate the management of local-regional and disseminated disease.*

Lecture ONBR200124

Gestational Trophoblastic Disease and Cancers of the Vulva and Vagina

Bradley J. Monk, MD

The goal of this program is to improve the comprehension and management of gestational trophoblastic disease. Upon completion of this program, the clinician will be better able to:

1. *Describe the diagnosis and evaluation of hydatidiform moles.*
2. *Explain the staging system for cancerous hydatidiform moles.*
3. *Discuss the use of chemotherapy in the setting of cancerous hydatidiform moles.*
4. *Describe the management of placental trophoblastic tumors.*

Lecture ONBR200125

Thyroid Cancer (Follicular, Papillary and Medullary)

Emad Kandil, MD, MBA

The goal of this program is to improve the comprehension and management of thyroid cancer. Upon completion of this program, the clinician will be better able to:

1. *Describe the types of thyroid cancer.*
2. *Describe the management of papillary thyroid cancer.*
3. *Explain the staging of medullary thyroid cancer.*
4. *Discuss the prognosis of anaplastic thyroid cancer.*

Lecture ONBR200126

Head and Neck Cancer

Nikhil Joshi, MD

The goal of this program is to improve the comprehension and management of head and neck cancer. Upon completion of this program, the clinician will be better able to:

1. *Describe the diagnostic workup for suspected head and neck pathologies.*
2. *Discuss changes to cancer staging made in the eighth edition of the AJCC staging manual.*
3. *Differentiate between the management of supraglottic, glottic, and subglottic laryngeal cancers.*
4. *Describe the management of salivary gland cancers.*

Lecture ONBR200127

Neuro-oncology

Tracy T. Batchelor, MD, MPH

The goal of this program is to improve the awareness of current practice for classification and epidemiology of primary brain tumors, and diagnosis and management of gliomas, meningioma, and primary CNS lymphoma. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the importance of the status of chromosomes 1p and 19q related to diagnosis of a primary brain tumor.*
2. *Identify treatment options for low-grade gliomas.*
3. *Discuss considerations for management of symptomatic and asymptomatic meningiomas.*
4. *Identify options for treating primary CNS lymphoma.*

Lecture ONBR200128

Sarcoma

Jonathan Trent, MD, PhD

The goal of this program is to improve the comprehension and management of soft tissue sarcomas. Upon completion of this program, the clinician will be better able to:

1. *Distinguish the etiology of sarcomas from carcinomas.*
2. *Describe the workup of a suspected soft tissue sarcoma.*
3. *Compare chemotherapeutic agents used to treat sarcomas.*
4. *Describe the use of adjuvant chemotherapy for sarcomas.*

Lecture ONBR200129

Neuroendocrine Carcinomas

Daniel M. Halperin, MD

The goal of this program is to improve the awareness of current practice for diagnosis and management of neuroendocrine tumors. After hearing and assimilating this program, the clinician will be better able to:

1. *Understand the modern WHO nomenclature for classifying neuroendocrine tumors.*
2. *Recognize and manage syndromes of functional neuroendocrine tumors.*
3. *Recommend tumor-control options for patients with neuroendocrine tumors based on the best available evidence.*

Lecture ONBR200130

Oncologic Emergencies

Saadia A. Faiz, MD

The goal of this program is to improve the comprehension and management of oncologic emergencies. Upon completion of this program, the clinician will be better able to:

1. *Describe the management of pulmonary embolism in the setting of malignancy.*
2. *Differentiate between the causes of hypercalcemia in the setting of malignancy.*
3. *Discuss the management of tumor lysis syndrome.*
4. *Explain the three types of cancer-related DIC.*

Lecture ONBR200131

Paraneoplastic Syndromes

Andrew McKeon, MB, BCh

The goal of this program is to improve the comprehension and management of paraneoplastic neurological disorders. Upon completion of this program, the clinician will be better able to:

1. *Discuss the pathogenesis of paraneoplastic neurological disorders.*
2. *List common neurological symptoms seen with paraneoplastic disorders.*
3. *Describe the workup for suspected paraneoplastic disorders.*
4. *Discuss treatments for paraneoplastic disorders.*

Lecture ONBR200132

Pain Management for Cancer Patients

Kieth Swetz, MD

The goal of this program is to improve the pain management of cancer patients. Upon completion of this program, the clinician will be better able to:

1. *Explain how pain is evaluated for patients with cancer.*
2. *Describe the use of opioids in pain management for patients with cancer.*
3. *Describe alternatives to opioids in pain management for patients with cancer.*
4. *Discuss the use of nerve blocks and ablations in the setting of pain management for cancer patients.*

Lecture ONBR200133

Gastrointestinal Symptoms

Kieth Swetz, MD

The goal of this program is to improve the comprehension and management of gastrointestinal symptoms in oncology patients. Upon completion of this program, the clinician will be better able to:

1. *Describe the management of constipation in cancer patients on opioids.*
2. *Discuss causes of diarrhea in oncology patients.*
3. *Compare various pharmacological treatments for nausea and vomiting in oncology patients.*
4. *Describe the management of oral mucositis in oncology patients.*

Lecture ONBR200134

Other Acute and Chronic Toxicities of Cancer and Cancer Treatment

Kieth Swetz, MD

The goal of this program is to improve the comprehension and management of acute and chronic toxicities of cancer treatment. Upon completion of this program, the clinician will be better able to:

1. *Describe the approach to fatigue in cancer patients.*
2. *Explain causes of sexual dysfunction in cancer patients.*
3. *List chemotherapeutic agents associated with cardiotoxicity.*
4. *Discuss treatments for chemotherapy-associated peripheral neuropathy.*

Lecture ONBR200135

Symptom Management for BMT Patients

Muzzafar H. Qazilbash, MD

The goal of this program is to improve the comprehension and management of complications of stem cell transplant and high-dose chemotherapy. Upon completion of this program, the clinician will be better able to:

1. *Describe the prevention of oral mucositis.*
2. *Explain common causes of diarrhea in the setting of chemotherapy.*
3. *Distinguish between drugs used to treat nausea and vomiting in the setting of chemotherapy.*
4. *Differentiate acute and chronic graft vs host disease.*

Lecture ONBR200136

Communication Challenges with Oncology Patients

Timothy Gilligan, MD

The goal of this program is to improve the oncologist's ability to communicate effectively with patients. After hearing and assimilating this program, the oncologist will be better able to:

1. *Discuss effective approaches for building strong relationships with patients.*
2. *Identify the essential components of informed consent for treatment and clinical trial participation.*
3. *Identify strategies for discussing end of life issues with oncology patients.*

Lecture ONBR200137

Infectious Disease and Oncology

Stephen M. Lipkin, MD, PhD

The goal of this program is to improve the comprehension, prevention, and management of infections in cancer patients. Upon completion of this program, the clinician will be better able to:

1. *Explain causes of neutropenia and neutropenic fever in cancer patients.*
2. *Describe antifungal management of cancer patients.*
3. *Describe risk factors for central line infections in cancer patients.*
4. *Discuss the approach to the vaccination of cancer patients.*

Lecture ONBR200138

Management of Brain Metastases

Adam Sonabend Worthalter, MD

The goal of this program is to improve the comprehension and management of brain metastasis. Upon completion of this program, the clinician will be better able to:

1. *List common and rarer sources of brain metastasis.*
2. *Differentiate leptomeningeal disease from dural or meningeal metastasis.*
3. *Describe the approach to diagnosis of a solitary brain metastasis.*
4. *Discuss the various management options for brain metastasis.*

Lecture ONBR200139

End-of-Life Care

Russell Portenoy MD

The goal of this program is to improve the awareness of current practice for palliative care and hospice. After hearing and assimilating this program, the clinician will be better able to:

1. *Define concurrent care and describe the objectives of palliative care.*
2. *Explain the Medicare hospice benefit.*
3. *Use symptoms and signs to predict poor prognosis.*
4. *Identify key assessments and treatments used in the management of the imminently dying patient.*

Lecture ONBR200140

Anti-Cancer Drugs I: Cell Cycle–Targeted Therapies

R. Donald Harvey, III, PharmD

The goal of this program is to create awareness of the different classes of anti-cancer agents that target the cell cycle, their mechanisms of action, and adverse events linked to their use. After hearing and assimilating this program, the clinician will be better able to:

1. *Identify the different classes of anti-cancer drugs.*
2. *Describe the mechanism of action of anti-cancer agents and their cell cycle specificity.*
3. *Recognize the adverse effects associated with anti-cancer drugs and how to ameliorate the adverse effects.*

Lecture ONBR200141

Anti-Cancer Drugs II: Bleomycin

Alex A. Adjei, MD, PhD

The goal of this program is to improve the comprehension and management of chemotherapeutic agents. Upon completion of this program, the clinician will be better able to:

1. *Distinguish between the two different syndromes of pulmonary toxicity caused by bleomycin.*
2. *Explain the cause of hypersensitivity reactions seen with L-asparaginase.*
3. *Discuss the use of fulvestrant in combination with CDK4/6 inhibitors.*
4. *Compare gonadotropin releasing hormone agonists and antagonists.*

Lecture ONBR200142

Anti-Cancer Drugs III: Targeted Therapies and Monoclonal Antibodies

R. Donald Harvey, III, PharmD

The goal of this program is to review the roles in treatment, mechanisms of action, and adverse effects of two groups of anticancer drugs, monoclonal antibodies and targeted therapies. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the mechanisms of action of selected monoclonal antibodies.*
2. *Compare and contrast the adverse event profiles of selected monoclonal antibodies.*
3. *Describe the role of selected monoclonal antibodies in cancer treatment.*
4. *Discuss the mechanisms of action of selected targeted therapies.*
5. *Compare and contrast the adverse event profiles of selected targeted therapies.*
6. *Describe the roles of selected targeted therapies in cancer treatment.*

Lecture ONBR200143

Anti-Cancer Drugs IV: Immunotherapy

Christian M. Capatini, MD

The goal of this program is to improve the comprehension of immunotherapy related to the management of cancer. Upon completion of this program, the clinician will be better able to:

1. *Describe various checkpoint inhibitors.*
2. *Discuss immune-related adverse events.*
3. *Explain the management of cytokine release syndrome.*
4. *Discuss the current limitations of cancer immunotherapy.*

Lecture ONBR200144

Clinical Trials and FDA Drug Approval Process

Bradley J. Monk, MD

The goal of this program is to improve the comprehension of drug development and clinical trials. Upon completion of this program, the clinician will be better able to:

1. *Describe type I and type II statistical errors.*
2. *Distinguish between fast track, breakthrough therapy, accelerated approval, and priority review.*
3. *Differentiate between phases of clinical trials.*
4. *Discuss the purpose of the IRB.*

Lecture ONBR200145

Ethical Issues in Oncology

Eric Kodish, MD

The goal of this program is to improve the comprehension of ethics and research in oncology as well as obtaining a better understanding for specific ethical issues in relation to genetic mutations. Upon completion of this program, the clinician will be better able to:

1. *Articulate the most common ethical dilemmas faced in the care of patients who are dying of cancer, and identify strategies to navigate these challenges.*
2. *Understand critical differences between the goal of clinical cancer research and the objective of pure oncology care.*
3. *Appreciate the growing number of conundrums that arise in the field of cancer genetics, including both somatic mutations and germline cancer predisposition syndromes.*

Lecture ONBR200146

Basics in Cancer Genetics

Stephen M. Lipkin, MD, PhD

The goal of this program is to improve knowledge of genetics and mutations as they relate to malignant diseases and management of related cancers. Upon completion of this program, the clinician will be better able to:

1. *Explain basic concepts of molecular biology.*
2. *Differentiate between different types of mutations.*
3. *Discuss the two-hit model for the development of cancer.*
4. *Describe the use of precision medicine to treat mutations in cancer.*

Lecture ONBR200147

Basics in Cancer Biology

Stephen M. Lipkin, MD, PhD

The goal of this program is to improve the comprehension of tumorigenesis, proteomics, and metastases related to the management of cancer. Upon completion of this program, the clinician will be better able to:

1. *Contrast genomic and somatic mutations.*
2. *Describe the application of proteomics to oncology.*
3. *Describe the pathology of tumor cell metastasis.*
4. *Discuss the use of liquid biopsy in precision oncology.*

Lecture ONBR200148

Familial Cancer Syndromes

James Church, MD

The goal of this program is to improve the comprehension and management of hereditary cancer syndromes. Upon completion of this program, the clinician will be better able to:

1. *Explain the genetic basis of hereditary cancers.*
2. *Discuss the current state of genetic testing.*
3. *Describe the management of familial adenomatous polyposis.*
4. *Differentiate multiple endocrine neoplasia types one and two.*

AudioDigest

Oncology
Board Review

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Acute Myelogenous Leukemia and Myelodysplastic Syndrome

Daniel Pollyea, MD, MS, *Associate Professor of Medicine, Department of Hematology and Medical Oncology, Cleveland, and Vice-Chair for Education, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Acute Myelogenous Leukemia

Acute myeloid leukemia (AML): myeloid malignancy resulting from accumulation of chromosomal abnormalities and gene mutations starting at stem-cell level

Normal blood cell development (hematopoiesis): depending on needs of body, blood stem cells mature or differentiate; if myeloid components (red blood cells [RBCs], platelets [PLTs], granulocytes) needed, cell receives signals for myeloid differentiation pathway; if lymphoid components (*eg*, B cells, T cells, natural killer cells) needed, signals for lymphoid pathway

Disruption of hematopoiesis: in AML, normal process hijacked and normal blood stem cells develop mutations or chromosomal abnormalities that cause it to go down myeloid pathway, but unable to differentiate or fully mature into normal components of hematopoietic system; left with immature blasts in myeloid development pathway that cannot mature or die properly; accumulate in bone marrow and ultimately shut down whole bone marrow function by basically overcrowding; patients cannot make enough RBCs, white blood cells (WBCs), and platelets; ultimately, they have complications from bone marrow failure

Epidemiology: unlike other cancers and blood cancers, AML uncommon (~30,000 cases/yr); affects elderly; median age at diagnosis, ~68 yrs; historically, poor treatment available; compared with other blood cancers that have been more successfully treated (*eg*, myeloma, Hodgkin disease, chronic myeloid leukemia [CML], chronic lymphocytic leukemia [CLL]), AML has lagged behind in outcomes; occurs from accumulation of mutations, chromosomal translocations, and other aberrancies in precursor cell (leukemia stem cell) resulting in stoppage in maturation and inappropriate signals that lead to inability of cells to properly die; most common acute leukemia in adults; rare in pediatric setting; exponential increases in diseases incidence with age; relatively rare until fifth or sixth decade, then accelerates; although many think of AML as disease affecting younger patients because outcomes dramatic and remembered from training, unusual situation, but disease really affects older people

Cause: frustrating determine, because we do not usually know; emerging evidence about inherited familial conditions or gene mutations that can contribute (but quite rare); most of time, do not understand cause; could be caused from environmental associations; benzine exposure at massive doses and radiation in industrial accidents have been known to trigger AML; patients who received chemotherapy or radiation for prior cancer and survived can rarely develop AML (treatment-related AML, particularly bad diseases subset); associations with other genetic abnormalities like Down syndrome and Fanconi anemia; associations between AML and other benign conditions; patients with aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH) have higher incidence of AML; other antecedent malignant conditions in myeloid family such as myelodysplastic syndrome (MDS) and myeloproliferative neoplasms can and do evolve into AML

Classification: has evolved over last several decades; in 1970s, categorized by morphology (appearance under microscope); now classified based on biologic features; recurrent chromosomal abnormalities 1 way to classify; certain chromosomal abnormalities associated with good-risk features; acute promyelocytic anemia (APL) associated with t(15;17) translocation; 8;21 translocation and inversion 16 diagnostic of core binding factor; other patients categorized based on chromosomal abnormalities if abnormalities well known and recurrent; World Health Organization (WHO) list helps categorize; some AML clearly comes from MDS (particular cellular appearances or known history of MDS); other categories (not otherwise specified), not treated any differently from other classifications

Example disease presentations:

Patient A: 50-year-old male; no past medical history; presents to local emergency department with flu-like symptoms and perirectal pain; laboratory investigation shows pancytopenia (WBC count=1, hemoglobin (Hg)=8, platelet (PLT) count=22)

Patient B: 45-year-old woman; medical history of rheumatoid arthritis; presents with sinus infection, shortness of breath, and cough; WBC count profoundly high (280,000); very anemic (Hg=4) and thrombocytopenic (PLT count=8

Signs: different presentations; person can have massive amount of circulating leukemia cells coming out of bone marrow into peripheral blood, or very low WBC count

Symptoms: AML, disease of bone marrow; circulates through blood, infiltrates every organ and tissue; wide variety of symptoms; common symptoms and signs related to bone marrow failure include fatigue from anemia, pallor, bleeding complications, fever, infection; uncommon things can happen; be on lookout for bone pain, joint pain, abdominal pain, disseminated intravascular coagulation (DIC), tumor lysis syndrome, infiltration into skin or

oral mucosa, central nervous system (CNS) involvement (headache, visual changes), pulmonary symptoms (effusions, shortness of breath)

Prognosis: chromosomal testing and gene testing important; 1 main principle, chromosomal testing

Karyotyping: look at all copies of chromosomes in disease cells; ~50% will have normal chromosomes (normal karyotype of 46XX from female or 46XY from male), which places patient into intermediate-risk group (not understood if good or poor risk); in such cases, cytogenetics not so helpful; other 50% of time, cytogenetics can be helpful

Cytogenetics: abnormal cytogenetics can indicate adverse risk or good risk; long list of cytogenetic changes can be associated with worse-than-expected outcomes; many involve chromosomes 5 and 7, but other patients have complex cytogenetics (>3 abnormalities), always associated with worse outcome; patients with more chromosomal abnormalities do not respond as well to conventional therapies

Multiple classification systems: to see where patient falls on spectrum (chromosomal abnormalities associated with favorable-, intermediate-, or unfavorable-risk disease); older patients have worse outcomes, likely because they have biologically worse disease; trends of chromosomal abnormalities show that favorable-risk groups (more common in younger patients; >20% of patients aged <50 yrs have favorable-risk chromosomal abnormalities); favorable-risk chromosomes in older patients becomes rarer (more prominent adverse-risk chromosomes with age); older patients do worse also because they have more comorbidities and less able to tolerate intensive chemotherapy; those with relatively good-risk cytogenetic features have cure rates of ~40%; *core binding factor AML*– translocation t(8;21) and inversion of 16, both of which disrupt large transcription-factor gene groups called core binding factor, involved in normal hematopoiesis and contribute to pathogenesis; patients with core binding factor AML uniquely sensitive to intensive chemotherapy (~90% response rate), but only minority have long-term remission or cure; almost always younger patients; for intermediate-risk group (50%) with no chromosomal abnormalities; how to risk stratify?

Genomic testing: series of gene tests performed at diagnosis to examine chromosomal abnormalities and specific gene mutations; good understanding of gene mutations in this disease; ~50 gene mutations contribute to AML; each patient usually has 2 to 5 different mutations; *how can we use gene testing to prognosticate, especially for intermediate-risk groups?* — good understanding of most common gene mutations (FLT3 and nucleophosmin [NPM1] and C/EBP-alpha) and their implications; many other genes can contribute, and prognosis depends on whole picture; just knowing status of 1 gene not as helpful as next-generation sequencing (strong prognostic power)

Routinely monitored genes:

FLT3: common; about one-third of patients with normal karyotype have FLT3 mutation; associated with worse outcomes; patients with FLT3 just as likely to achieve remission as those without FLT3, but relapse limits life expectancy; worse overall survival; associated with proliferative disease; as with Patient B, FLT3 drives disease to high peripheral blood WBC levels that can be dangerous (end-organ damage, pulmonary complications, etc); *2 types of FLT3 mutations* — internal tandem duplication, classic FLT3 mutation associated with bad outcomes (causes proliferative disease); tyrosine kinase domain mutations less clear for prognostic implications, but generally viewed as poor; FLT3 also important because of emerging treatment options; drugs specifically designed to target cells with mutant copies of FLT3, some of which have been FDA approved; *eg*, for newly diagnosed patient with FLT3 mutation and good candidate for intensive induction chemotherapy (7+3), midostaurin inhibits FLT3 and some other kinases; adding midostaurin to induction chemotherapy on day 8 for 2 wks associated with improved overall survival; now standard of care; gilteritinib, another recently FDA-approved FLT3 inhibitor; single-agent pill approved for relapsed FLT3+ AML; in randomized study, better than chemotherapy with respect to response and overall survival (still modest); considered standard of care for relapsed or refractory FLT3+ AML

NPM1: common mutation in AML, mostly in patients with normal karyotype; biology of NPM1 interesting; associated with better-than-typical outcome (relative); with NPM1 mutation, expect better outcome; implications for whether transplant or consolidation chemotherapy recommended

Isocitrate dehydrogenase (IDH): 2 isoforms, IDH1 and IDH2; genes known to contribute to glioblastoma and some other solid tumors; only recently discovered as recurrent gene mutation in AML; these 2 isoforms in 15% to 20% of patients with AML; important because targeted therapies exist for patients with IDH mutations, enasidenib (IDH2 inhibitor) and ivosidenib (IDH1 inhibitor); both approved in relapsed and refractory AML with IDH1 or IDH2 mutation; need to know which mutation present; modest responses and long-term outcomes, but benefits in right setting; considered standard of care; recently, ivosidenib approved for upfront treatment of IDH1+ AML in older patient or unfit for intensive chemotherapy

Other mutations: many mutations without targeted therapy or therapy selection based on mutations; several associated with worse outcomes (*eg*, RUNX1, ASXL1, p53); only mutation besides NPM1 associated with better-than-average outcome, C/EBP-alpha; ever-changing field that requires attention of specialists who keep current new developments

Therapy-related AML: ~10% of AML develops in patients who had prior exposure to chemotherapy or radiation for another malignancy; usually triggers worse cytogenetics and worse outcomes; exposure to alkylating therapies have ~5- to 7-year latency to developing AML; patients often evolve through antecedent MDS; topoisomerase II inhibitors frequent culprits with 1- to 2-year latency to developing AML that usually does not go through MDS; patients often have rearrangements in KMT2A gene (formerly known as MLL gene rearrangement); t(9;11) translocation common, but others possible

Younger patients: standard of care for younger patients deemed fit for intensive regimen, 7+3 regimen; combination of cytarabine (continuous infusion for 7 days) plus anthracycline (daily for 3 days); anthracycline usually daunorubicin or idarubicin, but other anthracyclines can

be considered; patient with FLT3 mutation getting 7+3 should also get midostaurin on day 8; patients with core binding factor AML (uniquely susceptible to intensive chemotherapy) could get intensification of cytarabine dose; recently reapproved CD33 antibody, gemtuzumab ozogamicin (antibody–drug conjugate that targets CD33); unique susceptibility in patients with good-risk cytogenetics (*eg*, core binding factor AML) to this agent when added to intensive chemotherapy at time of diagnosis; many consider this standard of care for newly diagnosed patient with good-risk features or core binding factor AML; treatment typically lasts 7 days; patients in hospital, blood counts become very low; usually check day 14 bone marrow biopsy, not to determine if patient has achieved remission, but to check for residual evidence of disease that would require intensification of chemotherapy regimen (~20% of time); look for emptiness (no cells, just hypocellularity with no increase in leukemia cell population); once patient recovers bone marrow (all blood counts have come back) and transfusion independent, perform another bone marrow biopsy (often as outpatient); if no morphologic evidence of disease, patient has achieved remission; next step important to determine if patient can be cured

Consolidation phase: patients with high-risk disease features (whether cytogenetic or molecular) after remission often receive either stem cell transplant if high-risk features or consolidation chemotherapy if no high-risk features; dependent on eligibility for transplant; disease potentially curable, so can be goal in right setting

Older patients or those unfit for intensive chemotherapy: median age at diagnosis 68 yrs; intensive chemotherapy with 7+3 difficult for older patient; recent approval of venetoclax, standard of care in this setting; oral therapy that targets BCL2; when paired with azacitidine, decitabine, or low-dose cytarabine, high response rates in older or unfit patients newly diagnosed with AML; combination of venetoclax with backbone therapies produces response rates of 60% to 70% with good, long-term overall survival (>1 yr); concerns with tumor lysis syndrome with venetoclax; close monitoring warranted; most effective therapy; another FDA-approved therapy, glasdegib (inhibits hedgehog signaling pathway) can be given with low-dose cytarabine to newly diagnosed AML patients; less enthusiasm for this strategy, but some patients derive benefit; recent standard of care in this setting, hypomethylator (azacitidine or decitabine) as single agent can be considered with add-on therapies; role of single-agent hypomethylator diminishing; some older patients too sick or unable to tolerate any therapy, so provide supportive care, transfusions, or even hospice

Relapse: major problem; how most patients with AML die; first question, "Is there a target that we can exploit with one of these new targeted therapies?" for FLT3 mutation, can use gilteritinib; if IDH mutation, can use enasidenib or ivosidenib; most patients do not have one of those targets; in that setting, decide whether patient good candidate for another round of intensive chemotherapy or single-agent hypomethylating therapy (*eg*, azacitidine or decitabine); clinical trials preferred in this situation because "we are bad at treating this and we need to get better"

Acute promyelocytic leukemia (APL): rare but important subtype; formerly known as AML M3 (old French-American-British [FAB] classification system); characterized by AML with translocation t(15;17), which rearranges PML and retinoic acid receptor (RAR) alpha genes into close proximity to each other; historically, worst subtype of AML when treated with chemotherapy (patients commonly died of bleeding complications); most common AML cause of DIC; awful complications in early days of treatment; now one of leukemias with best outcomes; cure rates border on 100%, in many cases with no chemotherapy; patients with low-risk disease (APL with WBC count <10) should receive all-trans retinoic acid (ATRA) and arsenic (Lo-Coco regimen); *this regimen can cause differentiation syndrome* — medical problem that needs to be recognized quickly and managed aggressively, often with steroids; differentiation syndrome can cause fevers, rash, fluid accumulation; need to be on lookout for it; once patients get through induction stage, then consolidation phase of ATRA and arsenic (usually outpatient); dramatic responses; key, early recognition of APL with genetic testing using polymerase chain reaction (PCR) or fluorescence in situ (FISH) testing for t(15;17); if APL suspected, ATRA should be started; ATRA, oral therapy of very high doses of vitamin A; among most potent therapies for APL; faster APL patient gets ATRA, less likely to die of bleeding complication; *APL patient types* — somewhat more common in younger patients, women, and Latinos; all of these can be clues, but if any suspicion, start patient ATRA, then discontinue if not APL; does no harm; because of good outcomes; APL in remission should not be treated with allogeneic stem cell transplant; relapsed APL rare but can be treated again with similar strategies; ATRA/arsenic/gemtuzumab regimen can have good success rate in relapsed APL; even autologous stem cell transplant, not used for any other form of AML in our country (always allogeneic), has role in this setting

Myelodysplastic Syndrome

Overview: type of myeloid malignancy; can be classified as acute (*eg*, AML) or chronic; chronic myeloid malignancies can be classified as myelodysplastic syndromes or myeloproliferative neoplasms (MPNs); MPNs include CML and myelofibrosis, polycythemia vera, and central thrombocythemia; MDS, own entity with different subtypes; MDS and MPNs can overlap, may be features of both diseases, as in chronic myelomonocytic leukemia (CMML), which has features of both MDS and MPN

MDS: clonal bone marrow neoplasm (cancer of bone marrow); sometimes patients have been told MDS not cancer by other doctors (even oncologists), but misinformation; MDS meets all criteria for cancer, even though it may not behave like other cancers; characterized by ineffective hematopoiesis (process of blood cell development in bone marrow) that happens inappropriately, improperly; leads to improper maturation of myeloid cells that crowd out bone marrow and cause bone marrow failure; bone marrow failure presents with cytopenias and symptoms related to bone marrow failure; bone marrow biopsy shows evidence of dysplasia (immaturity); experienced pathologists can recognize this under microscope; about one-third of patients with MDS progress to AML (related condition)

Epidemiology: disease of older patients; median age, ~70 yrs; increase in incidence with age; rare in younger patients; rare pediatric and even middle-aged patients; almost always in fifth or sixth decade; true incidence

hard to know because likely underestimated; many people with anemia or other cytopenias associated with older age or inflammation probably have MDS

Diagnosis: criteria include presence of ≥1 cytopenia (in either erythroid, neutrophil, or megakaryocyte lineage, without alternative hematopoietic or nonhematopoietic cause), and dysplasia (morphologic evidence of immaturity) in ≥1 bone marrow lineage in >10% of cells in that lineage; may have dysplasia or increased blasts; 5% to 19% blasts in bone marrow diagnostic; if 20% blasts, AML; patient may have 1 of several chromosomal abnormalities pathognomonic, or diagnostic, for MDS; many meet several criteria

Classification: recently updated by WHO (2016); reflects diagnostic system; different classifications exist if ≥1 lineage of MDS with immaturity, ≥1 cytopenia; some allowances for percentage of blasts; >5% blasts, high-grade MDS; 5% to 9% blasts, high-grade MDS with excess blasts-1 (MDS-EB1); 10% to 19% blasts, MDS with excess blasts-2 (MDS-EB2); categorization complicated

New diagnostic entities: some patients do not meet criteria of MDS but have something wrong

Clonal hematopoiesis of indeterminate potential (CHIP): now recognized based on large-scale genomic testing that some people have mutations in genes responsible for normal hematopoiesis; those genes often implicated in MDS and AML; not every patient with mutation meets criteria for MDS; patient who does not meet diagnostic criteria for MDS may have one of CHIP genes (DNA methyltransferase 3 alpha [DNMT3A], tet methylcytosine dioxygenase 2 [TET2], additional sex combs like–1 [ASXL1], etc); incidence increases with age; most patients do not develop MDS but have increased risk (0.5%-1% risk per year); higher risk for cardiovascular complications; thought to be like monoclonal gammopathy of undetermined significance (MGUS) in myeloma or monoclonal B-cell lymphocytosis in CLL; precancerous condition that can evolve to MDS or AML

Clonal cytopenia of undetermined significance (CCUS): cytopenia but no other diagnostic criteria for MDS in presence of CHIP genes; do not meet diagnostic criteria for MDS; greater chance of evolving to MDS; many consider treating like MDS; implication that recognition and treatment of pre-MDS conditions may impact disease

Prognosis: main prognostic system Revised International Prognostic Scoring System (IPSS-R; simple calculator using biological features of patient's disease); assesses cytogenetic category, number of blasts in bone marrow, and number and degree of cytopenias; gives score that places patient into low-risk, high-risk, or intermediate-risk group; distinct groups with respect to risk of evolving to AML and overall survival; this standard scoring system should be used for every MDS patient; valid only at time of diagnosis; cannot recalculate if disease progression; gives good sense of expectations for how patient might do; wide range of disease courses in MDS, so important to recognize position of patient on that spectrum for treatment decisions; *natural history of MDS* — ~50% of patients die from cytopenias or other functional cell defects related to MDS (infectious, bleeding, or anemia-related complications) but will not transform to AML; ~30% will transform to AML and most often die from disease; ~20% die *with* MDS but not *from* MDS; some patients never need treatment, even for yrs or decades, and some need minor treatment; IPSS-R score at diagnosis used to divide into lower-risk and higher-risk MDS to determine treatment

Lower-risk MDS: with anemia as only cytopenia, look at chromosomes; *deletion 5q syndrome* — if patient has deletion 5q and only 1 other abnormality or no other chromosomal abnormalities, or 1 other abnormality not involving chromosome 7, patient may have deletion 5q syndrome; important MDS subtype to recognize because lenalidomide effective treatment option; two-thirds of patients with deletion 5q syndrome can be treated effectively with lenalidomide and experience deep and durable remissions; *not every patient with deletion 5q has deletion 5q syndrome* — patients with multiple chromosomal abnormalities who also have deletion 5q do not have deletion 5q syndrome and do not have as good chance of deep and durable response to lenalidomide; *other presentations* — anemic patient that does not have deletion 5q and has low serum erythropoietin may benefit from erythroid stimulating agent; anemic patient with no deletion 5q syndrome and normal to high serum erythropoietin level should be considered for FDA-approved hypomethylating agent (azacitidine or decitabine); if anemia and another cytopenia (thrombocytopenia, or neutropenia) or all 3), patient should receive hypomethylating agent unless deletion 5q syndrome; consider lenalidomide

Higher-risk MDS patients: first ask, "Is patient candidate for stem cell transplant?" if yes, consider moving immediately or quickly to allogeneic stem cell transplant; may or may not want to use hypomethylating agent to bridge to transplant; in some settings (younger, fitter patient with ≥15% blasts), treat as for AML, with intensive chemotherapy; *if patient not candidate for allogeneic stem cell transplant*– best option either azacitidine or decitabine; azacitidine and decitabine approved based on randomized data; with azacitidine, survival benefit compared with conventional care regimens (intensive chemotherapy, low-dose cytarabine, or supportive care); decitabine does not technically provide survival benefit, but some issues with how that study was done, so decitabine reasonable for newly diagnosed, higher-risk MDS patient or lower-risk MDS patient who meets criteria discussed previously; *hypomethylating agents* — unfortunately, although hypomethylating agents have proven benefit in conventional treatment, they do not work very well; ~20% of patients achieve complete response; probably no patients cured with hypomethylating agent; ~10% to 15% of patients who do not achieve response can achieve hematologic improvement, fewer transfusions, improvement in blood counts, feeling better, improved quality of life; duration of response may be ≤1 yr; usually well tolerated; no big problems with toxicity; do not work very well, but only treatments we have; patients should be considered for clinical trial, acknowledging this deficit; when patients progress or relapse after hypomethylator, or do not respond at all, poor

outcomes; most patients live ≤1 year; 2-year survival ~15%; really challenging to treat these patients

Suggested Reading

Arber DA et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-405; **Greenberg PL et al:** Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndrome. *Blood.* 2012;120:2454-65; **Rao AV:** Fitness in the elderly: how to make decisions regarding acute myeloid leukemia induction. *Hematology Am Soc Hematol Educ Program.* 2016;2016(1):339-47; **Shouval R et al:** External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. *Blood Adv.* 2019;3(12):1881-90.

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Chronic Lymphocytic Leukemia

Hamid Sayar, MD, MS, *Assistant Professor of Clinical Medicine, Division of Hematology/Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN*

Chronic lymphocytic leukemia: pathologic terminology for this disease, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); malignant or clonal disease of mature B lymphocytes; disease of older adults; with expansion of lymphoblasts in bone marrow and blood, less room for normal cells and hematopoietic elements to grow; patients develop anemia, thrombocytopenia, or neutropenia

Presentation: most patients asymptomatic at diagnosis (diagnosis made by accident); lymphocytosis most common presentation; other forms of presentation include lymphadenopathy, spleen enlargement, liver enlargement, or less commonly, involvement of other organs such as skin; only ~5% to 10% present with generalized symptoms (*eg*, fatigue, night sweats, poor appetite); other forms of presentation, uncommon in practice, include autoimmune hemolytic anemia, thrombocytopenia, or pure red cell aplasia (form of severe anemia); autoimmune hemolytic anemia occurs in ~10% of CLLs, thrombocytopenia in <5%, and pure red cell aplasia uncommon; hypogammaglobulinemia (low immunoglobulin [Ig] levels) in ~25% of cases along course of disease; for lymphocytosis to qualify for CLL diagnosis, number of absolute lymphocytes should be >5000/µL; *monoclonal B-cell lymphocytosis* — lymphocytes <5000/µL and clonal; not considered CLL, but could be pre-CLL condition

Diagnosis: *blood and bone marrow* — most commonly, testing peripheral blood smear and immunophenotyping; bone marrow examination not necessarily required for CLL diagnosis; microscopic examination of peripheral blood smear shows increased number of mature lymphocytes; some may be cleaved, some may be reactive looking, but mature without nucleoli, also may be smudge cells (but lack of smudge cells does not exclude diagnosis of CLL); to prove clonality and confirm CLL diagnosis, need immunophenotyping by flow cytometry on peripheral blood; positive CD markers in CLL indicative of CLL diagnosis include CD5, CD19, CD20 (usually dim), and CD23; most important distinction from mantle cell lymphoma (can present with similar picture to CLL), in mantle cell lymphoma, CD23−, in CLL, CD23−; *biopsy* — occasionally, bone marrow examination in cases of questionable diagnosis; in cases that present with lymph node enlargement, needle biopsy or excisional biopsy of lymph node required for diagnosis if blood does not show lymphocytosis; excisional biopsy preferred, or at least core needle biopsy; fine-needle aspiration typically inadequate for diagnosis of lymphoproliferative disorders (cannot identify disease subtype)

Staging: *Rai staging system* — most common staging system for CLL; 5 stages; stage 0, only lymphocytosis; stage I, lymphadenopathy, typically in addition to lymphocytosis; stage II, enlarged liver or spleen, with or without lymphadenopathy; stage III, lymphocytosis and anemia (hemoglobin <11 g/dL), may or may not include liver, spleen, or lymph node enlargement; stage IV, lymphocytosis and thrombocytopenia with platelet counts <100,000/µL, with or without anemia, and with or without liver, spleen, or lymph node enlargement

Prognostication: 3 elements help prognosticate CLL; not all 3 need to be available

Cytogenetics: good prognostic cytogenetics include 13q deletion and trisomy 12; poor prognostic cytogenetic findings include 17p deletion and 11q deletion; 17p deletion distinct type of CLL, confers poor prognosis for response to treatment, duration of remission, and survival

Mutation status of Ig heavy chain variable regions: mutated Ig heavy chain variable region associated with good prognosis; unmutated Ig heavy chain variable regions associated with unfavorable prognosis, higher risk of relapse, shorter overall survival

Expression of markers: recorded on flow cytometry; ZAP70 and CD38, if positive, associated with less-favorable prognosis; don't necessarily coexist; positive ZAP70 or CD38 considered when >30% of cells express ZAP70 or CD38; strong association between ZAP70 positivity and unmutated Ig heavy chain variable region gene; ZAP70-positive CLLs more frequently have unmutated Ig heavy chain variable region gene

Treatment: in general, CLL considered incurable disease; treatment given mainly to improve blood counts, relieve symptoms, and improve overall survival (OS); in small fraction of patients with CLL, allogeneic stem cell transplantation can offer long-term disease-free survival (DFS), considered equivalent to cure; newly diagnosed patient with CLL typically observed without active treatment if acceptable blood counts and not symptomatic; also applies to patients with unfavorable prognostic marker; having poor prognostic marker not in itself indication to start treatment; indications for treatment include abnormal blood counts or symptoms such as severe fatigue, poor appetite, pain, splenomegaly, painful lymphadenopathy, or bulky lymph nodes; generally, hemoglobin levels <10 g/dL and platelet count <100,000/µL indications

to initiate treatment for previously untreated CLL; once patient considered candidate for treatment, pretreatment evaluation preferred; typically includes bone marrow examination in patients with cytopenia; bone marrow examination helps to understand extent of involvement of bone marrow by disease, general structure of bone marrow, and morphology of other lineages; cytogenetic study preferred, ideally on bone marrow or peripheral blood to understand underlying or baseline cytogenetic abnormalities; preferred, but not required, to check for mutation status of Ig heavy chain; computed tomography (CT) scan at baseline not required prior to treatment for every patient, but in patients who may have internal lymphadenopathies, CT scan can provide understanding of internal organs and lymphadenopathies

Initial therapy: no standard first-line treatment for CLL; based on some factors, can make therapeutic decisions; one important factor, 17p deletion or mutation in gene TP53 (tumor-suppressor gene located on short arm of chromosome 17); 17p deletion equivalent to TP53 mutation; patients who carry 17p deletion or TP53 mutation generally at high risk for either not responding to treatment, or if they respond, tend to relapse quickly; chemoimmunotherapy less effective in this group of patients; chemoimmunotherapy typically consists of single chemotherapy drug or regimen of chemotherapy drugs, and addition of CD20 monoclonal antibody (mAb); in these patients, treatment that includes chemotherapy not preferred; ibrutinib treatment of choice (small-molecule Bruton tyrosine kinase [BTK] inhibitor) given orally and taken continuously every day; can induce response in variety of CLLs, regardless of cytogenetics, mutation status, or other prognostic factors

Initial therapy in patients without 17p deletion or TP53 mutation: factor that can help decide how to treat them, Ig heavy chain mutation status; *patients with unmutated Ig heavy chain CLL* — treatment with ibrutinib probably more effective than treatment with chemoimmunotherapy, regardless of age; *patients with mutated Ig heavy chain* — divided into younger (typically aged <70 yrs) and older (aged >70 yrs); in patients with mutated Ig heavy chain and aged <70 yrs have better prognosis, treatment of choice chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) regimen; in older patients with mutated Ig heavy chain, chemoimmunotherapy reasonable choice, but if concern regarding tolerability of chemoimmunotherapy, given age, performance status, or comorbidities, ibrutinib reasonable choice as well; if chemoimmunotherapy chosen for these patients, typically treat with lighter regimens than FCR (*eg*, bendamustine/rituximab, fludarabine/rituximab, or old-fashioned cyclophosphamide/vincristine/prednisone [CVP] with rituximab); in general, chemoimmunotherapy offers higher rate of complete response (CR)_ than ibrutinib, but equal progression-free survival

Initial therapy in patients not candidates for chemoimmunotherapy or ibrutinib: ibrutinib can cause atrial fibrillation or bleeding tendency; patients with preexisting cardiac arrhythmia or who take anticoagulation therapy may not be candidates for ibrutinib; very old patients, those with multiple comorbidities, or those with poor performance status may not be candidates for chemoimmunotherapy; in those patients, choice of chlorambucil and addition of one of anti-CD20 mAbs (*eg*, rituximab, obinutuzumab, or ofatumumab); small but real risk of reactivation of hepatitis B with anti-CD20 mAbs; any patient who will receive these agents must be checked for hepatitis B, typically by testing for hepatitis B surface antigen and hepatitis B core antibody

Relapsed and refractory CLL: need to confirm relapse, and importantly, make sure no transformation; ~5% of CLLs can transform into different histology (*eg*, large-cell lymphoma, blastic transformation, prolymphocytic leukemias, typically more aggressive and treated differently); need to review blood smear, may need to repeat flow cytometry, or take biopsy if lymph node suspicious for transformation; signs and symptoms that suggest histologic transformation may include rapid lymph node enlargement or involvement of unusual sites or symptoms less common with typical CLLs (*eg*, fever, significant weight loss, night sweats); unexpected high elevation of lactate dehydrogenase (LDH) may indicate transformation; transformation can happen in some areas and not others; *eg*, if patient has generalized lymphadenopathy, probably only 1 or 2 lymph nodes transformed; in these cases, positron emission tomography (PET) scan can help determine what area may have transformed and what area to biopsy; bone marrow examination may be indicated if cytopenia, particularly if rapid progression of cytopenia; decision when to treat relapsed disease or residual CLL based on clinical picture, similar to beginning initial treatment; diagnosis of relapsed disease not by itself indication to initiate therapy; can monitor and observe patients with relapsed or residual disease and start treatment when indications occur; whenever patient with relapsed or residual CLL considered candidate for treatment, prefer to have repeat cytogenetic study done, either on peripheral blood or bone marrow (cytogenetics can change during disease course); patient who did not have 17p deletion at beginning may have developed 17p deletion after relapse

Treatment: type of previous treatment and time to progression from last response important factors; patients who receive FCR, if progression happens after 2 to 3 yrs of response, can be treated with same regimen, but if progression happens earlier, then prefer to switch to different therapy; timeframe for other chemoimmunotherapy regimens (*eg*, bendamustine/rituximab, CVP/rituximab) ~1 yr; if patient has progressed in less time, then ibrutinib, idelalisib, or venetoclax would be choice of therapy; patient who previously received chemoimmunotherapy and now, upon relapse, has 17p deletion or TP53 mutation, must be treated with one of these oral targeted agents, in particular, ibrutinib, even if that patient has had long duration of remission in past

Stem cell transplantation in CLL: transplant not done in CLL in previously untreated patients; transplant reserved only for second-line therapy or beyond; allogeneic stem cell transplant preferred for CLL; *2 types of transplant*

for allogeneic stem cell transplantation — myeloablative and nonmyeloablative transplant; myeloablative transplants carry high (≤50%) risk of mortality in CLL; nonmyeloablative (also called reduced-intensity allogeneic stem transplantation) preferred type of transplant for CLL; typical case scenario for allogeneic stem cell transplantation in CLL, younger patient with high-risk disease (*eg*, 17p deletion) who has already been treated with agent and had some response or who has chemoimmunotherapy and had achieved good partial or complete remission; in general, patients in complete remission have better long-term outcome with transplant; if patient has residual or refractory disease, prefer that patient to somehow be placed into remission state before undergoing transplant

Complications: *infection* — patients with CLL have disturbed cellular and humoral immunity; may be neutropenic, some have low Ig levels, so at risk of infections; give intravenous immune globulin (IVIg) only to patients who have recurrent or serious infections in setting of low Ig levels; *thrombocytopenia* — can be result of expansion of disease in bone marrow or of hypersplenism; autoimmune thrombocytopenia (type of idiopathic thrombocytopenic purpura [ITP] particular type of thrombocytopenia that occurs in ~5% of CLL patients; these patients typically experience rapid and severe decline in platelets; bone marrow examination may show normal or even increased megakaryocytes; those patients typically treated similarly to ITP, with steroids, rituximab, or combination of steroids and rituximab; ~50% may respond; those who do not respond to this kind of mild treatment will typically be treated for CLL; about one-third of patients with autoimmune thrombocytopenia may also have autoimmune hemolytic anemia (Evans syndrome) at same time; *anemia* — may be result of various etiologies, including membrane filtration by CLL cells; sometimes patients may have gastrointestinal blood loss from use of steroids; may have hypersplenism; 1 type of anemia may be autoimmune hemolytic anemia (occurs in ~10% of patients with CLL); patients experience isolated drop in hemoglobin with normal platelet count and with not very high number of white blood cells (WBCs); tests for hemolysis (*eg*, low haptoglobin level, high LDH) usually positive; typically positive direct Coombs test, and bone marrow, if checked, shows reasonable production of erythroids; typically treated like other autoimmune hemolytic anemias, again, with steroids or rituximab, and if no response, need to treat for CLL; red cell aplasia (basically underproduction of red blood cells in bone marrow) rare type of anemia in CLL; bone marrow exam shows no or limited erythroid precursors, with profound reduction of reticulocyte count as opposed to autoimmune hemolytic anemia, in which reticulocyte count typically elevated; check for parvovirus, which can be etiology of red cell aplasia, and if parvovirus negative, could be from cytokine effect from CLL; treat with combination of cyclosporine and prednisone (*ie*, immunosuppression)

Acute lymphoblastic leukemia (ALL): acute lymphoblastic leukemia/lymphoma (ALL/L) correct pathologic terminology; can present as leukemia (*ie*, involvement of blood and bone marrow) or as lymphoma (*ie*, involvement of lymph nodes); many patients present with features of both leukemia and lymphoma, and some patients present only with lymphoma, meaning no involvement of blood or bone marrow, but same disease process grows in their lymph nodes; ALL results from overproliferation of lymphoblasts, (immature lymphoid cells); common malignancy in children (~25% of all malignancies in children), but incidence decreases with age; lowest incidence ~30 yrs to 50 yrs and 60 yrs; after age 60 yrs, another mild peak of ALL, and slightly increased incidence in older individuals

Presentation: *leukemic form* — more common; typically presents with leukocytosis, sometimes circulating blasts in blood, anemia, thrombocytopenia, and neutropenia; some patients may have lymphadenopathies as well; *acute lymphoblastic lymphoma* — presents with lymphadenopathy only; either form of disease can involve liver, spleen, other tissues; central nervous system (CNS) involvement occurs more commonly in children, but not uncommon in adults; patients may have bone and joint pain (likely from expansion of leukemic blasts inside bone marrow); in some cases, disease can be slow growing, over several mos as opposed to few wks (more typical)

Diagnosis: examination of blood and bone marrow smears and immunophenotyping through flow cytometry; morphology of blood or bone marrow shows increased blasts, lymphoblasts (typically small blasts with large nuclei, scant cytoplasm); may be few granules inside cytoplasm, but most commonly, cytoplasm lacks granules; no Auer rods; may look like hand mirror; on immunostains, ALL blasts myeloperoxidase (MPO) negative and periodic acid-Schiff (PAS) positive; *distinction between ALL and acute myeloid leukemia (AML)* — in AML, cells MPO positive and PAS negative; on immunophenotyping, B-cell ALLs almost always express CD19, CD22, and CD79b; often also express CD10 and/or TDT; may express CD20; CD13 and CD33 expression (markers for AML) can occur in ALL as well, and their expression does not exclude diagnosis of ALL; expression of MPO does exclude diagnosis of ALL in favor of AML; T-cell ALL often presents as lymphoma, particularly with mediastinal mass, not necessarily in form of leukemia; CD3+ and CD7+, and not typically B-cell markers

Cytogenetics: in children with ALL, total number of chromosomes in leukemic cells important prognostically; if total number of chromosomes in leukemic cell >46 to 50, hyperdiploidy (favorable prognostic sign); if total number of chromosomes in leukemic cell <46, hypodiploidy (poor prognostic sign); in adults with ALL, number of chromosomes less important

Important chromosome abnormalities in adults: translocation between chromosomes 9 and 22 (Philadelphia [Ph] chromosome)**,** basis of chronic myeloid leukemia (CML); can have Ph chromosome in ALL; translocation results in rearrangement between 2 genes of ABL and BCR, resulting in fusion gene called ABL/BCR; breakpoint on BCR gene different between ALL with Ph chromosome and CML with Ph chromosome; when PCR tests done to detect and quantify ABL/BCR, 2 types of transcripts to check; P190 transcript (responsible for most ALLs) and P210 transcript (responsible for most CMLs); ALLs with

Ph chromosome usually B-cell ALLs and have P190 transcript on PCR test and, of course, translocation between chromosomes 9 and 22 on chromosome analysis; these ALLs comprise ~25% of all B-cell ALLs, carry poor prognosis; *other chromosome abnormalities* — translocation between chromosomes 4 and 11, which typically causes a breakage on band q23.3 of chromosome 11, chromosome abnormality that can confer poor prognosis to ALL in adults; translocation between chromosomes 12 and 21, more favorable prognostic chromosome abnormality

Other prognostic factors: with increasing age, worse the prognosis because of many factors, including biology of disease and tolerability of treatment; in general, patients aged >30 yrs to 40 yrs do worse with ALL than younger patients; in B-cell ALLs, WBC count of >30,000 at presentation poor prognostic finding, <30,000 better; in T-cell ALLs, presenting WBC count >100,000 considered poor prognostic finding, and <100,000 not as bad; expression of CD20 in B-cell ALLs typically confers less-favorable outcome

Treatment: some drugs effective for treatment of ALL (*eg*, steroids, anthracyclines, cyclophosphamide, vincristine, asparaginase), given in different dose schedules as part of different chemotherapy regimens; asparaginase used mostly for treatment of children and young adults; can be quite toxic in older individuals; regardless of chemotherapy regimen used, large majority of patients with ALL achieve a complete remission with induction chemotherapy; the rate of complete remission with different chemotherapy regimens typically ~80% to 90%; long-term survival for ALL ~30% to 40%, depending on disease subtype, patient age, and other factors; many patients with ALL experience relapse and some may die along the course of induction or further treatments; overall, the survival rate not as great the complete remission rate

Once patient achieves a complete remission, 2 main directions to be taken: 1. continue on further chemotherapy, which typically includes multiple cycles of chemotherapy (consolidation therapy), followed by 2 yrs to 3 yrs of mild, usually oral, chemotherapies (maintenance therapy); 2. allogeneic stem cell transplantation; decision of whether patient should be continued on consolidation followed by maintenance vs allogeneic stem cell transplantation depends on several factors (*eg*, ALL subtype, patient age, availability of donor); if candidate for transplant, transplant better performed sooner rather than later; prefer not to go far on consolidation route and then decide to do transplant

Case scenarios: Ph+ ALL historically has poor long-term outcome; addition of tyrosine kinase inhibitor (TKI) to chemotherapy regimen essential part of treatment for Ph+ ALL; patients should be referred for allogeneic stem cell transplantation; small fraction of CD20+ B-cell ALLs typically have worse outcomes compared with CD20-negative ALLs; addition of rituximab to CD20+ ALL in individuals aged <60 yrs definitely improves outcome, but not necessarily in patients aged >60 yrs; typically, older individuals treated with milder, less-intense therapies; if Ph+ disease, can be treated only with TKI and prednisone as opposed to chemotherapy; high rate of CNS involvement in ALL, so all patients receive some prophylaxis or treatment for CNS disease (mostly intrathecal chemotherapies); craniospinal radiation therapy routine practice in past, but not commonly used today

Allogeneic stem cell transplantation: preferred for patients with Ph+ ALL and patients with translocation of chromosomes 4 and 11; other case scenarios include highly elevated WBC count at presentation, and postremission minimal residual disease; for B-cell ALL, presenting WBC count >30,000/μg considered high risk, for T-cell ALL, WBC count >100,000/μg; those patients will benefit from allogeneic stem cell transplantation; patients with measurable minimal residual disease after achievement of complete remission would be candidates for transplant; regardless of indication, typical patient for transplant younger patient, usually aged <40 yrs; older patients, even with indication for transplant, may not be easy candidates and may not do very well with transplant; in some centers, patients aged <60 yrs may be considered for transplant

Relapsed and refractory ALL: refractory ALL defined as patient not achieving a complete remission with induction chemotherapy; relapsed ALL defined as patient who has been in remission and disease comes back

Treatment: chemotherapy always option; for relapsed ALL, if >2 yrs between complete remission and relapse, reasonable chance of achieving second remission by using same chemotherapy regimen as used at beginning; if duration of remission <2 yrs, chance of achieving second remission with same regimen smaller; some nonchemotherapy treatments used for relapsed/refractory ALL more frequently than chemotherapies

Blinatumomab: anti-CD19 mAb, given by continuous IV infusion over 4 wks; ~25% chance of remission; main adverse events include neurologic side effects, ranging from headache to lethargy or even seizures; also possibility of cytokine-release syndrome (sepsis-like condition resulting from quick release of cytokines); blinatumomab effective only for treatment of B-cell ALL

Inotuzumab ozogamicin: anti-CD22 mAb conjugated to chemotherapy agent, calicheamicin, given once weekly for 3 cycles. offers remission rate as high as 80%; hepatic toxicity main side effect, can cause veno-occlusive disease in liver; inotuzumab ozogamicin also used for B-cell ALL

Chimeric antigen receptor (CAR) T-cell therapy: can be highly effective, with a complete remission rate ~80%, but can also be highly toxic; US Food and Drug Administration approved only for patients aged ≤25 yrs

Nelarabine: approved for relapsed or refractory T-cell ALL; can induce complete remission in ~20% to 30% of cases; neurotoxicity main adverse event

Hairy cell leukemia: malignant disease of B cells; B lymphocytes have small cytoplasmic projections (thus called hairy cells); gradual onset, cytopenia; *presentation* — typically neutropenia, but can be anemia or thrombocytopenia; patients can have splenomegaly; *diagnosis* — peripheral blood shows lymphocytes with small cytoplasmic projections; bone marrow has so-called "fried egg" appearance (pathognomonic or morphologic

feature of hairy cell leukemia); typically, bone marrow aspirate in hairy cell leukemia dry tap, so end up doing biopsy; on flow cytometry, cells positive for CD19, CD20, CD22, and CD11c; most importantly, BRAF mutation; *treatment* — patients can be observed as long as not severely cytopenic; typically, once patients become anemic (hemoglobin <10 g/dL), thrombocytopenic (platelet count <100,000/µg), or neutropenic (absolute neutrophil count [ANC] <1), consider treatment; purine analogs (in particular, cladribine), but pentostatin also used

Large granular lymphocyte (LGL) leukemia: malignant or clonal disease of T cells in ~85% of cases and natural killer (NK) cells in ~15%; gradual disease course, with gradual onset of anemia or neutropenia, and, occasionally, both, but typically not thrombocytopenia; *presentation* — patients have peripheral lymphocytosis; morphologic examination of peripheral blood or bone marrow shows increased number of lymphocytes, larger, more cytoplasm than normal lymphocytes, and some purplish or dark purplish granules inside cytoplasm; has association with rheumatoid arthritis (RA); some patients with long-term RA may develop LGL leukemia; not every patient with LGL leukemia has history of RA; *diagnosis* — typically, bone marrow examination, although diagnosis can also be made with examination of peripheral blood; immunophenotyping of peripheral blood or bone marrow in case of T-cell LGL shows cells positive for CD3 and CD57; flow cytometry of NK cell LGL shows cells negative for CD3 and positive for CD56; *treatment* — patients typically followed by observation as long as ANC >1 or hemoglobin >10 g/dL; once patient becomes more neutropenic or more anemic, treatment started, either oral cyclophosphamide or oral methotrexate; treatment must be continued for long time until response achieved; some patients may take up to 6 mos to 9 mos before showing response

Suggested Reading

Paul S et al: Treatment of relapsed/refractory acute lymphoblastic leukemia. *Clin Adv Hematol Oncol*; 2019;17(3):166-75; **Strati P, Ferrajoli A:** Treating older patients with chronic lymphocytic leukemia: a personalized approach. *Drugs Aging*. 2019 May 4. doi: 10.1007/s40266-019-00678-5. [Epub ahead of print.] **Yeung CCS, Shadman M:** How to choose the best treatment and testing for chronic lymphocytic leukemia in the tsunami of new treatment options. *Curr Oncol Rep*. 2019;21(8):74.

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Multiple Myeloma

Shaji Kumar, MD, *Professor of Medicine and Consultant, Division of Hematology, Mayo Clinic, Rochester, MN*

Multiple myeloma (MM) epidemiology: malignancy of terminally differentiated plasma cells; second most common hematologic malignancy after non-Hodgkin lymphoma; ~30,000 patients diagnosed with MM and ~12,000 die annually in United States(US); considered incurable with current treatments; *monoclonal gammopathies* — MM belongs to spectrum of disorders known as monoclonal gammopathies; majority of gammopathies, monoclonal gammopathy of undetermined significance (MGUS), which does not require treatment; prevalence of monoclonal gammopathy increases with age; ~10% of patients aged >70 yrs have monoclonal protein in serum or urine; majority of patients will have MGUS; these patients have relatively low levels of clonal plasma cells in bone marrow and make small amounts of monoclonal protein that can be detected in blood or urine; ~20% of these patients, over 25- to 30-yr period, will have progression of underlying plasma cell clone evolving into MM requiring treatment; in between, phase called smoldering MM, in which clone has increased in size as reflected by increasing amounts of monoclonal protein in serum or urine, or increasing amount of clonal plasma cells in bone marrow; smoldering MM has increased risk of progression to MM compared to MGUS and about half of these patients will progress to MM over 10-yr period; what distinguishes smoldering MM and MGUS from symptomatic MM, these patients have no end-organ damage typically seen with MM

Pathophysiology: unclear what leads to the formation of clonal plasma cells, but various factors have been described that increase risk of developing monoclonal gammopathy; *risk factors* — exposure to radiation, petroleum products, and pesticides, suggesting environmental influence; family members of patients with monoclonal gammopathies have increased risk, suggesting genetic component to developing monoclonal gammopathies; certain populations (*eg*, African Americans) have increased risk of monoclonal gammopathies; monoclonal gammopathy likely originates sometime in second or third decade of life; most people go through life without being diagnosed with monoclonal gammopathy; often diagnosed incidentally when person undergoes workup for unrelated condition; most patients with MGUS never develop active myeloma that needs treatment or any other related condition like light-chain amyloidosis or light-chain deposition disease, which also require treatment

MGUS: characterized by small clonal burden of plasma cells and relatively low levels of monoclonal protein in serum or urine; most patients will have elevated levels of immunoglobulins that make up monoclonal protein; smaller proportion of patients may have only elevated kappa or lambda free light chains without elevation of intact immunoglobulins (light-chain MGUS)

Smoldering MM: in small proportion of patients with MGUS, size of clone can increase over time, increasing amounts of protein in serum or urine, but patients still may not have end-organ damage that characterizes MM; these patients often referred to as having smoldering MM; requires closer follow-up; risk of developing active MM in patient with smoldering MM higher than in MGUS; in MGUS, risk of progression ~1% per yr and remains constant; in contrast, patients with smoldering MM have increased risk of developing MM; nearly 50% will have progressed to MM during first 5 yrs; in subsequent 5 years, another 15% will develop smoldering myeloma; remaining third of patients have low risk of progression comparable with those with MGUS

Diagnosis: presence of end-organ damage distinguishes active or symptomatic myeloma from both MGUS and smoldering myeloma; end-organ damage in MM typically takes form of hypercalcemia, renal insufficiency, anemia, or bone disease (CRAB); diagnosis of MM requires presence of monoclonal plasma cells, which often secrete monoclonal protein, and end-organ damage (CRAB); *updated criteria* — recently, diagnostic criteria of myeloma have undergone change, with inclusion of patients without end-organ damage, but instead having characteristics that predict high likelihood of developing end-organ damage in relative short timeframe; these include bone marrow plasma cell percentage ≥60%, involved or uninvolved free light-chain ratio ≥100, and presence of >1 bone marrow lesions seen on magnetic resonance imaging (MRI) or positron emission tomography (PET) scan, but without bone destruction characteristic of myeloma; definition of myeloma changed to extend treatment to those patients with smoldering MM at high risk of developing MM before they develop bone disease or renal failure, which can be permanent; *diagnosing symptomatic or active myeloma critical* — should be done in systematic fashion, with assessment of monoclonal protein in serum and urine, bone marrow biopsy to look at clonal plasma percentage in bone marrow, and advanced imaging studies (eg, MRI of spine or whole-body low-dose computed tomography [CT]) scan to assess for presence of bone destruction secondary to MM

Risk stratification: after diagnosis comes risk stratification; unlike solid tumors, in which staging system often refers to extent of disease spread outside area of origin, in MM,

which starts at multiple areas in bone marrow at same time, staging system more reflective of aggressiveness of underlying disease or reflective of disease biology; several prognostic factors have enabled clinicians to predict how disease may behave; genetic abnormalities most important; clonal plasma cells, or myeloma cells, in patients with MM can be analyzed using fluorescence in situ hybridization (FISH) that allows looking for numeric and structural abnormalities involving various chromosomes

Genetic abnormalities: genetic abnormalities in MM can be divided into trisomies that often involve odd-numbered chromosomes and translocations that often involve chromosome 14 at immunoglobulin heavy-chain locus; certain partner chromosomes always involved in this translocation with chromosome 14; they include chromosomes 4, 6, 11, 16, and 20, and less commonly, chromosome 8; these translocations can lead to enhanced function of certain genes that may play role in phenotype seen in patients with MM; these translocations and trisomies often referred to as primary genetic abnormalities; secondary abnormalities may occur and may increase over time; these include deletion of short arm of chromosome 17 (deletion 17p or monosomy of chromosome 17), amplification of chromosome 1q, deletion of chromosome 13q (monosomy of chromosome 13), all of which often present only in subset of myeloma cells; proportion of cells carrying abnormality increases over time as patients go through multiple lines of treatment

International Staging System (ISS) for Multiple Myeloma: another risk stratification system; uses simple blood measurements (serum albumin and serum beta-2 microglobulin); with these tests, patients can be grouped into 3 ISS stages with different survival outcomes; building on ISS, Revised International Staging System incorporates genetic findings of FISH and third blood test, serum lactate dehydrogenase (LDH); also groups patients into 3 different groups with different survival outcomes

Novel and emerging technology: current risk stratification systems do not completely explain the heterogeneity in outcomes seen in MM; MM now seen as heterogeneous group of disorders that may appear similar under microscope when myeloma cells looked at, but clinical behavior that can be quite different, with survival ranging from <3 yrs to >10 yrs; various genetic factors and immune factors may play role in explaining heterogeneity; novel technology has been applied to try to explain heterogeneity seen in outcome of these patients; gene expression profiling measures expression of different genes in cell; different gene expression profiling signatures have been developed to predict patient outcomes more accurately than with traditional risk-stratification systems; recent technology has also started looking at presence of mutations in different genes; ~12 different genes consistently mutated in patients with myeloma and in myeloma cells have been identified; proportion of cells carrying these mutations also increases with time and with disease relapses, just as with secondary chromosomal abnormalities

Initial treatment: before initial treatment, determine if patient able to undergo autologous peripheral blood stem-cell transplant (APSCT), commonly used treatment for MM; eligibility criteria for APSCT have changed over time; age most common criterion; most clinical trials in APSCT have studied patients ≤65 yrs, though other studies have shown that patients ≤75 yrs may derive benefit from APSCT with careful patient selection; these factors include overall functional status and presence of comorbidities (eg, heart or lung disease); eligible patients undergo initial treatment with given regimen for 4 to 6 cycles, or 4 to 6 mos, then they receive single APSCT, given with high doses of chemotherapy followed by infusion of stem cells collected from peripheral blood prior to chemotherapy; many patients get additional therapy following APSCT as consolidation or maintenance therapy; in contrast, ineligible patients receive another treatment regimen often continued for long period of time, often until lack of treatment response

Goals of initial treatment: goals, control disease and decrease tumor burden to lowest level possible; treatment regimen should also rapidly and effectively control disease and reverse disease-related complications (eg, renal failure or neurologic complications); initial treatment should be effective in decreasing risk of early death from infection (common in this immunocompromised state), especially in those eligible for APSCT, treatment should not impede collection of peripheral blood stem cells for use after APSCT

Initial treatment of APSCT-eligible patients: in patients eligible for APSCT, initial treatment includes combination of proteasome inhibitor (bortezomib [Velcade] most commonly used), immunomodulatory drug (lenalidomide [Revlimid] most commonly used), and dexamethasone ([eg, Decadron]; corticosteroid); this 3-medication combination given for 4 to 6 cycles, each of which would be 4 wks in length; after this, patients undergo peripheral blood stem-cell collection in preparation for APSCT; peripheral blood stem-cell collection involves administration of a growth factor filgrastim (Neupogen) that stimulates stem cells in bone marrow and allows them to appear in peripheral blood circulation; here, they can be collected through apheresis; rarely, plerixafor (Mozobil) will be additionally needed to stimulate these stem cells to move into bloodstream so they can be collected for APSCT; after stem-cell collection, patients typically receive melphalan (Alkeran, Evomela) intravenously at high dose capable of ablating most of bone-marrow cells; immediately following administration of chemotherapy, peripheral blood stem cells previously collected will be reinfused into bloodstream and return to bone marrow and restart making normal bone-marrow cells; APSCT has been demonstrated to be effective in multiple phase 3 randomized trials in prolonging disease control in patients with MM; some earlier studies have shown that patients who receive APSCT can live longer than patients who do not receive APSCT; though some recent trials have not demonstrated overall survival (OS) benefit, most likely because these patients received APSCT later in disease course; if patient wishes, may have stem cells collected without undergoing transplant right away; cells may be frozen and kept for later APSCT to treat MM relapse

Maintenance therapy: after APSCT, maintenance therapy administered as single medication given at

slightly lower dose than initially; different clinical trials have varied duration of maintenance therapy; current approach, continue maintenance therapy for at least 2 yrs and often until recurrence, which can be up to 5 to 6 yrs on average; lenalidomide most commonly used maintenance therapy; pill given either continuously or 3 out of 4 wks; patients with high-risk MM, with presence of high-risk cytogenetic abnormalities, often put on maintenance therapy with proteasome inhibitor (eg, bortezomib), either alone or in combination with immunomodulatory drug (eg, lenalidomide); additional therapy, as consolidation therapy, may be administered after APSCT, prior to starting maintenance treatment; these consolidation approaches have included either additional cycles of multiple drug combinations (*eg*, combination prior to APSCT, for an additional few cycles) or second APSCT back-to-back with first one (tandem autologous stem-cell transplant); phase 3 trials have demonstrated varying benefits of tandem autologous stem-cell transplant or consolidation therapy; among patients receiving highly effective combinations such as bortezomib, lenalidomide, and dexamethasone before transplant, may be limited role in using consolidation therapy or tandem autologous stem-cell transplant; however, patients with high-risk cytogenetic abnormalities may benefit from tandem autologous stem-cell transplant; in MM patients, stem cells often collected for ≥1 transplant (can be used for tandem autologous stem-cell transplant or second APSCT)

Emerging treatments: carfilzomib (Kyprolis)—, new-generation proteasome inhibitor being studied, in lieu of bortezomib, in 3-drug induction or maintenance combination; initial phase 2 trials look promising; another approach, replacing proteasome inhibitor with monoclonal antibody (mAb; *eg*, daratumumab) targeted towards specific protein, CD38, on surface of myeloma cells; yet another approach, combining these 3 medications with dexamethasone to form quadruplet (4-drug combination); combination of daratumumab, bortezomib, thalidomide (Thalomid), and dexamethasone has been studied in Europe; trial showed quadruplet more effective at controlling disease in terms of both depth and duration of treatment response vs triplet therapy; trial exploring adding daratumumab to combination of bortezomib, lenalidomide, and dexamethasone to see if better than using just those 3 medications, prior to APSCT; in maintenance therapy after APSCT, other trials comparing survival benefit from use of combination drugs compared with single agents

Treatment of patients not eligible for APSCT: these patients historically treated with combination of new drug combined with melphalan and prednisone; melphalan used for myeloma treatment for ~50 yrs; recently developed drugs often combined with melphalan to assess if this would improve outcomes; consequently, combinations such as bortezomib, melphalan, and prednisone, studied in phase 3 trials and shown to be effective; similarly, combination of melphalan, prednisone, and thalidomide shown to be effective in controlling MM; recently, there has been push towards avoiding medications such as melphalan in setting of newly diagnosed myeloma, because of cumulative long-term effect on bone marrow and blood cell counts

Phase 3 trial of combination of lenalidomide and dexamethasone, in older patients with myeloma: demonstrated that combination increased depth and duration of response compared with melphalan, prednisone and thalidomide combination; resulted in increased use of melphalan-free, or alkylating agent–free, initial therapy in patients with myeloma ineligible for APSCT

ALCYONE trial: recently, ALCYONE trial compared effect of adding newer drugs like daratumumab to bortezomib, melphalan, prednisone (VMP) regimen; found that addition of daratumumab substantially improved progression-free survival (PFS) with no appreciable impact on OS so far

Continuing same regimen used in transplant-eligible patients: combination of bortezomib, lenalidomide, and dexamethasone (VRD); in contrast to transplant-eligible patients, older patients unable to tolerate full doses of these medications, hence modifications have been developed (VRD-lite); uses lower doses of lenalidomide and less-frequent administration of bortezomib and dexamethasone; studies have shown that abbreviated regimen able to control myeloma to same degree seen in younger patients with full doses; further refinement of this approach, replacing bortezomib with newer agent like daratumumab (mAb)

Phase 3 trial of addition of daratumumab to lenalidomide and dexamethasone: demonstrated significantly increased PFS and depth of response with addition of daratumumab, in newly diagnosed patients with myeloma not eligible for APSCT

Other approaches, especially in older patients who cannot come to clinic for weekly injections: using combinations of oral medications; ixazomib (Ninlaro), proteasome inhibitor similar to bortezomib but given orally once per wk; has been combined with lenalidomide and dexamethasone in phase 2 and 3 trials; may be option for patients who visit clinic frequently; older and/or frail patients should be treated initially with lower doses of medications and preferably with 2 drugs instead of 3; subsequently, drugs can be added based on tolerability

Duration of initial treatment: ongoing approaches trying to define how laboratory parameters impact treatment duration; one such approach, measurement of minimal residual disease (MRD) in bone marrow using sensitive techniques like flow cytometry or next-generation sequencing; multiple trials and meta-analysis have shown that patients achieving MRD– status have improved PFS and OS, regardless of treatment; however, still unproven if MRD negativity should be target of treatment for all patients; considerable evidence suggests that achieving MRD– state beneficial for patients with high-risk disease; hence, many treat high-risk patients more intensely to reach MRD– state; in contrast, in standard-risk patients, treatment until MRD negativity may not be necessary; these topics being explored in phase 3 trials; achievement of MRD negativity good prognostic factor; however, achieving MRD negativity and losing it rapidly usually indicates aggressive disease that needs to be carefully monitored and treated

Treatment of relapsed disease: median time to disease relapse after initial treatment of MM varies from 3 to 6 yrs depending on initial treatment choice; most patients with MM will continue to relapse; predicted that most patients in coming years will have relapsed rather than newly diagnosed MM, given that incidence of MM has not significantly changed over past 2 decades; *certain principles in treatment of relapsed MM* — 1. high-risk disease, which can be determined differently in patients with relapsed disease; patients who relapse soon after initial treatment or who do not respond to initial treatment often have high-risk disease even without high-risk factors discussed earlier, (*eg*, high-risk cytogenetics); critical attention should be paid to initial treatment response duration; 2. patients with relapsed myeloma should be treated with combination of 2 or 3 drugs that they have not been previously exposed to; ≥1 drug should be from drug class patient has not previously been exposed to; *several factors need to be taken into account when deciding medications and doses* — performance status, age, comorbidities, toxicities from prior treatment, residual toxicities from prior therapy; increasingly, clinicians seek maximum response possible, followed by maintenance on 1 of drugs from combination therapy for as long as patients can tolerate

Specific regimens: classes of drugs available for treatment of relapsed MM slightly broader than those employed in the setting of newly diagnosed disease; *mAbs*– *eg*, daratumumab, elotuzumab; daratumumab targeted towards protein on myeloma cells, CD38; elotuzumab targeted towards another protein, SLAMF7; both medications effective in treatment of MM, especially in combination; *proteasome inhibitors* — bortezomib, carfilzomib, ixazomib; bortezomib given subcutaneously, often once per wk; carfilzomib given intravenously once or twice per wk; ixazomib given orally once per wk; *immunomodulatory drugs* — thalidomide, lenalidomide, pomalidomide (Pomalyst); while thalidomide and lenalidomide can be used in newly diagnosed myeloma, pomalidomide can be used only in relapsed disease, based on prior studies; these 3 classes of drugs often combined with corticosteroids (eg, dexamethasone, prednisone); *alkylating agents* — melphalan, cyclophosphamide(Cytoxan), bendamustine (Bendeka, Treanda); *other chemotherapy medications and new classes of drugs introduced for treatment of MM*– histone deacetylase inhibitors (*eg*, panobinostat [Farydak]) and new class, inhibitors of nuclear transport protein (eg, selinexor [Xpovio]); list of different drug classes to treat MM expected to increase over next few years; in setting of relapse, depending upon first-line treatment and medication resistance, treatment decisions can be made; *eg*, patients without resistance to immunomodulatory drugs, particularly lenalidomide, can receive lenalidomide in combination with a proteasome (*eg*, bortezomib, carfilzomib, ixazomib), or in combination with mAb (*eg*, daratumumab, elotuzumab); patients sensitive to bortezomib can receive either immunomodulatory drug (*eg*, lenalidomide, pomalidomide) in combination with bortezomib, or mAb (eg, daratumumab, elotuzumab) in combination with bortezomib or carfilzomib; in patients sensitive to both lenalidomide and bortezomib, combination of bortezomib, lenalidomide, and dexamethasone can be reemployed; patients sensitive to all available classes of drugs have variety of choices; in contrast, when patients become resistant to immunomodulatory drugs and proteasome inhibitors, mAb needs to be combined with newer-generation proteasome inhibitor or immunomodulatory drug; example of this approach includes using daratumumab, or carfilzomib, or ixazomib in combination with pomalidomide and dexamethasone, or mAb (*eg*, daratumumab) in combination with next-generation proteasome inhibitor (*eg*, carfilzomib); fundamental underlying principle, use drug patient not previously exposed to, or preferably, class of drug patient not previously exposed to; however, increasingly difficult, as patients go through multiple lines of treatment and different combinations, thus they gradually becoming resistant to all available medications

Emerging treatments: several new approaches in clinical trials; immunotherapy has moved to forefront of MM therapy

Chimeric antigen receptor T cells (CAR-T cells): technology that alters T cells to enable them to recognize and attack tumor cells; T cells removed from patient by apheresis, modified using virus to insert these receptors, then reinfused; goal for these T cells to now more efficiently recognize and eliminate tumor cells; this principle proven effective in early clinical trials; many trials have studied use of CAR-T cells targeted against variety of antigens on myeloma cells, most commonly B-cell maturation antigen (BCMA); CAR-T cells have shown ability to completely eradicate myeloma cells below detectable levels, based on current technology; however, many patients still relapse after CAR-T cell therapy, despite undetectable levels of myeloma cells; this suggests need for novel approaches to MM treatment

Other immunotherapy approaches: *bispecific T-cell engagers (BiTEs)* — proteins or antibodies that bring patient's T cells close to tumor cells to allow T cells to recognize and attack tumor cells; unlike CAR-T cells, T cells not removed from patient's body, allowing treatments to be given without delay; *mAbs* — use of mAbs targeted towards BCMA, but conjugating mAbs to toxins, which can then kill myeloma cells once antibody binds to them; given genetic abnormalities seen in MM, treatments being developed that may be targeted towards individual genetic abnormality; *venetoclax (Venclexta)* — currently closest candidate medication; inhibitor of antiapoptotic protein, BCL2, widely expressed in myeloma cells, particularly in patients with translocation 11;14, or t(11;14), present in ~15% to 20% of patients with myeloma; venetoclax used in combination with dexamethasone demonstrated disease control in patients with t(11;14); when used in combination with other myeloma drugs, appears to be effective in patients with other cytogenetic abnormalities outside of t(11;14); may be first example of personalized- or precision-medicine approach for those with MM; ongoing clinical trials looking at combining these drugs, targeted to specific genetic mutation, and using them with traditional myeloma therapy

Supportive care: *renal failure* — needs speedy management to avoid long-term kidney damage and dialysis; patients with renal failure may benefit from plasma exchange, which removes high levels of serum free light chain

(present in majority of these patients), while myeloma therapy takes effect; these patients should be treated aggressively with multidrug therapy, primarily including proteasome inhibitor (*eg*, carfilzomib, bortezomib); can be combined with other medications that do not need modifications in presence of renal failure; combining approaches can reduce levels of serum free light chain (most reliable predictor of renal function recovery in these patients); infections — patients with newly diagnosed myeloma have high rate of infections; MM often associated with low levels of normal immunoglobulins (Igs), though there high levels of abnormal Ig (M-spike); other aspects of immune system also suppressed in patients with myeloma; increased risk of infection can be controlled with antibiotic prophylaxis, especially in first 2 to 3 months after diagnosis; even in patients not on prophylaxis, early recognition of infection and immediate intervention with appropriate antibiotic therapy remain key part of myeloma management; high doses of steroids often used for treatment of MM can further suppress immune system; patients should be on prophylaxis against specific type of infection, pneumocystis pneumonia; *hypercalcemia* — can be decreased by use of bisphosphonates; RANK ligand inhibitors can also be used for same effect; tightly linked with bone disease, seen in majority of patients with MM; often includes development of lytic lesions in bone that lead to bone weakening and possibly pathologic fracture of long bones or vertebrae; phase 3 trials have shown that use of bisphosphonates (eg, zoledronic acid [Reclast, Zometa], pamidronate [Aredia]) can decrease risk of bone fractures and increase bone strength in long term; moreover, studies have shown control of MM better with these bone therapies and patients may live longer using these bone-strengthening agents compared with not using them; recently, phase 3 trials have shown the benefit of recently approved RANK ligand inhibitors, including denosumab (Xgeva)

Summary: diagnosis of MM requires the presence of monoclonal plasma cells and end-organ damage (CRAB symptoms); risk stratification based on presence of specific genetic abnormalities and/or blood test results; approach to initial treatment of MM divided between patients eligible or ineligible for APSCT; eligible patients will undergo initial treatment, which may include proteasome inhibitor, immunomodulatory drug, and corticosteroid; then they will receive single APSCT; some receive additional therapy as consolidation or maintenance therapy; in contrast, ineligible patients will receive another treatment regimen for long period of time; this regimen typically contains melphalan, though attempts to decrease its use, because of long-term side effects; relapsed myeloma treatment guided by principles including presence of high-risk relapsed disease, and treatment avoiding medications patient had been previously exposed to

Suggested Reading

Mateos MV et al: Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med*. 2018;378(6):518-28;
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Stem Cell Transplantation

Corey S. Cutler, MD, MPH, *Associate Professor of Medicine, Harvard Medical School, and Director of Clinical Research, Stem Cell Transplantation Program, Dana-Farber Cancer Institute, Boston, MA*

Transplantation: performed for several reasons, mainly to eliminate and replace diseased, poorly functioning, immunologically compromised, or metabolically compromised bone marrow; also stem cell transplants done to protect against ultra-high doses of chemoradiotherapy that otherwise would permanently kill normal human bone marrow; also done to establish immunologic platform upon which effective immunotherapy can be delivered

Transplantation decisions: autologous vs allogeneic transplant; intensity of conditioning to deliver with transplant or preparative regimen; donor type (*ie*, self, for autologous transplantation, or related or unrelated donor for allogeneic transplantation; determine degree of match, if perfectly matched as in autologous, or varying degrees of mismatch in allogeneic; determine source of stem cells

Autologous transplantation: reserved for small number of diseases and indications; transplant consists of high doses of chemotherapy with or without radiation (generally without), designed predominantly to kill tumor cells and to overcome resistance of tumor cells with dose intensity; because of high doses of chemotherapy administered in this type of transplant, need to rescue patient's bone marrow by taking it out, cryopreserving it, then reinfusing it after transplant so that it does not get exposed to ultra-high doses of chemotherapy and radiation therapy; often referred to as stem cell rescue; done largely in US for treatment of multiple myeloma, where it serves as disease-prolongation mechanism or therapy; also done with curative intent for some diseases (*eg*, relapsed Hodgkin disease, non-Hodgkin lymphoma, and other types of lymphoma), and in even rarer instances for some germ cell tumors and other rare indications

Allogeneic transplantation; different from autologous transplant; not only can get benefits of high-dose chemotherapy and/or radiation to kill tumor cells, but allogeneic transplantation relies on second, probably more important, mechanism, immunologic mechanism, to try to cure patient; referred to as immunologic donor-vs-host immunoreaction, or graft-vs-tumor reaction, as probably more important component of 2 mechanisms of tumor cell kill; allogeneic transplantation done largely for diseases like acute leukemias, myelodysplastic syndromes (MDSs), myeloproliferative diseases (MPDs), and in addition to some rare malignant conditions; also performed for some nonmalignant diseases (**eg**, aplastic anemia, diseases of altered immunity; decision whether to use autologous or an allogeneic transplant type really disease, stage, and patient specific

Intensity of conditioning: degree and drugs or radiation used in conditioning regimen determined by several factors, mainly tumor type; some tumor types treated exclusively with autologous or allogeneic transplant; some tumor types treated exclusively with low or high doses of conditioning; determine stage of disease at transplantation to determine intensity of conditioning; determine whether effective graft-vs-tumor effect in that disease, and then, just as importantly, look at performance status and comorbidity of recipient of that transplant to determine what type of conditioning intensity he or she can receive; several regimens exist; *for allogeneic transplantation* — regimens differ in intensity and toxicity; intensive regimens, myeloablative conditioning regimens; formal definitions of what constitutes myeloablative transplantation; often based on doses of chemotherapy drugs or dose of radiation used; *eg*, regimen that contains 9 mg/kg busulfan, >150 mg/m^2 melphalan, or that consists of >800 cGy total body irradiation, fractionated in any fashion, considered ablative; definitions published by Center for International Blood and Marrow Transplant Research (CIBMTR), revised regularly; in allogeneic transplant, not only relying on toxic effects of chemotherapy and radiation; thus, can do lower-intensity transplants, which rely on reduced intensity or nonmyeloablative doses of chemotherapy and/or radiation, simply to suppress recipient's immune system enough to get allogeneic stem cell source into patient; *in autologous transplantation* — goal to kill tumor cells with dose-intense chemotherapy, so no role for reduced-intensity or nonmyeloablative preparative regimens; in autologous transplantation, all conditioning regimens considered myeloablative

Intensive myeloablative vs reduced-intensity regimen in allogeneic transplant: depends on disease and patient being treated; older recipients have more difficulty tolerating fully myeloablative conditioning regimens; in patients beyond certain physiologic age, should not administer total myeloablative regimens because too toxic; choice of myeloablative or reduced-intensity regimen doesn't really matter; *recent study published by Blood and Marrow Transplant Clinical Trials Network Group (BMTCTNG), BMT CTN 0901* — patients with advanced MDS or acute myeloid leukemia (AML) in remission randomized to receive one of several myeloablative or reduced-intensity regimens; study demonstrated clear advantage in relapse-free survival in myeloablative arm, largely seen in the AML group;

preferred approach in AML, myeloablative regimen in patients who can tolerate it

Type of donor: in autologous transplantation, always self (perfectly matched donor); in allogeneic transplantation, determine whether to use related or unrelated donor; goal in allogeneic transplant always to match donor and recipient pairs; match based on human leukocyte antigen (HLA) molecules, encoded on chromosome 6 at major histocompatibility complex (MHC); some matching at non-HLA loci, may be done more readily in future; *HLA system comprises several genes* — classes I, II, and III, found on chromosome 6; class I (HLA-A, HLA-B, HLA-C) and II (HLA-DR, HLA-DP, HLA-DQ loci) genes commonly matched for transplantation; when we talk about matching, we talk about resolution of matching, meaning matching serologically or antigenically; also degree of matching with respect to how many of these HLA genes being matched between donors and recipients; for full match, 12 of 12, which means patient matched with donor at HLAs A, B, C, DR, DP, and DQ; within family members, because HLA molecules inherited as haplotype; less important to talk about all extended HLA loci, so we generally speak about entire haplotype passed between parents and children; siblings matched fully, but haplotypes not; for unrelated individuals, genes dispersed more haphazardly, so becomes more important to talk about degree of HLA match; thousands of variations among each of HLA molecules, so HLA-A, -B, and -C have thousands of potential polymorphisms, therefore, infinite number of potential combinations between donors and recipients; some linkage disequilibrium among different ethnic and racial groups, such that not all HLA combinations exist, although some people unique

Likelihood of match: depends on background and whether unrelated donor registries have sufficient representation of ethnic backgrounds; for individuals of Western European descent, using common registries, can find perfectly matched donor for ~70% to 80% of individuals; for nearly all others, rate of finding perfect match in registries may be as low as 20% to 30%, particularly for some ethnic minorities unrepresented in registries; less-than-perfectly matched transplants allow finding suitable donors for larger number of individuals; however, in general, with less-well-matched transplants, outcomes go down; *if perfectly matched donor not found in registry, can use half-matched donors (haploidentical donors)* — these individuals may be half-matched sibling or obligate half-matched donor (*eg*, parent or child); because HLA haplotypes inherited as such, all individuals have haploidentical donor in parent or child, and ~50% of siblings haploidentical; in some individuals, need for transplant high enough that even less-than-perfectly-matched donor acceptable; as transplantation has improved, results with haploidentical or half-matched transplant have improved quite considerably; *final alternative source when cannot find perfectly matched donor* — umbilical cord blood; contains high proportion of hematopoietic stem cells, which can be used in transplantation; do not have to match as stringently between donor and recipient pairs because immunology of umbilical cord blood very immature; T cells transferred with graft tend to be less mature and cause fewer problems, such as graft-vs-host disease; several hundred thousand units in unrelated donor cord blood registries, making it easy to find match for almost all patients

Stem cell source: from adult donors, 2 choices for stem cells (bone marrow, where stem cells actually reside in body, or harvesting stem cells from peripheral blood); we have stem cells that circulate in small numbers at all times; using medications (*eg*, granulocyte colony-stimulating factor [GCSF]) can stimulate release of our own stem cells into bloodstream, and can then be collected using apheresis machine; bone marrow harvest alternative to apheresis collection, which requires time in operating room (OR; general anesthesia usually used for healthy donors)

Ease of collection: much easier to collect umbilical cord blood stem cells from individuals because those cord blood cells waiting to be ordered from bank; peripheral blood stem cells require donor to undergo GCSF mobilization (but easier for collection than donor going to OR room for bone marrow collection)

Engraftment: peripheral blood stem cells engraft, on average, 12 to 15 days from transplantation, whereas bone marrow takes 18 to 21 days; and umbilical cord blood takes longest, average of 21 to 40 days

Immunologic reconstitution: peripheral blood stem cells reconstitute slightly better than bone marrow because slightly higher number of T cells; umbilical cord blood reconstitutes poorest because of immaturity and number of T cells included in that graft; *graft-vs-host disease (GVHD)* — opposite side of immune reconstitution; umbilical cord blood traditionally associated with fairly low rates of GVHD, but peripheral blood stem cells have slightly higher rates of GVHD (in particular, chronic GVHD, because of number of mature T cells)

Graft-vs-tumor effect: unknown if cord blood different or better or worse, or if bone marrow better or worse than peripheral blood stem cells

Complications: after relapse, GVHD next most common cause of treatment failure after transplantation; 2 syndromes, acute GVHD and chronic GVHD, that occur after transplantation; previously defined by their temporal relationship to time of transplant (acute, early; chronic, late), but now defined based on clinical features because better understanding of different pathobiology; different clinical features, different pathobiologic background, and different diseases

GVHD: when kidney transplanted into body, immune system easily and immediately recognizes that transplanted organ as something foreign and rejects it; in allogeneic transplantation, transplanting into immune system; transplanted immune system attacks normal host tissues (*eg*, skin, liver, intestinal tract); recognized as GVHD; increasing amounts of GVHD associated with treatment failure and death after transplantation; T cells and immunologic mechanisms that underpin GVHD, same mechanisms that underpin graft-vs-tumor or graft-vs-leukemia; if T cells taken away or patients don't get any GVHD, slightly higher rate of relapse after transplantation; *GVHD double-edged sword* — want to see some GVHD, but unable to separate it from graft-vs-leukemia; complex system of immunologic processes, generally started in host tissue damage from conditioning therapy, production of inflammatory cytokines, induction of allogeneic response by donor T cells, perhaps with

host antigen presentation cells playing role; donor cells expand under influence of inflammatory cytokines, and specifically set up attack against recipient tissues (*eg*, skin, liver, gut)

Steps in GVHD (preventing GVHD focuses on these steps): *first step* — antigen in T-cell receptor interaction; can't get GVHD if donor T cells don't recognize foreign antigen; prevent by taking away T cells, or depletion of lymphocytes, using medications like anti-thymocyte globulin (ATG); *second step* — T-cell receptor signal has to be transduced down to nucleus; transduction mechanisms within T cells can be blocked using drugs such as cyclosporine or tacrolimus; disrupt upregulation of interleukin-2 (IL-2)-based signaling using IL-2 receptor blockade; signaling of IL-2 can be blocked using mammalian target of rapamycin (mTOR) inhibitor, sirolimus; third step — T cells need to divide in order to mount effective GVHD response; prevent cell-cycle progression and growth of T cells using DNA synthesis blockers (*eg*, mycophenolate and methotrexate); these drugs remain underpinnings of drugs used to prevent GVHD; *GVHD does occur despite what we consider effective GVHD prophylaxis* — acute GVHD happens in 35% to 40% of individuals who undergo matched-related donor transplant, ≤50% of individuals who undergo unrelated donor transplant

Risk factors for acute GVHD: HLA disparity greatest risk factor; other risk factors include matching between sexes, donor parity, donor age (older donors worse), donor ABO subtype, cytokine gene polymorphisms, cytomegalovirus (CMV) serostatus; these things generally cannot be controlled; can control stem cell source, so peripheral blood stem cells having slightly higher rates than bone marrow, and graft composition, which can sometimes be controlled by looking at T-cell dose within graft, and can deplete graft of T cells to prevent GVHD

Acute GVHD: "earlier" version of GVHD; clinicopathologic syndrome involving 3 organs only (skin, liver, intestinal tract); skin most commonly affected organ in acute GVHD; ~75% of all GVHD patients will have some degree of cutaneous involvement, and 40% to 45% of patients with acute GVHD have skin manifestations only; *presentation* — maculopapular rash, often confused with drug eruption but tends to involve areas of skin (*eg*, palms and soles) generally not involved in drug reactions; gastrointestinal (GI) tract e second most common organ involved, and most important because often most difficult organ to control; acute GVHD of gut presents as profuse, watery diarrhea, sometimes hemorrhagic, and when it progresses, can result in ileus; diarrhea often happens during conditioning for transplantation, so need to exclude conditioning-related injury to gut or infections of GI tract (common in transplantation), mimicking acute GVHD and causing profuse diarrhea; liver, third, and least commonly affected (<20% of cases) organ; presents as cholestatic jaundice, often with transaminitis; and main diagnostic considerations include drug reactions and veno-occlusive disease of liver; imaging of liver generally not helpful in GVHD, and biopsy of all 3 organs diagnostic standard, although biopsies used relatively infrequently, particularly when skin main organ manifestation, because maculopapular rash often distinct; s*everity of acute GVHD*– individual organ stages; each organ staged 1 through 4, and degree of involvement of each organ given progressively higher stage; when 3 organ stages combined yields overall grade of GVHD, graded I through IV (roman vs Arabic numerals to differentiate)

Treatment: depends on stage and grade of involvement; individuals with stage 1 or grade I disease often require topical therapy only, but those with stage 2 to 4 GVHD more commonly require systemic therapy; *initial therapy* —, corticosteroids dosed at 1 mg/kg to 2 mg/kg methylprednisolone or equivalent steroid, yielding ~50% to 60% overall response rate; 20% to 25% relapse rate with acute GVHD, and another 20% to 25% have primary steroid-resistant acute GVHD; outcomes fairly poor in advanced GVHD; some estimates suggest long-term outcome for individuals with advanced steroid-refractory GVHD as low as 10%- to 20%; rate improving with newer, more effective second-line agents and better supportive care; problem with advanced GVHD, piling on courses of immunosuppression, resulting in multiple infections, often cause of death; *several lines of therapy for second-line GVHD* — drugs that block inflammatory chemokines; several monoclonal and polyclonal antibodies directed against specific T-cell antigens and other cellular antigens; several agents, particularly JAK inhibitors, in development for treatment of acute GVHD

Chronic GVHD: ~50% of related and unrelated recipients end up with some degree of chronic GVHD; important cause of late morbidity and mortality in posttransplant period, requires chronic therapy; associated with functional deficits and real reductions in quality of life; any organ system can be affected by chronic GVHD, but skin, mouth, and eyes most commonly affected; musculoskeletal system, GI tract, liver, lungs, neurologic system, serosal surfaces, hematopoietic system, and immunologic system can be affected; also stage and grade chronic GVHD; *most important system to know, National Institutes of Health (NIH) scoring system* — divides patients into mild, moderate, or severe chronic GVHD based on number of organs involved and degree of severity; mild GVHD, mild disease in only 1 or 2 organ systems without lung involvement; severe chronic GVHD, severe manifestation in single organ or moderate to severe lung involvement; all other patients scored as moderate chronic GVHD

Treatment: determined by involvement; local symptoms often treated with local therapy; supportive and local immunosuppressive strategies for most organs (*eg*, eyes, mouth, skin); document by NIH Consensus Project on chronic GVHD published in 2015 covers supportive care of all these different organ systems; access through the American Society of Transplantation and Cellular Therapy (ASTCT) website; *systemic treatment* — use drugs such as corticosteroids; typically start with slightly lower doses, prednisone or equivalent, at dose of 1 mg/kg daily or every other day; often use calcineurin inhibitors (*eg*, tacrolimus or cyclosporine) in conjunction with steroids as kind of steroid-sparing effect; possible, based on emerging data from Bone Marrow Transplant Clinical Trials Network, that mTOR inhibitor sirolimus might be more effective; individuals, once they start therapy for chronic GVHD, may be on therapy for as long as ~2 yrs; supportive measures to prevent chronic complications of steroid use such as close monitoring of

blood glucose, bisphosphonates to prevent osteoporosis, and sleep aids important; *risk of infection* — with chronic GVHD and immune suppression comes infection; important that patients remain on effective prophylaxis throughout at-risk period; in early posttransplant period, worry about bacterial pathogens, particularly during neutropenic period; individuals with prolonged neutropenic periods or on long-term corticosteroids for treatment of acute or chronic GVHD at risk of fungal infections, so effective antifungal prophylaxis important; viral pathogens important, so things like herpesvirus (*ie*, HSV and VZV) can be prophylaxed effectively with drugs such as acyclovir or newer versions; need to worry about another member of the herpesvirus family, CMV; treat either preemptively with drugs as CMV viral loads rise or, more recently, in certain patients, give prophylactic drugs to prevent viral reactivation against CMV with drugs such as letermovir; understand your patient and risk for acquiring bacterial, viral, or fungal pathogens at any given time, and ensure proper prophylaxis; patients also require reimmunization; well-published reimmunization strategy we use, providing vaccines starting as early as 6 to 9 mos from transplantation, extending through 2 yrs, at which point can provide live virus vaccines

Veno-occlusive disease (sinusoidal obstruction syndrome of hepatic sinusoids): another complication related to allogeneic stem cell transplantation;; complication of high doses of chemotherapy and radiation, really primary injury at level of hepatic sinusoidal endothelium; incidence as low as 5% to 10% for severe veno-occlusive disease; generally occurs in first 4 to 6 wks after myeloablative transplantation, although can occur in individuals undergoing reduced-intensity transplantation, and does occur in individuals undergoing autologous transplantation (to lower degree); *presentation* — with classic triad of hepatomegaly and right upper-quadrant pain, jaundice, fluid retention with weight gain ascites; *differential diagnosis* — includes sepsis syndromes, GVHD, drug reactions, renal failure, all of which can mimic veno-occlusive disease to some degree

Diagnosis: abdominal ultrasound, most importantly with Doppler measurements of portal flow (portal system most affected); abdominal ultrasound will detect enlarged liver, ascites, attenuated hepatic portal vein flow, and reversal of portal flow (found in later or severe veno-occlusive disease); useful to exclude mass lesions or cardiac causes of diseases that may mimic veno-occlusive disease; liver biopsy used infrequently, but considered gold standard; at time of liver biopsy, can do pressure measurements across hepatic portal system to determine hemodynamics of veno-occlusive disease

Treatment: 1 drug approved, defibrotide; demonstrated in prospective, phase 2 studies to improve outcomes; supportive measures (*eg*, prevention of renal failure, giving colloid to keep vascular system expanded, avoiding hepatotoxins and nephrotoxins, monitoring for infection, excluding peritonitis when suspected) just as important

Idiopathic pneumonia syndrome (diffuse alveolar hemorrhage): uncommon finding after transplant, occurring in <5% of individuals who undergo ablative transplantation; *presentation* — rapidly evolving hypoxia, often with hemoptysis; *diagnosis* — best imaged using CT scan; *treatment* — high doses of corticosteroids, sometimes with drugs such as tumor necrosis factor (TNF) blockers, which may be beneficial; requires exquisite supportive care, often with intubation; long course of recovery

Other complications: cyclophosphamide cardiotoxicity (infrequent); oropharyngeal mucositis (fairly frequent complication); mucositis can be staged and graded according to several grading systems; oral mucosal assessment scale (OMAS) most frequently used; *treatment* — largely supportive with pain medications, meticulous mouth and throat care, and prevention of worsening with drugs such as methotrexate

Suggested Reading

Chang YJ, Huang XJ: Is human leukocyte antigen-matched sibling donor transplant always better than haploidentical allograft? *Semin Hematol*. 2019;56(3):201-8; **Hill L et al:** New and emerging therapies for acute and chronic graft vs host disease. *Ther Adv Hematol*. 2018;9(1):21-46; **Scott BL et al:** Myeloablative vs reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-61.

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Screening and Localized Breast Cancer

Chirag Shah, MD, *Director, Breast Radiation Oncology and Clinical Research, Cleveland Clinic , Cleveland, OH*

Epidemiology: breast cancer represents most common non-cutaneous cancer among women in US; estimated >250,000 new cases of breast cancer diagnosed yearly in US; up to one quarter of these diagnoses represent ductal carcinoma in situ (DCIS) or other non-invasive entities; more than one million cases of breast cancer diagnosed yearly worldwide; >400,000 deaths attributed to breast cancer worldwide

Risk factors: female gender; female breast cancer cases far outnumber male cases; incidence increases with age; in US, white race; personal history of breast cancer; family history of breast cancer, with highest familial risk in patients with multiple first-degree family members; genetic syndromes associated with breast cancer, including BRCA mutations; hormone exposure, including age at menarche, menopause, and first birth, as well as use of hormone replacement therapy; data suggest lifestyle and dietary factors associated with development of breast cancer; prior radiation therapy, for example, for Hodgkin's lymphoma, may also be associated with development of breast cancer; predictive models including Gail and Tyrer-Cuzick models used to evaluate potential risk for development of breast cancer

Protective factors: oophorectomy before age 45; risk reduction therapy with tamoxifen, raloxifene, or bilateral mastectomy

Breast cancer biology: increasingly important in prognosis and treatment of patients with newly diagnosed breast cancer; prognosis traditionally based on clinical and pathologic features such as tumor size, number of lymph nodes involved, and presence or absence of metastatic disease; increasingly, data demonstrate outcomes for breast cancer driven primarily by tumor biology, rather than by tumor, nodal, and metastatic staging (TNM); receptor status was among earliest recognized forms of tumor biology; receptors assessed at time of biopsy include estrogen, progesterone, and HER2 (human epidermal growth factor receptor 2); estrogen receptor positive cancers consistently demonstrate better outcomes; hormone receptor positive patients can receive endocrine therapy; associated with reductions in rate of recurrence; HER2 positive targeted therapies include trastuzumab, pertuzumab, and lapatinib; now available for neoadjuvant, adjuvant, and metastatic setting

Newer breast cancer subtypes: luminal A, luminal B, HER2-like, and basal-like; outcomes dependent on subtype; luminal A subtype has most favorable prognosis; high ERPR (estrogen receptor, progesterone receptor) expression and low proliferation rate; luminal B cancers have lower ERPR expression and higher proliferation rates; basal-like cancers represent triple negative breast cancers — estrogen, progesterone, and HER2 receptor negative; similar to grade 3 cancer; HER2-like cancers typically HER2 positive; can be hormone receptor negative or positive with more aggressive grade 3-like appearance; treatment now being driven by these subtype determinations; example — luminal A breast cancers now evaluated for treatment de-intensification, including omission of radiation therapy following breast-conserving surgery; conversely, role of treatment intensification studied in patients with triple-negative breast cancers; example — use of capecitabine in patients with triple-negative breast cancer who have residual disease following neoadjuvant chemotherapy; studies underway

Histopathology: divided into non-invasive and invasive cancers; non-invasive cancers include primarily lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS); Paget's disease non-invasive entity typically associated with DCIS or invasive cancer

LCIS: defined by non-infiltrating lobular proliferations; multicentric involvements often noted; up to 90% of mastectomy specimens demonstrate multicentricity with bilateral involvement in 30% to 60% of cases; associated with development of subsequent invasive breast cancer; can occur in either breast; mastectomy no longer standard of care in management; pleomorphic LCIS more consistent with DCIS; often treated with breast-conserving surgery; outcomes currently limited

DCIS: usually asymptomatic; represents up to one-quarter of new breast cancer diagnoses in US; attributed to increased use of screening mammography; presents with microcalcifications >75% of time; heterogeneous spectrum of histologic appearances on pathology; all arise from and confined to ductal lumens of breast; estrogen positive in 65% to 80% of cases; 90% of low-grade and 25% of high-grade cases estrogen positive

Invasive ductal carcinoma: most common form of invasive cancer; estrogen positive 70% to 80% of time

Invasive lobular carcinoma: ≈10% of all new breast cancer diagnoses; bilateral in about 5% to 20% of cases; patients eligible for breast conserving therapy; comparison of outcomes to invasive ductal cancers found better early disease-free survival and overall survival; worse late outcomes observed; outcomes similar to invasive ductal cancers when stratified by estrogen receptor status

Rare histologies: tubular, mucinous, and cribriform cancers have good prognoses compared to invasive ductal cancers; secretory and medullary cancers have similar outcomes to invasive ductal cancer; worse outcomes observed in micropapillary and metaplastic cancers

Prevention and screening: controversial topic; multiple guidelines exist to guide treatment and screening; factors include patient age, family history, lifestyle, and reproductive history; average-risk patients aged 25 to 40 recommended to undergo clinical encounter every 1 to 3 years; no mammogram; patients 40 years or older recommended to undergo annual clinical encounter and mammogram with consideration of tomosynthesis mammography; role of tomosynthesis mammography in screening of women for breast cancer continues to grow; data remain controversial on benefits in all women; patients at increased risk for breast cancer include those with prior history of breast cancer, >20% lifetime risk, previous thoracic radiation, and 5-year risk estimates of >1.7% in women over 35; additional factors include pedigree suggestive of genetic predisposition; history of atypical ductal hyperplasia, atypical lobular hyperplasia, and LCIS; clinical exam recommended every 6 to 12 months in higher-risk patients; begin screening when patient identified as higher-risk candidate or when >21 years; genetic counseling also recommended; annual mammogram recommended 10 years prior to age of diagnosis of youngest family member with breast cancer; role of breast MRI remains controversial in high-risk patients; typically recommended for those with >20% lifetime risk or previous history of thoracic radiation; for patients with history of thoracic radiation, screening should begin 10 years after RT was received and should include screening mammography and MRI; risk reduction strategies for patients at higher risk include tamoxifen, raloxifene, and mastectomy

Bilateral mastectomy: increasingly used in patients at increased risk for breast cancer; only consider in patients with genetic mutation conferring high risk; survival advantages limited to BRCA carriers; 90% reduction in development of breast cancer in at-risk patients

Medical therapy: National Surgical Adjuvant Breast Project (NSABP) randomized trial of patients 60 years or older, those 35 to 59 with 5-year risk of at least 1.7%, or history of LCIS found tamoxifen reduced risk of invasive and non-invasive cancers and osteoporotic fractures; follow up study compared tamoxifen to raloxifene; found raloxifene as effective in reducing invasive cancers; lower rates of thromboembolic disease and cataracts; raloxifene associated with higher risk of non-invasive cancers; aromatase inhibitors more recently utilized in post-menopausal women wishing to undergo risk reduction

Staging: continues to evolve; classic breast cancer staging followed tumor, nodal, and metastasis (TNM) staging; still represents anatomic staging; new eighth edition of staging system now includes prognostic staging

Tumor staging: T0 — no evidence of primary tumor; Tis — DCIS or Paget's disease; LCIS no longer listed in Tis staging; T1 — cancers 2cm or less in total size; T1 further divided into mi (microscopic) for tumors 1mm or less; T1A — tumors >1mm and ≤5mm; T1B — >5mm and ≤10mm; T1C — >10 mm but ≤2cm; T2 — >2cm but ≤5cm; T3 — tumors >5cm; T4 — tumors with direct extension to chest wall or skin, as noted by ulceration or skin nodules; T4A — extension to chest wall and invasion or adherence to pectoralis muscle without chest wall stricture; T4B — ulceration of skin and presence of macroscopic satellite nodules or edema, including peau d'orange; T4C — combination of T4A and T4B; T4D — inflammatory breast cancer — primarily clinical diagnosis

Nodal staging: divided into clinical and pathological staging

Clinical: N0 — node negative; N1 — metastasis movable, ipsilateral level 1-2 lymph nodes and micrometastasis; N2 — metastases in level 1-2 fixed or matted; N2A — ipsilateral level 1-2 lymph nodes; N2B — ipsilateral internal mammary lymph nodes in absence of axillary lymph node disease; N3 — ipsilateral infraclavicular level 3 lymph node involvement with or without level 1 or 2 involvement or ipsilateral internal mammary lymph node involvement with level 1-2 lymph node involvement; supraclavicular involvement also included in N3 staging; N3A — ipsilateral infraclavicular lymph node disease; N3B — ipsilateral internal mammary disease and axillary disease; N3C — supraclavicular disease in ipsilateral side

Pathological: PN0 — node negative disease; PN0i positive disease — only isolated tumor cells no larger than 0.2mm; PN0 molecular positive — cancer cells within lymph nodes with no isolated tumor cells detected using RTPCR (reverse transcriptase polymerase chain reaction) technique; PN1 — micrometastasis and one to three lymph nodes involved in axilla with negative internal mammary disease; PN1Mi — micrometastases, 200 cells or more, and <0.2mm but not >2mm; PN1A disease — one to three lymph nodes in axilla with one at least 2mm; PN1B — ipsilateral internal mammary lymph nodes, excluding isolated tumor cells; PN1C — combination of PN1A and PN1B; PN1B documents role of sentinel node in detecting ipsilateral internal mammary nodes; PN2 — metastatic disease in four to nine axillary lymph nodes or positive internal mammary lymph nodes by imaging in absence of axillary lymph node metastasis; PN2A — metastases in four to nine axillary lymph nodes with at least one >2mm; PN2B — metastatic disease and clinically detected internal mammary lymph nodes with or without confirmation with pathologically negative axillary nodes; PN3 — metastatic disease in 10 or more axillary lymph nodes, infraclavicular disease, or positive ipsilateral internal mammary lymph nodes by imaging in presence of one or more level 1 or 2 axillary lymph nodes; can also include presence of supraclavicular disease; PN3A — 10 or more axillary lymph nodes with at least one >2mm, or metastatic disease in infraclavicular level 3 lymph nodes; PN3B — P1NA or PN2A disease in presence of positive internal mammary nodes by imaging or presence of PN2A disease in presence of PN1B disease; PN3C — supraclavicular ipsilateral disease

Metastatic disease: M1 — presence of metastatic disease by clinical radiographic means; C prior to M1 and P represents any histologically proven metastatic disease; with increasing use of neoadjuvant chemotherapy, treatment responses now documented with use of YC for post-neoadjuvant clinical assessment; YP for post-neoadjuvant pathological assessment; CR for complete response; PR for partial response; NR for no response

Anatomic staging: consistent with previous guidelines; Tis — stage 0 disease; T1N0 — stage IA; T0 to T1 with N1 microscopic disease — IB; N1 — stage II; T0 and T1N1 — stage IIA; T2N0 also stage IIA; T2N1 and T3N0 — stage IIB; stage IIIA — N2; T0 to T3 also includes

T3N1; stage IIIB includes T4N0, T4N1, TRN2; stage IIIC includes all N3 disease; stage IV includes any M1 disease

Management of localized and locally advanced disease: surgery and radiation therapy standard of care

Surgical options: include breast-conserving surgery (lumpectomy) and mastectomy

Breast-conserving surgery: multiple randomized trials with long-term follow-up have demonstrated equivalent outcomes comparing lumpectomy to mastectomy; no difference in overall survival between mastectomy and breast preservation with 20-yr follow up; studies have demonstrated young age not contraindication to breast-conserving therapy; ineligibility criteria for breast-conserving therapy include persistent positive margins after lumpectomy, multicentric disease, diffuse microcalcifications, and prior radiation therapy; relative contraindications to breast conservation include connective tissue disease and large tumor-to-breast ratios; guidelines for margins following breast-conserving surgery have evolved over past decade; meta-analyses have demonstrated that no tumor on ink or >0 mm margin appropriate for invasive cancers; national guidelines support use of no tumor on ink standard for invasive cancers or invasive cancers with associated DCIS; for pure DCIS patients undergoing lumpectomy, guidelines recommend 2mm or greater margin based on meta-analysis; clinician discretion with margin 0 to 2mm; multiple randomized trials evaluating lumpectomy *vs* mastectomy evaluated role of radiation therapy following breast-conserving surgery; radiation therapy reduces relative risk of local recurrence by 50% or more; radiation therapy associated with improvement or reduction in breast cancer mortality compared to patients undergoing adjuvant radiation therapy

Lumpectomy: approach continues to evolve with increased use of oncoplastic surgery; includes breast reduction, mastopexy, and tissue rearrangement; goal of optimizing cosmetic outcomes while not sacrificing clinical outcomes

Mastectomy: started with radical mastectomy as performed by Halsted in 1894; consisted of en bloc removal of breast, overlying skin, pectoralis major/minor, and levels 1 to 3 of axilla; procedure not now routinely used; most common mastectomies now include modified radical mastectomy — removal of breast and pectoralis major fascia; preserves pectoralis minor and level 1-2 lymph nodes; alternative total mastectomy with breast tissue only removed in conjunction with sentinel lymph node; NSABP04 found no benefit to radical mastectomy compared to total mastectomy; new mastectomy procedures include nipple-sparing mastectomies; appropriate clinically if no risk of disease to nipple-areola complex; skin-sparing mastectomies aid with reconstruction; mastectomies increasingly associated with reconstructions; include autologous, tissue expander base, or implant-based

Lymph node biopsy: node sampling performed in most surgeries with exception of low-risk DCIS; axillary lymph node dissection standard of care for decades whether as part of breast conservation or mastectomy; historically, 10 or more lymph nodes considered adequate for axillary lymph node dissection; typically consisted of dissection of level 1 and 2 axillae; data demonstrated no benefit to level 3 dissection; over past 2 decades, axillary lymph node dissection in clinically node-negative patients replaced by sentinel lymph node biopsy; multiple randomized studies in clinically negative patients have confirmed role of sentinel lymph node over axillary lymph node dissection; sentinel lymph node has success rate of >95%; 10% or less rate of false negatives; no difference in clinical outcomes with survival or regional control; sentinel lymph node standard of care for most node-negative patients

Management of axillary positive disease: has changed over past decade; previously, clinically node negative patients underwent sentinel lymph node biopsy; underwent axillary dissection if found to have positive axillary nodes; two trials have changed management; ACOSOG Z11, closed early and underpowered, evaluated role of axillary dissection *vs* whole-breast radiation for patients clinically node negative; no difference in clinical outcomes noted at 10 years; AMAROS study compared patients with positive sentinel lymph nodes undergoing axillary dissection *vs* regional nodal radiation; with long-term follow-up, similar outcomes seen with reduced toxicities, including lymphedema, with use of axillary radiation; clinically node-negative patients found to have limited sentinel lymph node disease able to omit axillary dissection and undergo radiation therapy with or without regional nodal radiation; areas of controversy include use of regional nodal radiation in patients with gross extranodal extension; data currently limited; axillary lymph node dissection remains standard of care for most patients with gross external extension; in IBCSG randomized trial patients found to have micrometastatic disease gained no benefit from axillary dissection; both trials primarily included patients undergoing breast-conserving surgery; raised question of omitting axillary dissection in patients undergoing mastectomy; most feel that axillary node dissection can be omitted in patients clinically node negative and with limited sentinel lymph node involvement at time of surgery

Radiation therapy: standard approach to patients with breast cancer; evaluated in multiple randomized trials for patients with DCIS undergoing breast-conserving surgery; found to reduce risk of local recurrence by 50%; significant in patients with DCIS because half of recurrences found to be invasive recurrences associated with increased risk of breast cancer mortality; radiation in past typically consisted of whole-breast radiation for 5 to 6 weeks; replaced with hypofractionated whole-breast irradiation over past decade; completes treatment in 3 weeks; alternatively, some patients undergoing lumpectomy for DCIS may receive partial breast irradiation; role of tumor bed boost evaluated in patients undergoing DCIS; considered for young, estrogen receptor negative, or close margins; limited role of radiation therapy for patients with DCIS undergoing mastectomy; data suggests marginal benefit even with positive surgical margins

Radiation in early-stage invasive disease: adjuvant radiation therapy following lumpectomy remains standard of care for patients with early stage invasive breast cancers, based on reductions in local recurrence and improvements in breast cancer mortality; four randomized trials have evaluated hypofractionated whole-breast irradiation; has become standard for early stage breast cancer patients following lumpectomy; partial-breast irradiation can also be considered for such patients, based on national guidelines from American Society for Radiation Oncology, American Brachytherapy Society, and American Society of Breast Surgeons

Can radiation be omitted in some patients? have been studies evaluating omission of radiation therapy in low-risk breast cancer patients; studies have evaluated patients with luminal A breast cancers and older patients 65 to 70 years of age with T1 or tumors <3cm with negative margins receiving endocrine therapy; have consistently demonstrated addition of radiation reduced local recurrence by 5% to 10% at 10 years but had no impact on survival

Role of radiation therapy in patients with early stage breast cancer undergoing mastectomy: primarily restricted to patients with positive lymph nodes and positive margins at time of surgery; clinically node negative patients found to have positive sentinel lymph nodes can undergo adjuvant radiation in lieu of axillary dissection; data extrapolated from clinical trials suggest patients undergoing axillary dissection with limited lymph node disease following mastectomy have benefit in reductions in local recurrence with addition of radiation therapy

Radiation therapy in more advanced breast cancers: radiation recommended for patients with more advanced breast cancers, tumors 5cm or greater, IET3 disease, T4 disease, and four or more lymph nodes or positive margins; role of radiation in patients with one to three lymph nodes continues to evolve; recent trials including MA20 trial have suggested addition of regional radiation in conjunction with axillary lymph node dissection and relatively modern chemotherapy provides benefit of reductions in local regional recurrence and improvements in distant metastasis-free survival; potential for survival advantage in estrogen receptor negative patients

Oligometastatic disease or limited number of metastatic foci: radiation therapy can be used as definitive treatment to metastatic sites using techniques such as stereotactic body radiation therapy; in patients undergoing mastectomy despite having metastatic disease, radiation therapy can be offered to reduce risk of local regional recurrence following surgery

Outcomes: continue to improve; local recurrence risk with breast-conserving surgery followed by adjuvant radiation 1% to 2% at 10 years with DCIS; roughly 10% to 15% at 10 years or greater without radiation; high-grade DCIS associated with higher rates of recurrence with omission of radiation; rates as high as 25% at 12 years; limited prospective data recently published for outcomes of DCIS following mastectomy; outcomes expected comparable to patients undergoing breast-conserving therapy; patients with DCIS expected to have low rates of breast cancer mortality — less than 5% long term; for patients with early-stage breast cancer, outcomes can be derived from recent randomized trials, including those evaluating partial-breast irradiation; studies have found rates of local recurrence in early-stage breast cancer patients to be less than 5% at 10 years; overall recurrence rates of 7% or less; trials evaluating hypofractionated whole-breast irradiation have found similar outcomes with 10-year local recurrence rates of 4% to 6%; distant metastatic disease rates of 5% to 15%; breast cancer mortality rates of ≈10%; overall survival 80% to 85% at 10 years; recent data evaluating regional nodal radiation for patients with locally advanced breast cancer demonstrated 10-year local regional recurrence rates of 5% to 10%; distant metastatic disease of 15% to 30%; breast cancer mortality of 10% to 25%; overall survival 70% to 80%; wide range of outcomes for locally advanced breast cancers; likely related to tumor biology; focus of current studies

Breast reconstruction: predominantly performed following mastectomy; includes multitude of techniques; reconstruction shown to improve cosmetic and psychological outcomes following surgery

Implant or expander-based reconstructions: most commonly utilized form of breast reconstruction; tissue expander placed at time of mastectomy and subsequently expanded with saline; patients undergoing radiation therapy typically receiving radiation therapy with tissue expander followed by replacement with permanent implant months later; some patients receive tissue expanders with expansion during chemotherapy and replacement with permanent implant followed by radiation therapy; patients more recently undergoing immediate implant-based reconstruction at time of surgery; implant-expander reconstructions also associated with higher risks of side effects, including infections and removal in patients undergoing radiation therapy

Autologous or tissue-based reconstructions: include latissimus dorsi, transverse rectus myocutaneous, and deep inferior epigastric perforator flaps; some institutions incorporate implant with autologous or tissue-based reconstructions; autologous reconstructions can be done immediately at time of mastectomy or in delayed fashion, where expander placed initially; tissue reconstruction performed months after radiation therapy; direct comparisons limited; studies comparing rates of side effects in patients undergoing radiation therapy typically find less side effects in patients receiving autologous reconstructions compared to those undergoing tissue- or expander-based reconstructions; compared to implant-expander reconstructions, autologous reconstructions associated with potential for donor site complications

New trends in breast reconstruction: use of pre-pectoral reconstruction; traditional reconstructions placed subpectorally or below reconstruction; pre-pectoral reconstruction — implant placed in front of pectoralis muscle in single procedure at time of mastectomy; can be difficulties associated with radiation therapy, including reconstruction failures; options include not utilizing approach in patients undergoing radiation therapy or utilizing pre-pectoral tissue reconstructions; air increasingly used to expand tissue expanders; self-filling tissue expanders; challenging with respect to radiation therapy planning; recommended to replace air with saline for tissue expanders or remove self-expanding expanders and replace with permanent implants prior to radiation therapy

Surgical complications: acute and subacute complications include potential for bleeding, infection, non-healing wounds, and deep venous thrombosis and pulmonary embolism due to immobilization; late toxicities include volume loss following breast-conserving surgery, lymphedema with axillary surgery, and potential for reconstruction toxicity

Radiation complications: acute side effects following breast-conserving surgery include fatigue, dermatitis; rates of grade 2 dermatitis 30% to 40%; rates of grade 3 dermatitis less than 5%

Outcomes: rates of grade 3 late toxicity typically less than 5%; excellent or good cosmesis in 70% to 80% of patients; similar side effect profiles to mastectomy patients undergoing radiation with addition of reconstruction toxicities

Lymphedema: important complication of surgery and radiation therapy; rates dependent on use of local regional and systemic therapies; can be <10% in patients undergoing lumpectomy with sentinel lymph node biopsy and whole-breast radiation; up to 50% in patients undergoing axillary lymph node dissection, regional nodal radiation, and chemotherapy; modern trials evaluating role of lymph node dissection and radiation therapy have demonstrated low rates of lymphedema at 10%; data demonstrate high-risk patients should be referred for lymphedema assessment with potential options including therapy and compression sleeve

Cardiac toxicity: growing concern, particularly with radiation therapy for left-sided breast cancers; data published in *New England Journal of Medicine* showed higher rates of cardiac side effects; modern techniques now available to reduce cardiac dose; recent studies demonstrated low rates of cardiac events at 1% to 2% with long term follow up

Pulmonary toxicity: concern in patients undergoing radiation therapy with dose to lung; rates of radiation pneumonitis typically 1% to 2%; long-term fibrosis 3% or less

Second cancers: can be associated with radiation therapy; recent data demonstrated risk of any second cancer ≈10% with long-term follow up; majority of these cancers not radiation associated; radiation-associated cancers typically occur within area of treatment in particularly high-dose areas; sarcomas and histologically angiosarcoma lymphangiosarcomas most commonly seen with radiation-associated breast cancer; wide incidence range from 1 in 1,000 to 1 in 10,000; younger patients likely to live longer than older patients and have lower incidence rates; radiation-induced angiosarcomas unique entity from other radiation-associated sarcomas; shorter latency from radiation and improved overall survival and distant metastatic-free survival

Surveillance: required following breast cancer diagnosis and treatment; history and physical exam every 3 months to 1 year for first several years; annually after 5 years; patients undergoing breast-conserving therapy recommended to undergo mammography every 12 months; routine imaging of reconstructed breast for patients undergoing mastectomy not recommended; some data suggesting single view can be considered; not currently recommended that patients who have undergone treatment for breast cancer undergo routine screening for metastatic disease; recommended patients who have received tamoxifen undergo gynecologic assessment every 12 months if uterus present

Long-term management: follow up for recurrence; management of side effects, including lymphedema; lifestyle management; guidelines from American Cancer Society and National Comprehensive Cancer Care Network

Suggested Reading

Bychkovsky BL, et al: Imaging in the evaluation and follow-up of early and advanced breast cancer: when, why, and how often? *Breast.* 2017 Feb;31:318-24; **Harbeck N, et al:** Breast cancer. *Lancet.* 2017 Mar 18;389(10074):1134-50; **Niell BL, et al:** Screening for breast cancer. *Radiol Clin North Am.* 2017 Nov;55(6):1145-62.

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Systemic Therapy for Localized and Locally Advanced Breast Cancer

Ruth O'Regan, MD, *Professor of Medicine, Division Chief, Medical Oncology, Hematology & Palliative Care, and Associate Director for Clinical Research, Carbone Cancer Center, University of Wisconsin School of Medicine, Madison, WI*

Overview: hormonal therapy; indications for perioperative chemotherapy; preoperative vs postoperative systemic therapy; choice of systemic therapy regimen; complications and toxicities; inflammatory breast cancer

Breast cancer subtypes: 4 or 5 breast cancer subtypes; 2 estrogen receptor (ER)+ subtypes, luminal subtype A and luminal subtype B; ERBB2 subtype (HER2+); basal subtype, or triple-negative breast cancer without ER, progesterone receptor (PR), or HER2/neu; normal breast subtype; each subtype differs in risk of recurrence and overall survival (OS); different therapy approaches for each subtype

Endocrine therapy: hormone receptor (HR)+ breast cancers; two-thirds of breast cancers (express ER or PR); treated with adjuvant endocrine therapy, sometimes with chemotherapy; National Comprehensive Cancer Network (NCCN) algorithm outlines treatment; *eg*, for early-stage node-negative breast cancer, cancer <5 mm consider adjuvant endocrine therapy; however, consider adjuvant chemotherapy if nodes present

21-gene recurrence score assay: decision about chemotherapy based on risk score; for low scores, give adjuvant endocrine therapy; for intermediate scores, give endocrine therapy; for high scores, adjuvant chemotherapy in addition; for node-positive disease, give adjuvant chemotherapy; however, molecular subtyping also used to decide; for any invasive breast cancer, adjuvant endocrine therapy recommended; chemotherapy indicated if node positive or patient has high scores

Tamoxifen: selective ER modulator; available for decades; used for metastatic breast cancer, then later as adjuvant therapy; recommended treatment 5 yrs in early-stage breast cancer; if given for 5 yrs, reduces risk of recurrence by 40% to 50%, improves survival by about one-third; tamoxifen binds ER and partially prevents stereoisomerization, turning off estrogenic signaling within cancer cell

Aromatase inhibitors (AIs): anastrozole, letrozole, exemestane; more recently introduced; act differently from tamoxifen; reduce circulating estrogen levels; in postmenopausal women, majority of estrogen from conversion of androgens to estrogens in adrenal glands, muscle, and adipose tissues through action of aromatase enzyme; therefore, inhibition of aromatase reduces circulating estrogen levels; not used in premenopausal women (small reduction of estrogen feeds back to pituitary, overstimulates ovaries without significant drop in estrogen); used only in postmenopausal women; letrozole and anastrozole competitive blockers of aromatase enzyme; exemestane noncompetitive (suicide blocker) of aromatase enzyme

Endocrine treatment comparisons: no clear difference between drugs in early stage; 5 yrs of AI superior to tamoxifen in terms of recurrence rate, although impact on survival less clear; if tamoxifen given for 2 to 3 yrs, then switching to AI within 5 yrs, more effective than tamoxifen for 5 yrs

ATAC study: compared AI with tamoxifen; patients with early-stage ER+ breast cancer randomized to anastrozole for 5 yrs, tamoxifen for 5 yrs, or combination of anastrozole and tamoxifen for 5 yrs; combination arm not superior to tamoxifen alone; able to compare tamoxifen with anastrozole; risk of recurrence reduced by ~2% at 3 yrs by using anastrozole vs tamoxifen and just />2% at 5 yrs, so modest difference; therefore, if AI not tolerated, reasonable to use tamoxifen

Tamoxifen effects: acts as antiestrogen on breast and other parts of body, including central nervous system (CNS), but has estrogen-like effects in certain tissues, including uterus and liver; antiestrogenic effects make it effective in treating breast cancer, reduces breast cancer recurrence; also used to prevent breast cancer; however, antiestrogenic effects can cause hot flashes; in contrast, estrogenic effects associated with increased risk of uterine cancer (average uterine cancer risk ~1/1000; tamoxifen treatment increases risk to ~4/1000) but such uterine cancers presented in early stage have good prognosis; can cause thromboembolic disease; however, also positive effects (*eg*, maintaining bone density in postmenopausal women, reducing LDL cholesterol)

AI effects: decrease estrogen to undetectable levels; therefore, antiestrogenic effects, side effect of hot flashes; however, no estrogenic effect on uterus, therefore no risk of uterine cancer; risk of thromboembolic disease much less than with tamoxifen; however, profound effect on bones resulting in bone loss and potentially osteopenia or osteoporosis (data suggest bisphosphonates may maintain bone density during AI treatment, also may reduce risk of breast cancer recurrence); joint pain common side effect, most common reason patients stop taking

SOFT and TEXT studies: in premenopausal patients, until 5 to 6 yrs ago, tamoxifen for 5 to 10 yrs standard of care; however, Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) studies evaluated addition of ovarian

suppression to endocrine therapy in premenopausal patients with HR+ breast cancer; *SOFT study* — randomized patients to either tamoxifen alone for 5 yrs, tamoxifen with ovarian suppression for 5 yrs, or exemestane with ovarian suppression for 5 yrs; *TEXT study* — ovarian suppression for all patients, then randomized to either tamoxifen for 5 yrs or exemestane for 5 yrs; for premenopausal patients who got chemotherapy, benefit in both trials with exemestane plus ovarian suppression compared with tamoxifen alone or tamoxifen plus ovarian suppression; in TEXT study, ~6% benefit in patients who received chemotherapy; in SOFT study, ~5% benefit for exemestane plus ovarian suppression vs tamoxifen; when no chemotherapy given, no benefit for ovarian suppression, adding ovarian suppression to tamoxifen or exemestane, or using AI compared with tamoxifen

Summary: premenopausal patients with good-risk cancer reasonable to give 5 yrs of tamoxifen; in contrast, patients with higher-risk cancer, give ovarian suppression in combination with AI; women aged <35 yrs who received chemotherapy benefit from addition of ovarian suppression and AI; likely that molecular profiling will help determine which patients need ovarian suppression in future; important, since addition of ovarian suppression to tamoxifen or AI associated with significant toxicity including menopausal symptoms, effects on bone, cardiovascular disease; for premenopausal patient with HR+ breast cancer, younger and receiving chemotherapy, recommend ovarian suppression and AI; older patients (aged 40-50 yrs) with lower-risk cancers not receiving chemotherapy, give tamoxifen alone

Length of endocrine therapy treatment: controversial; historically, tamoxifen given for 5 yrs because small study in patients with early-stage ER+ breast cancer (node negative) showed higher risk of recurrence if tamoxifen continued for 10 yrs vs 5 yrs; led National Cancer Institute (NCI) to recommend stopping tamoxifen at 5 yrs; however, controversial because patients in study had low-risk cancers; ER+ breast cancers can recur many yrs after diagnosis; >50% of recurrences and deaths from breast cancer occur after 5 yrs; therefore, longer-term endocrine therapy may be appropriate; however, currently unknown which patients most likely to have late recurrences; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found higher risk of late recurrence depending on cancer size and number of positive lymph nodes, and even stage I breast cancers had risk of long-term recurrences; overall, patients with stage I breast cancer have significant risk (14%) of long-term recurrence; recurrence rate can go up to ~50% for larger tumors and node positivity; evaluation of some molecular profiles in attempt to determine appropriate longer durations of therapy; several trials studied extended adjuvant therapy after tamoxifen

National Surgical Adjuvant Breast and Bowel Project (NSABP) trial: studied tamoxifen treatment lengths (10 yrs vs 5 yrs) showed increased risk of recurrence if tamoxifen continued >10 yrs

ATLAS study and aTTom study: larger studies; compared tamoxifen treatment lengths (10 yrs vs 5 yrs); both studies showed 10 yrs of tamoxifen superior to 5 yrs; however, effect of longer duration of tamoxifen not seen until >10 yrs after diagnosis because of carryover effect of 5 yrs of tamoxifen; in patients who receive 5 yrs of tamoxifen, data support continuing for another 5 yrs; if menopausal in first 5 yrs of tamoxifen treatment, reasonable and effective to switch to an AI after 5 yrs

MA17 and NSABP 33: studied 5 yrs tamoxifen followed by AI for 5 yrs or placebo for 5 yrs; both studies showed benefit for extended adjuvant endocrine therapy; MA17 study showed significant reduction in recurrence rate with letrozole for 5 yrs following 5 yrs of tamoxifen, particularly in node-positive disease; MA17 and NSABP B33 showed benefit for using exemestane for 5 yrs following tamoxifen treatment

Extending AI treatment >5 yrs: controversial; trials studied extending AIs for 10 yrs vs 5 yrs; MA17R studied patients given 5 yrs of tamoxifen, then AI for 5 yrs, then randomized to receive another 5 yrs of AI vs placebo; ~30% of patients in MA17R had not received tamoxifen before AI; 4% benefited after 10 yrs vs 5 yrs of AI treatment; however, majority of benefit in prevention of contralateral breast cancers; more modest impact on distant recurrences therefore controversial; likewise, in NSABP B-42 study, patients received AI for 5 yrs or AI/tamoxifen combination for 5 yrs then randomized to AI for further 5 yrs or placebo; showed absolute benefit of 3% in favor of extending AI; again, majority of benefit in prevention of contralateral breast cancers; therefore assess on patient-by-patient basis; for high-risk cancer, often continue AI for up to 10 yrs; for low-risk cancer, likely stop because of increased risk of toxicity by continuing AI up to 10 yrs, particularly effect on bones

Comparing durations of AIs: DATA study, 6 yrs vs 3 yrs of AI (after 2-3 yrs of tamoxifen) showed ~4% benefit in disease free-survival (DFS) for longer duration; IDEAL study compared 2.5 yrs vs 5 yrs of AI after either tamoxifen, AI, or AI/tamoxifen combination; showed 3% benefit with longer duration; however, larger ABCSG-16 trial comparing 2 yrs vs 5 yrs of anastrozole (patients had received AI or tamoxifen for 4-6 yrs) showed no significant benefit in longer AI therapy; overall, decision to extend AI >5 yrs made on patient-by-patient basis; consider risk of recurrence (initial stage of cancer), and potential side effects (*eg*, bone mineral density) with longer duration of treatment

Adjuvant chemotherapy: systemic adjuvant therapy for HR−, HER2− breast cancer or HR+, HER2− breast cancer in patients who require chemotherapy; for triple-negative breast cancers, NCCN recommends no adjuvant therapy if tumor <5 mm; if tumor 6 mm to 1 cm, consider adjuvant chemotherapy; if tumor >1 cm, adjuvant chemotherapy recommended; for node-positive disease, adjuvant chemotherapy recommended; for HR+, HER2− breast cancer, consider size and stage of cancer and 20-gene recurrence score assay results

Summary: if node-positive disease, give adjuvant endocrine therapy with adjuvant chemotherapy; 21-gene recurrence score and 70-gene signature may be used; in patients with node-negative breast cancer, tumor size <0.5 cm, give adjuvant endocrine therapy alone; for node-negative cancer >5 mm, consider 21-gene

recurrence score assay, unless biologic criteria suggestive of cancer that either would or would not benefit from chemotherapy; depending on 21-gene recurrence score result, chemotherapy may or may not be recommended, particularly if high-risk cancer, for which adjuvant chemotherapy recommended in addition to adjuvant endocrine therapy; *EBCTCG meta-analyses* — benefit of adjuvant chemotherapy more significant in women aged <50 yrs and with node-positive breast cancer; benefit of chemotherapy more modest in women aged >50 yrs, particularly with node-negative breast cancer; chemotherapy more effective in ER− breast cancers compared with ER+ breast cancers, especially in women aged <50 yrs, in whom ER− breast cancers have significant benefit from chemotherapy; likewise in ER+ breast cancer, but more modest impact; in older women (both ER− and ER+), modest benefit from chemotherapy, particularly in older women with ER+ breast cancers; however, patients with ER+ breast cancers did appear to benefit from chemotherapy, so routinely treated with chemotherapy; 21-gene recurrence score assay then developed

21-gene recurrence score assay: applicable only for patients with early-stage HR+ breast cancer; made up of 6 cancer-related genes; include genes associated with ER signaling, HER2 and proliferation, also includes 5 reference genes; algorithm results in recurrence scores; initial data with recurrence score divided ER+ breast cancers into 3 groups (low risk [scores <18], high risk [scores ≥31], and intermediate risk [scores 18–31]); initial data with 21-gene recurrence score utilize tumors from NSABP B-14 study, in which patients treated with tamoxifen for 5 yrs for node-negative, ER+ breast cancer; showed 21-gene recurrence score prognostic in that patients with low-risk cancers with recurrence scores <18 had 10-year rate of distant recurrence of only 7% compared with patients whose tumors had recurrence scores of ≥31, with 10-year risk of distant recurrence of 31% (statistically significant difference); importantly, in this group of node-negative breast cancers, ~50% of cancers low risk (recurrence scores <18), ~25% intermediate risk (recurrence score 18-30), and ~25% high risk (recurrence scores ≥31)

NSABP B-20 study: patients with ER+, node-negative breast cancer randomized to receive either tamoxifen alone or tamoxifen plus cyclophosphamide (Cytoxan), methotrexate and 5-fluorouracil (5-FU) (CMF)–type chemotherapy; retrospectively applied 21-gene recurrence score on subset of cancers from this study; in patients with low recurrence score (<18), no benefit for addition of chemotherapy to tamoxifen (10-year risk of distant recurrence 96% if tamoxifen alone; 95% if tamoxifen plus chemotherapy); in contrast, marked benefit for addition of chemotherapy in high-risk groups (recurrence scores ≥31), such that risk of recurrence of 10 yrs with tamoxifen 40% vs 12% for chemotherapy and tamoxifen; intermediate-risk group (score of 18-30) showed no benefit from addition of chemotherapy to tamoxifen; however, wide confidence intervals, so addition of chemotherapy in patients with recurrence scores of 18 to 30 may be beneficial

TAILORx study: prospectively evaluated ability of 21-gene recurrence score to select patients who would benefit from chemotherapy with ER+, node-negative breast cancer; if score ≤10, endocrine therapy given alone; if score ≥26, chemotherapy plus endocrine therapy given; patients with recurrence scores 11 to 25 randomized to endocrine therapy alone or chemotherapy plus endocrine therapy (numbers different from initial analysis to avoid undertreating patients who would benefit from chemotherapy); in patients with recurrence scores <10 received endocrine therapy alone, risk of distant recurrence at 9 yrs good prognosis, only 3%; in those with recurrence scores ≥26, distant recurrence rate 13%, despite having chemotherapy and endocrine therapy (thus endocrine-resistant disease, thus newer agents may be useful); patients with recurrence scores 11 to 25 demonstrated no benefit of chemotherapy in addition to endocrine therapy; no benefit of chemotherapy for scores ≤25; *exploratory analysis for chemotherapy treatment interactions in 11-to-25 group* — cohorts of recurrence score (11-15 vs 16-20, 21-25, 11-17 vs 18–25), tumor size, tumor grade, menopausal status, or clinical risk category did not significantly result in chemotherapy treatment interaction; however, statistically significant chemotherapy treatment interaction based on age; therefore, younger women appear to benefit from chemotherapy; age, menopause, and cohorts of recurrence score also associated with chemotherapy benefit; patients ≤50 yrs no benefit of chemotherapy for recurrence score 11 to 15; however, patients with recurrence score 16 to 20 showed ~2% benefit in distant recurrence for addition of chemotherapy to endocrine therapy; those with recurrence scores 21 to 25 showed benefit of ~6%; therefore, younger women with scores 16 to 25 will have some benefit from chemotherapy

Systemic chemotherapy: optimal systemic chemotherapy depends on cancer stage and whether ER+ or ER−; (for ER+, chemotherapy recommended only if node positive or if recurrence scores indicate benefit from chemotherapy)

Chemotherapy regimens: CMF old regimen; still used in some centers; if looking at trials comparing anthracycline-based regimens with CMF, no striking benefit for addition of anthracyclines to chemotherapy; meta-analysis from EBCTCG showed significant benefit for anthracycline-containing regimens vs CMF; however, if closely review individual trials, no clear benefit for anthracyclines vs CMF

NSABP B-15 study: largest study; compared doxorubicin (Adriamycin) plus cyclophosphamide (Cytoxan) (AC) with CMF; no significant benefit for anthracyclines; CMF reasonable regimen for low-risk cancers; however, longer therapy and increased rate of nausea; anthracycline-based chemotherapy standard in 1990s

Cancer and Leukemia Group B (CALGB) 9344 study: review benefit of adding taxane; node-positive breast cancer patients received either 1) 4 cycles of AC or 2) 4 cycles of AC followed by paclitaxel; significant improvement in DFS (~6%) in favor of addition of paclitaxel

NSABP B-28 study: reviewed benefit of adding taxane; randomized patients with node-positive breast cancer to AC or AC followed by paclitaxel; ~4% benefit for addition of paclitaxel following AC

TAC regimen: dose attacks of doxorubicin plus cyclophosphamide, compared with 5FU plus doxorubicin plus cyclophosphamide; used quite commonly in Breast Cancer Research Group (BCRG) study; showed advantage for taxane; TAC improved DFS compared with non–taxane-based regimen; benefit also for OS; addition of taxane to doxorubicin/cyclophosphamide either sequentially or concurrently became standard therapy

Intergroup 9741 study: caused another change in treatment; dose-dense chemotherapy; compared chemotherapy given every 2 wks vs every 3 wks; also evaluated concurrent administration of drugs (as in CALGB study AC followed by paclitaxel, or sequential regimen of doxorubicin followed by paclitaxel followed by cyclophosphamide); no difference in outcome for sequential or concurrent treatment; however, significantly improved outcome for dose-dense treatment (*ie*, every 2 wks vs every 3 wks (~7% improvement in DFS; ~2% benefit in OS); drugs given every 2 wks with growth factors if anthracycline given (granulocyte colony-stimulating factor [G-CSF] used in study; however, longer-acting growth factors now used); dose-dense regimen became standard; standard treatment for patients who required adjuvant chemotherapy became AC given dose-dense followed by paclitaxel either dose-dense or weekly; however, benefit of adding taxane and dose-dense drug administration dependent on ER status; in CALGB 9344 study, benefit of adding paclitaxel seen in ER− breast cancers; in contrast, cancers no significant benefit in ER+ breast; likewise, in CALGB 9741 study, dose-dense approach beneficial for ER− breast cancers, whereas no significant benefit for ER+ breast cancers

Summary: for ER− breast cancers, optimal therapy AC followed by paclitaxel (AC given every 2 wks), paclitaxel given either every 2 wks or once weekly; for ER+ breast cancers (benefit of chemotherapy less), less-toxic regimens that can be used; however, in patients with multiple lymph node involvement, still use AC followed by paclitaxel given either dose-dense or weekly

ECOG 1199 study: reviewed giving taxanes after AC for early-stage breast cancer; 4 cycles of AC, then either paclitaxel every 3 wks or once weekly, or docetaxel every 3 wks or once weekly; most effective and least toxic regimen compared with others was weekly paclitaxel; *not clear which of following superior* — giving paclitaxel every 2 wks in dose-dense manner vs weekly for 12 weeks; both reasonable options, particularly patients with ER− breast cancer; US Oncology 9735 study examined potential de-escalation of chemotherapy for early-stage breast cancer; two-thirds of patients had ER+ breast cancer; ~50% had node-negative breast cancer; patients randomized to receive 4 cycles of AC or 4 cycles of docetaxel plus cyclophosphamide (TC); showed significant benefit for latter option; difference in DFS of ~6% and difference in OS of ~6%; TC has become widely used, particularly for lower-risk cancers, especially if ER+; advantage of this regime, no anthracycline, so cold caps can be used to prevent hair loss

ABC trials: studies comparing TC with taxane/anthracycline regimen; early-stage breast cancer patients randomized to either TC or taxane and anthracycline; overall, taxane option had improved 4-year invasive DFS; however, benefit only ~2.5% and mainly in HR−, not HR+, cancers until multiple involved lymph nodes; in HR− cancers, benefit of anthracycline/taxane vs TC ~2% for node-negative breast cancer, 11% for N1 disease (≤3 positive lymph nodes) and 11% for patients with ≥4 positive nodes; in contrast, in HR+ cancers, no significant benefit for either regimen in patients with node-negative breast cancer; benefit 2% in patients with N1 disease; significant benefit for anthracycline-based regiment only when ≥4 positive nodes

PlanB study: patients with HR− breast cancers randomized to either TC for 6 cycles or epirubicin plus cyclophosphamide(EC) for 4 cycles followed by docetaxel for 4 cycles; 21-gene recurrence score used for patients in HR+ group; if score >11 (even if positive lymph nodes), patients randomized to TC followed by EC, followed by docetaxel; however, patients who had either node-negative or N1 disease with recurrence scores of ≤11, just received endocrine therapy (therefore not included in analysis); therefore HR− or high-risk HR+ cancers; showed no benefit for anthracycline-containing regimen compared with TC regimen

Summary: *HR− breast cancers* — if higher risk (*ie*, larger or node positive), optimal regimen anthracycline-based regimen either followed by or given concurrently with taxane; for lower-risk cancers, consider TC for smaller node-negative breast cancers; *HR+ breast cancers* — for node-positive disease or high recurrence score, chemotherapy generally required; reasonable to treat most with TC; however, if multiple lymph nodes involved, anthracycline-plus-taxane regimen used

Chemotherapy toxicity: short-term side effects include myelosuppression (consider growth factors to reduce neutropenia and risk of febrile neutropenia), nausea, alopecia (in taxane-only regimens can be prevented using cold caps), mucositis, and fatigue; longer-term side effects include: neuropathy, cardiotoxicity with anthracycline (often irreversible), ovarian suppression or infertility (luteinizing hormone-releasing hormone [LHRH] agonist can reduce risk of permanent menopause in younger women); small risk of leukemia with nearly all chemotherapy agents

Perioperative chemotherapy (preoperative vs postoperative): NSABP study compared 4 cycles of doxorubicin given before vs after surgery; ~13% of patients who received preoperative AC had pathologic complete response (pCR; no invasive cancer in breast), associated with favorable long-term outcome; preoperative treatment downstages tumor, allowing less surgery; also downstages lymph nodes; long-term results showed no difference in OS or DFS whether preoperative or postoperative treatment; study conducted before breast cancer subtyping used; not known whether ER− breast cancers better treated with preoperative treatment, since not studied; patients with pCR had significantly improved outcome (both DFS and OS) compared with patients with any invasive cancer in breast at time of surgery; neoadjuvant therapy allows breast-conserving surgery, and fewer surgeries to lymph nodes; complete pCR predictive of long-term outcome, especially if ER−; very often for

ER− breast cancer, use regimens preoperatively rather than adjuvantly; same regimens used before surgery to downstage cancer and to see if working

HER2+ breast cancer: overexpression of HER2 protein receptors on cell surface; HER2+ breast cancers often aggressive; high risk of recurrence soon after diagnosis; recommend combination of adjuvant chemotherapy and HER2-directed therapy; for signs of HER2+ breast cancer (except cancers <5 mm, for which adjuvant chemotherapy and HER2-directed therapy considered); if 6 mm to 1 cm, adjuvant chemotherapy and trastuzumab recommended; if cancers >1 cm and node positive, recommend adjuvant chemotherapy and HER2-directed therapy

Trastuzumab: survival benefit shown in metastatic setting if trastuzumab added to chemotherapy in HER2+ metastatic breast cancer; risk of cardiotoxicity when added to chemotherapy, particularly with anthracycline; 2 trials reviewed patients with early-stage HER2+ breast cancer; standard chemotherapy with AC followed by paclitaxel, or AC followed by paclitaxel and trastuzumab; another study compared) AC followed by docetaxel with AC followed by docetaxel plus trastuzumab with nonanthracycline regimen (docetaxel/carboplatin/trastuzumab); in HERO study, after adjuvant chemotherapy, patient randomized to observation or to trastuzumab for 1 yr or 2 yrs; within BCRG and HERO studies, ~70% had node-positive breast cancer, 30% had node-negative breast cancer; all studies showed significant benefit with trastuzumab plus standard chemotherapy in early HER2+ breast cancer; Intergroup study and NSABP study examined in joint analysis; compared AC followed by paclitaxel alone, or AC followed by paclitaxel plus trastuzumab in node-positive HER2+ breast cancer; showed significant benefit with trastuzumab; in BCRG study, trastuzumab with AC or trastuzumab with docetaxel plus carboplatin, showed significant reduction with trastuzumab compared with standard treatment with AC followed by docetaxel; likewise, HERO study showed significant benefit for trastuzumab compared with observation only; Intergroup study compared sequential use of chemotherapy with trastuzumab; showed trastuzumab starting with paclitaxel superior to giving AC followed by paclitaxel, then trastuzumab; concurrent approach of trastuzumab starting with paclitaxel now standard of care; anthracycline increases risk of cardiotoxicity

AlTO study: addition of tyrosine kinase inhibitor, lapatinib, with trastuzumab-based chemotherapy did not show significant benefit, therefore not used

AFFINITY study: modest benefit for addition of pertuzumab (monoclonal antibody targets HER2 in early-stage breast cancer), more marked in node-positive breast cancer; adding pertuzumab to trastuzumab-based chemotherapy considered

APT study: paclitaxel with trastuzumab for 12 wks and then 1 yr to complete trastuzumab treatment; showed favorable outcomes; this regimen considered for stage I HER2+ breast cancer

Preoperative therapy: widely used for HER2+; if >2 cm and node positive (considered even for cancers >1 cm), consider preoperative approach; if patients have pCR, highly prognostic for outcome, particularly if HR−; high rate of pCR to these chemotherapy and HER2-directed therapy based regiments (~≥50%; higher in ER− compared with ER+ breast cancers)

NeoSphere study: patients received either paclitaxel plus trastuzumab, paclitaxel/trastuzumab/pertuzumab, or paclitaxel/pertuzumab before surgery, then anthracycline-based chemotherapy after surgery; for both trastuzumab and pertuzumab in combination with taxane, pCR rate almost 50%

TRYPHAENA study: designed to study cardiotoxicity; compared anthracycline/trastuzumab/pertuzumab-based regimens with docetaxel/carboplatin/trastuzumab/pertuzumab, preoperatively; showed proven pCR rates with second regimen compared to anthracycline-based regimen; common preoperative regimen

KATHERINE trial: in patients who failed to achieve pCR to chemotherapy and HER2-directed therapy given preoperatively, showed antibody drug conjugate trastuzumab DM1 (trastuzumab emtansine) highly effective compared with trastuzumab; patients with HER2+ breast cancer who did not achieve pCR to standard HER2-directed therapy and chemotherapy randomized to trastuzumab DM1 or standard trastuzumab; at 3 yrs, 11% difference in invasive DFS in favor of using trastuzumab DM1 (recently approved by FDA)

Inflammatory breast cancer: erythema or peau d'orange at least one-third of breast for clinical diagnosis; pathology often shows cancer cells in dermal lymphatics but not needed for diagnosis; diagnosis clinical; inflammatory breast cancer can be any subtype; treat with preoperative systemic therapy, usually chemotherapy alone or chemotherapy plus HER2-directed therapy followed by mastectomy, chest wall radiation, and further systemic therapy (either HER2-directed or endocrine therapy); markedly improved outcomes

Suggested Reading

Gianni L et al: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32; **Sparano JA et al:** Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;12(2):111-21.

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Metastatic Breast Cancer

Ruth O'Regan, MD, *Professor of Medicine, Division Chief, Medical Oncology, Hematology & Palliative Care, and Associate Director for Clinical Research, Carbone Cancer Center, University of Wisconsin School of Medicine, Madison, WI*

Metastatic breast cancer (MBC): ~10% of patients present with metastatic disease at time of diagnosis; majority of MBC in presenter's practice comes from patients initially diagnosed with early-stage breast cancer who then develop metastatic disease; probability of having sustained response depends on prior treatments patients received, if visceral (*eg*, liver) metastasis, number of organ sites they have involved, and subtype of breast cancer; median survival 18 to 24 mos, depending on breast cancer subtype; breast cancer heterogeneous disease

Treatment goals: reduce tumor-related symptoms, maximize progression-free survival (PFS) and overall survival (OS), enhance and maintain patient's performance status and functionality, minimize toxicity, enhance convenience and control for patients, and specifically for hormone receptor–positive (HR+) metastatic breast cancer, delayed use of chemotherapy

Breast cancer subtypes: not all 1 disease; molecular profiling in early 2000s showed that breast cancers heterogeneous; at least 2 estrogen receptor-positive (ER+) subtypes, luminal A and luminal B; ErbB2+ or HER2-positive (HER2+) subtype; basal or triple-negative subtype, characterized by absence of ER, progesterone receptor (PR); HER2/neu; treatment dependent on subtype

Workup: history and physical exam; in general, recommend computed tomography (CT) scans of chest and abdomen or positron-emission tomography (PET) scan; if suspicion of bone metastasis, also bone scan or PET scan; if concern for brain metastasis, brain MRI; if back pain, consider spine MRI; most importantly, biopsy area of metastatic disease and measure ER, PR, and HER2; in patients with HER2- breast cancers, consider BRCA testing, since agents now available for patients with BRCA mutations

ER+ breast cancer: tends to metastasize to bone and sometimes lymph nodes, although can metastasize to visceral organs; endocrine therapy treatment of choice, either alone or with targeted agents; chemotherapy generally not indicated at time of diagnosis unless patients have visceral crisis (*ie*, lymphangitis or significant liver metastasis); if believed cancer would start damaging vital organs by 1 more tumor doubling, may want to use chemotherapy to start, because it works more rapidly than endocrine therapy; overall, data support that endocrine therapy more effective and less toxic for patients with ER+ MBC

- Treatment: tamoxifen initially approved in 1970s, 1980s; aromatase inhibitors (AIs) approved toward end of 1990s; fulvestrant (ER downregulator) approved in 2000s, and at different dose schedule in 2012; more recently, targeted agents, including cyclin-dependent kinase (CDK) inhibitors and everolimus, have been approved and have enhanced use of endocrine therapy; endocrine therapies alone, several different categories
  - *S*elective ER modulators*:* tamoxifen (most commonly known); toremifene (chlorinated derivative of tamoxifen), can be used as alternative to tamoxifen
  - AIs*:* all 3 AIS (anastrozole, letrozole, and exemestane) used to treat MBC; anastrozole and letrozole cross-resistant, so if patient has had one, not recommended to use other; in patient who has had anastrozole or letrozole, exemestane can be effective
  - Fulvestrant*:* unusual because, unlike other oral endocrine agents, given by intramuscular *(IM)* injection
  - Other agents*:* progestins; megestrol acetate useful in some patients, and also as appetite stimulant; estrogen effective in treating ER+ MBC; androgens can be useful; tamoxifen effective in both pre- and postmenopausal women; generally given in combination with ovarian ablation to premenopausal women
  - Studies have compared AIs (anastrozole, letrozole, and exemestane) with tamoxifen in first-line setting for ER+ MBC; trials showed significant improvement in PFS for use of AI compared with tamoxifen
- Fulvestrant: initially approved at standard dose of 250 mg given every 4 wks; interest in looking at higher doses and incorporating loading dose; *CONFIRM study* — compared standard fulvestrant (250 mg every 4 wks) with fulvestrant 500 mg every 4 wks; showed significant improvement in time to progression for higher dose compared with lower dose; approved by FDA; now, fulvestrant dose 500 mg administered IM every 4 wks, along with loading dose, such that drug given every 2 wks for first month; fulvestrant superior to anastrozole in first-line setting; *first study* — phase 2; compared fulvestrant with anastrozole in patients with untreated ER+ MBC; showed significant improvement in time to progression and in survival of ~8 mos for fulvestrant compared with anastrozole; *FALCON study* — phase 3; designed to confirm results of first study; patients with untreated HR+ MBC randomized to receive fulvestrant at higher dose (500 mg with loading dose) compared with anastrozole; in intent-to-treat population, 3-mo improvement in PFS with fulvestrant; in patients who did not have visceral metastasis, ~10-mo improvement in PFS with fulvestrant compared with anastrozole; in patients with visceral disease, fulvestrant and anastrozole fairly equivalent

Endocrine combinations: *SWOG 0226 study* — included patients with untreated HR+ MBC randomized to receive fulvestrant at standard 250-mg dose with anastrozole or anastrozole alone; significant improvement in both PFS and ~6-month improvement in overall survival (OS) for fulvestrant plus anastrozole vs anastrozole alone; *FACT study* — essentially identical; did not show significant improvement in time to progression or OS for combination vs single-agent anastrozole; difference between these trials appears to be that more patients on SWOG study had endocrine-sensitive disease; option for patients in first-line setting fulvestrant alone or with anastrozole if patient deemed likely have endocrine-sensitive disease

CDK inhibitors: changed first-line management of HR+ MBC; CDKs, group of serine/threonine kinases that play role in regulating cell cycle; CDKs actually cause cancER−cell division; using inhibitors of CDK can shut down cell division and sensitize cancer cells to endocrine therapy; as shown in preclinical studies, primarily effective in ER+, rather than ER− cancers

3. CDK4/6 inhibitors approved by FDA — palbociclib (first to be approved), ribociclib, and abemaciclib; palbociclib and ribociclib given for 3 out of 4 wks, in combination with endocrine therapy; they cause neutropenia and wk off allows recovery of blood counts; abemaciclib given twice daily; does not cause as much neutropenia, but can cause significant diarrhea

PALOMA-1: enrolled patients with untreated HR+ breast cancer randomized to receive palbociclib with letrozole or letrozole alone; showed doubling in PFS for patients who received palbociclib plus letrozole; final OS did not show significant benefit in favor of CDK inhibitor, although showed benefit of about 3 mos; each agent has been studied in first-line setting

PALOMA-2: confirmatory study for PALOMA-1; looked at addition of palbociclib to letrozole in first-line setting; demonstrated significant doubling of median PFS

MONALEESA-2: studied letrozole, with or without ribociclib, in first-line setting; showed significant improvement in PFS

MONARCH 3: patients received nonsteroidal AIs, with or without abemaciclib; showed significant benefit in PFS, with hazard ratios of 0.55 across all of these trials

MONALEESA-3: studied fulvestrant with or without ribociclib; in first-line setting, addition of CDK inhibitor to fulvestrant showed significant benefit

Premenopausal patients with HR+ MBC: only 2 randomized trials to date;

First trial: randomized premenopausal patients with HR+ MBC to tamoxifen alone, luteinizing hormone-releasing hormone (LHRH)agonist alone, or combination of tamoxifen plus LHRH agonist; showed improvement in both PFS and OS with combination of tamoxifen plus LHRH agonist; following this trial, rendering patients postmenopausal by using LHRH agonist, oophorectomy, or ovarian radiation now standard of care for patients with premenopausal MBC

MONALEESA-7: designed to evaluate addition of CDK inhibitor ribociclib to ovarian suppression and tamoxifen or nonsteroidal AI in premenopausal patients with HR+ breast cancer; study enrolled who were pre- or perimenopausal patients with untreated HR+ breast cancer; all patients received tamoxifen or nonsteroidal AI in combination with LHRH agonist goserelin; randomized to receive ribociclib or placebo; as in other first-line studies, addition of ribociclib significantly improved PFS, with almost doubling of median PFS for patients who received CDK inhibitor; looking at control arms of study, patients did just as well if they got ovarian suppression with nonsteroidal AI vs tamoxifen plus ovarian suppression; important because it can take some time to suppress ovaries in patients receiving LHRH agonist; because AIs don't work in premenopausal patients, concern that tamoxifen may be better option for those patients; data from MONALEESA-7 show that, patients who got tamoxifen plus ovarian suppression had PFS of 11 mos vs 13.8 mos in patients who received anastrozole plus ovarian suppression

CDK inhibitors in second-line setting and beyond: endocrine-refractory setting

PALOMA-3: patients with multiple lines of prior therapy randomized to fulvestrant, with or without palbociclib; significant improvement in PFS with palbociclib

MONARCH 2:slightly less heavily pretreated patients received fulvestrant with or without abemaciclib; significant improvement in PFS (almost doubled)

MONALEESA-3: included patients treated first- or second-line; studied addition of ribociclib to fulvestrant; significant improvement in median PFS;

Looking at CDK inhibitors: abemaciclib proven single-agent activity in heavily pretreated patients; all CDK inhibitors have data for both first- and second-line therapy; overall, addition of CDK inhibitor to endocrine therapy in first-line setting now standard of care; not known if patients who don't need these drugs in first-line setting; ER only biomarker for these drugs

Endocrine-resistant cancers: *increased signaling through growth factor receptors on cell surface* — HER2, insulin growth factor receptor (IGFR), and vascular endothelial growth factor receptor (VEGF); sets off phosphorylation cascades in cancer cells through phosphatidylinositol 3-kinase (PI3K)/AKT pathway; mitogen-activated protein [MAP] kinase pathway); these pathways all end up on protein called mammalian target of rapamycin (mTOR); signaling alters ERs so that endocrine therapy no longer good option; because we have inhibitors of growth factor receptors, studies designed to see if we could restore endocrine sensitivity by inhibiting single growth factor receptors; data disappointing

mTOR inhibitors: if target mTOR,(single common protein of these different pathways), appears to be effective in endocrine-resistant breast cancers

TAM-RAD study: first study that came out with mTOR inhibitor everolimus; patients randomized to tamoxifen or tamoxifen plus everolimus; showed doubling of PFS from 4.5 months to 9 months with addition of everolimus

BOLERO-2 study: patients with endocrine-refractory disease randomized to exemestane plus placebo or exemestane plus everolimus; showed significant improvement in PFS, from 4 mos in control arm up to 11 mos in everolimus arm; led to FDA approval;

PrECOG study: patients with endocrine-resistant disease treated either with fulvestrant alone or with everolimus; showed doubling of PFS, from 5 mos in control arm to 10 mos with everolimus; everolimus approved with

exemestane for patients with endocrine-resistant cancer; stomatitis most common side effect, can be prevented by use of prophylactic steroid mouthwash; other side effects include hyperglycemia and potential pulmonary toxicity (generally subclinical); useful drug in patients who have undergone prior treatment; not much data showing efficacy in patients who had received CDK inhibitors, but no reason why it would not work

PI3K inhibitors: looking at same pathway, PI3K upstream of mTOR; several of PI3K inhibitors being evaluated in ER+ MBC; most studies have produced disappointing results, apart from SOLAR-1 study

SOLAR-1: looked at selective PI3K inhibitor alpelisib in combination with fulvestrant; patients with endocrine-refractory, pretreated, HR+ breast cancer randomized to fulvestrant alone or fulvestrant plus PI3K inhibitor alpelisib; patients specifically divided into group with PIK3CA mutations (thought to be predictive of benefit from this agent) and patients without PIK3CA mutations; patients with PIK3CA mutations had significant improvement in PFS if they received PI3K inhibitors, with ~35% reduction in risk of progression or death; alpelisib recently approved by FDA; does not appear to be effective in patients without PIK3CA mutations; toxicity concerns (*eg*, hyperglycemia)

HER2+ breast cancer: National Comprehensive Cancer Network (NCCN); CLEOPATRA regimen (trastuzumab-DM1 [T-DM1) in patients who had trastuzumab adjuvantly or in other trastuzumab-based regimens preferred first-line regimen

Initial study in HER2+ breast cancer: patients treated first-line with standard chemotherapy (either doxorubicin [Adriamycin] plus cyclophosphamide [Cytoxan]; AC) or paclitaxel alone, or in combination with trastuzumab); showed significant improvement in PFS in patients who received trastuzumab in addition to chemotherapy, and significant improvement in OS of 5 mos, more meaningful because several patients on control arm went on to get trastuzumab at time of disease recurrence; first study also to show trastuzumab associated with risk of cardiotoxicity, particularly in patients who have received anthracyclines

Canadian study: looked at docetaxel vs docetaxel plus trastuzumab in patients with HER2+ breast cancer; showed improvement in time to progression and OS with use of trastuzumab

Trastuzumab-based chemotherapy: overall, trastuzumab-based chemotherapy for HER2+ metastatic disease has changed course of this aggressive cancer; patients treated with trastuzumab and other HER2-directed therapy have improved survival over other MBC subtypes

Available agents: *trastuzumab* — molecular antibody that targets HER2; *pertuzumab* — another antibody that targets HER2, but different domain of the receptor than trastuzumab; specifically targets domain that dimerizes with HER3, which may be resistance mechanism for HER2-directed therapy; *other available agents* — tyrosine kinase inhibitors, lapatinib (targets both EGFR or HER1 and HER2), and neratinib (pan-HER2 tyrosine kinase inhibitor, mainly used in early-stage disease); *T-DM1* — antibody-drug conjugate in which trastuzumab conjugated by linker to chemotherapy moiety; antibody attaches to HER2 receptor on cancer cell, molecule internalized, and linker broken down within cell, allowing direct delivery of chemotherapy into HER2+ breast cancer cells

Data in first-line setting:

CLEOPATRA: pivotal study; first-line study of patients with HER2+ MBC who received standard regimen of docetaxel plus trastuzumab and placebo or docetaxel plus trastuzumab and pertuzumab (dual HER2-targeted therapy); PFS significantly improved from 12 mos with trastuzumab plus docetaxel to ~19 mos with pertuzumab plus trastuzumab plus docetaxel; OS most notable finding, improved by ~16 mos with addition of pertuzumab to docetaxel and trastuzumab; median OS for patients in control arm 41 mos, extended to 57 mos for patients who received pertuzumab, trastuzumab, and docetaxel; good news for patients because it means median survival for these patients now approaching ~6 yrs; first-line regimen of choice for most patients with HER2+ MBC, unless they have recently received pertuzumab in adjuvant or neoadjuvant setting; minimal increase in toxicity by adding pertuzumab, trastuzumab, and docetaxel; can cause diarrhea, which tends to be minor; in first-line setting, several studies have investigated T-DM1

MARIANNE study: first-line study of patients with HER2+ MBC who received trastuzumab with either docetaxel or paclitaxel as standard arm or T-DM1 either with placebo or pertuzumab; did not show significant difference in PFS between arms; in T-DM1 arms given with either pertuzumab or placebo, PFS ~15 mos vs 14 mos in standard trastuzumab-plus-taxane arm; no group appeared to benefit from T-DM1; reason NCCN recommended first-line therapy for HER2+ MBC pertuzumab, trastuzumab, and taxane

Patients who have received HER2-directed therapy and now have progressive disease: continue to block HER2 through progression; *German study* — randomized patients who received prior trastuzumab to capecitabine alone or capecitabine plus trastuzumab; patients did better with trastuzumab; *another study* — looked at switching trastuzumab to lapatinib in addition to capecitabine vs capecitabine alone; showed significant improvement for continuing HER2-directed therapy; *non-chemotherapy study* — patients with prior trastuzumab treatment randomized to either continue trastuzumab and receive lapatinib or to receive lapatinib alone showed benefit for dual HER2 therapy with lapatinib and trastuzumab; good regimen because it doesn't contain chemotherapy, but would most commonly be used in third-line or further setting

EMILIA study: standard, NCCN-recommended, second-line therapy based on EMILIA study; — patients with HER2+ MBC who previously received exemestane and trastuzumab randomized to T-DM1 or lapatinib plus capecitabine; patients receiving T-DM1 had significantly improved PFS of 10 mos compared with 6 mos with capecitabine and lapatinib; OS also significantly improved in patients who received T-DM1, with ~5-mo improvement in OS; T-DM1 associated with some side effects (*eg*, thrombocytopenia, increased transaminases); black box warning for cardiotoxicity because of trastuzumab component; capecitabine and lapatinib, reasonable third-line regimen, can be associated with significant diarrhea and hand-foot syndrome from capecitabine

TH3RESA: compared T-DM1 vs physician's choice in more heavily pretreated patients with HER2+ breast cancer; all patients had received prior trastuzumab, taxane, and lapatinib; randomized to receive T-DM1 or physician's choice, which could be chemotherapy, hormonal therapy, or HER2-directed therapy; PFS significantly improved in T-DM1 arm vs physician's choice arm (6 mos vs 3 mos); OS also significantly improved

Summary: for HER2+ breast cancer, CLEOPATRA regimen of pertuzumab, trastuzumab, and taxane (docetaxel or paclitaxel) standard first-line regimen, unless patient had recent pertuzumab in first-line setting, in which case T-DM1 reasonable option; at progression, EMILIA regimen of T-DM1 recommended; in third-line setting and beyond, many options, including trastuzumab plus further chemotherapy, lapatinib plus further chemotherapy, and clinical trials, as new HER2-directed therapies in pipeline

Chemotherapy: for triple-negative breast cancer, chemotherapy standard of care and only available treatment until approval of atezolizumab; applicable to patients with triple-negative MBC, but also to patients with HR+ MBC who have run out of endocrine therapy options; recommend starting with first-line chemotherapy, then switching to another line of chemotherapy; combination regimens not necessarily better than sequential single-agent regimens in terms of long-term outcomes, and at least in triple-negative breast cancer, not clear that one chemotherapy regimen definitely superior to another

Options recommended by NCCN: several options for patients with HER2− MBC, either ER+ and have exhausted endocrine therapy options, or triple negative; anthracyclines, doxorubicin, or liposomal doxorubicin; liposomal doxorubicin would be better choice for patients because can only give certain amount of doxorubicin because of risk of cardiotoxicity; taxanes (*eg*, paclitaxel, docetaxel, nanoparticle albumin-bound [nab]-paclitaxel); antimetabolites (*eg*, capecitabine, gemcitabine); microtubulin inhibitors (*eg*, vinorelbine, eribulin); poly (ADP-ribose) polymerase (PARP) inhibitors (*eg*, olaparib, talazoparib) options for patients who have HER2− breast cancer and germline BRCA-1 or BRCA-2 mutations; most commonly used combination regimens anthracycline based, but limited by amount of therapy that can be given because of risk of cardiotoxicity; options include docetaxel plus capecitabine, gemcitabine plus paclitaxel, and gemcitabine plus carboplatin

Single-agent chemotherapy: response rates of single agents tend to be modest (between 10% and 35%-40%, depending on line of therapy); complete responses tend to be quite uncommon; whether to use combination therapy or single-agent chemotherapy important; trial that really evaluated this, ECOG study; *ECOG study* — patients treated first-line with either doxorubicin alone, paclitaxel alone, or doxorubicin plus paclitaxel; with combination, higher response rate; time to treatment failure or PFS tends to be longer; regarding OS, generally no benefit for combination vs single agent because patients who receive single agent will go on to get second line of treatment; study important because patients who got doxorubicin went on to get paclitaxel at disease progression and patients who got paclitaxel went on to get doxorubicin at disease progression, so switchover; in general, sequential single agents preferred in patients with HER2− MBC; combination therapy reserved for patients with high-volume, metastatic disease and concern exists about organ dysfunction rapid response or response to treatment not achieved; *capecitabine plus docetaxel study* — combination vs single-agent study; randomized patients between docetaxel and 100 mg/m^2 every 3 wks, or docetaxel 70 mg/m^2 every 3 wks plus capecitabine; showed improved response rate with combination therapy; PFS and OS improved by ~2 mos with combination; *risks and recommendations* — with combination treatment vs single-agent chemotherapy markedly increases risk of toxicity; in this study, more neutropenic fever and fatigue with combination; in general, recommend single agents for patients with HER2− breast cancer, triple-negative breast cancer, or HR+ breast cancer who have exhausted endocrine therapy, reserving combination treatment for patients believed to have high-volume disease and response a will be key for their survival

PARP inhibitors: approved for ovarian cancer and MBC; currently approved only for patients with BRCA mutations; impact DNA repair, but in cell does not have BRCA mutation, if given PARP inhibitor, homologous recombination induced by BRCA actually repairs DNA and cell doesn't die; in absence of BRCA, PARP inhibitor damages DNA and it cannot be repaired because of homologous recombination deficit seen in cells, so double hit on cancer cells and they die; both PARP inhibitors, olaparib and talazoparib, compared with physician's choice chemotherapy in patients with BRCA mutations and HER2− breast cancer; both showed PARP inhibitor superior to physician's choice chemotherapy and also had better toxicity profile; important to consider genetic testing in patients with triple-negative or HR± breast cancer because may be candidate for PARP inhibitor if they have BRCA mutation

Immunotherapy: first first approved for MBC in 2019

IMpassion study: patients with triple-negative breast cancer in first-line setting randomized to nanoparticle albumin-bound (nab)-paclitaxel alone or nab-paclitaxel plus checkpoint inhibitor atezolizumab; modest but significant improvement in PFS for patients who got atezolizumab in combination with nab-paclitaxel; greater improvement and outcome in patients with PD-L1 expression on their immune cells; PFS improved only ~2 mos with addition of atezolizumab to nab-paclitaxel, but survival actually improved by 10 mos; led to the FDA approval of atezolizumab and nab-paclitaxel for triple-negative breast cancer in patients whose tumors have expression of PD-L1 on immune cells; typical side effects seen with immune therapy; other checkpoint inhibitors being evaluated for MBC, so other options likely

Summary: for HR+ MBC, first-line therapy in most cases should be endocrine therapy, generally in combination with CDK inhibitor; chemotherapy reserved for patients with significant visceral disease; *following progression on CDK inhibitor* — several options, including everolimus; if PIK3CA mutation, alpelisib or chemotherapy; *for HER2+ breast cancer* — whether ER− or ER+, CLEOPATRA regimen (pertuzumab/trastuzumab/docetaxel) first-line

regimen of choice; paclitaxel also option; should be used in all patients apart from those who have received recent adjuvant therapy that included pertuzumab; in that case, T-DM1 good option for patients; *at progression* — optimal treatment likely T-DM1, based on EMILIA study; following this, choices include trastuzumab with further chemotherapy, lapatinib with further chemotherapy, or lapatinib plus trastuzumab, keeping in mind several new HER2-directed therapies under investigation; *triple-negative breast cancer* — in first-line setting, measure PD-L1 expression on immune cells; in ~40% of patients whose tumors express PD-L1 on immune cells, atezolizumab plus nab-paclitaxel optimal therapy; if no PD-L1 expression on immune cells, standard chemotherapy optimal choice; for patients who have received chemotherapy, sequential single-agent therapy generally preferred, with combination therapy being reserved for patients with extensive visceral disease, keeping in mind that if patient has BRCA mutation and HER2- MBC, candidate for PARP inhibitor (olaparib or talazoparib)

Suggested Reading

Finn RS et al: Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-36; **Swain SM et al:** Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-34.

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Pancreatic and Biliary Cancer

Lei Zheng, MD, PhD, *Medical Oncologist, Johns Hopkins University School of Medicine, Baltimore, MD*

Pancreatic cancer: most aggressive malignant disease; uncommon, but third leading cause of death from malignant disease; late diagnosis among major reasons for aggressiveness; often presents with metastatic disease at time of diagnosis; similar to many other cancers, particularly solid tumors, surgical resection only curative treatment modality for pancreatic cancer

Classification: staging of pancreatic cancer different from many other cancer types; does not use TNM as clinical staging system; commonly staged based on whether cancer localized or metastatic; localized pancreatic cancer further categorized into resectable, borderline resectable, unresectable/locally advanced; only ≈20% of pancreatic cancer diagnosed as resectable; difference between resectable, borderline resectable, and locally advanced unresectable pancreatic cancer is based on relationship between pancreatic cancer and surrounding blood vessels, including superior mesenteric vein, portal vein, superior mesenteric artery, celiac artery; resectability should be evaluated in multidisciplinary setting; no consensus guidelines; NCCN (National Comprehensive Cancer Network) and surgical society provide guidelines for distinguishing between resectable, borderline resectable, and locally advanced unresectable pancreatic cancer

Resectable pancreatic cancer: does not involve surrounding blood vessels; neoadjuvant chemotherapy increasingly recommended because of high risk of recurrence; no evidence to support neoadjuvant chemotherapy for resectable pancreatic cancer in general; recommend upfront surgery; consider neoadjuvant chemotherapy for patients with high-risk features, including tumor markers such as high level of CA 19-9, extensive lymphadenopathy in imaging studies, or significant symptoms

Surgery: pancreaticoduodenectomy, also called Whipple procedure, for tumor in head, neck, and uncinate of pancreas; distal pancreatectomy used for tumor in tail and body of pancreas

Adjuvant chemotherapy: well established treatment following surgical resection of resectable pancreatic cancer; CONKO-001, phase three study published in 2003, compared gemcitabine as single-agent adjuvant chemotherapy with observation; confirmed benefit of adjuvant chemotherapy in disease-free and overall survival; ESPAC-3 study compared gemcitabine with 5-FU; gemcitabine and 5-FU found equivalent as adjuvant therapy for resectable pancreatic cancer, and gemcitabine became standard of care [in US]; another phase three study compared gemcitabine and S-1, a 5-FU prodrug; showed S-1 superior to gemcitabine in disease-free and overall survival; S-1 has become standard of care in Japan and East Asia; ESPAC-4, phase three study, compared combination of gemcitabine and capecitabine with gemcitabine alone; gemcitabine and capecitabine found superior to gemcitabine alone as adjuvant therapy in prolonging disease-free and overall survival; combination of gemcitabine and capecitabine has become standard of care adjuvant therapy option in Europe and in US since ESPAC-4; PRODIGE 24, phase three study in Europe, compared combination modified folfirinox (irinotecan, oxaliplatin, and 5-FU) with single-agent gemcitabine; 21.6-month median disease-free survival in modified folfirinox group *vs* 12.8 months in gemcitabine group; 54.4 month median overall survival in modified folfirinox group *vs* 35 months in gemcitabine group; population studied in PRODIGE-24 was comprised of patients with good performance status (Eastern Cooperative Oncology Group [ECOG] scores zero to one); folfirinox now standard-of-care option for patients with good performance status; gemcitabine/capecitabine combination remains standard-of-care option for all patients with surgical resection; single-agent gemcitabine reasonable option as adjuvant therapy for patients with poor performance status following surgical resection

Borderline resectable pancreatic cancer: technically resectable but with very high risk of microscopic positive margin due to blood vessel involvement; consensus is for neoadjuvant chemotherapy prior to reevaluation for surgical resection; four to six monthly cycles of neoadjuvant chemotherapy recommended before re-evaluating for surgical resection; regimen includes folfirinox or combination gemcitabine/abraxane; no direct data to suggest which regimen superior in neoadjuvant setting; either regimen reasonable; no consensus on length of neoadjuvant chemotherapy; at least four cycles of neoadjuvant chemotherapy generally recommended; determine exact regimen of neoadjuvant chemotherapy and length of adjuvant chemotherapy for individual patient in multidisciplinary setting; role of neoadjuvant radiation not established; many institutions still recommend radiation therapy; following completion of neoadjuvant chemotherapy, patient should be reevaluated for surgical resection and considered for neoadjuvant radiation therapy; stereotactic body radiation and conventional chemoradiation reasonable options; choice of radiation at discretion of treatment team; recommend patient receive adjuvant chemotherapy following surgical resection if tumor deemed surgically resectable following neoadjuvant chemotherapy and/or radiation therapy; if patient responded to neoadjuvant chemotherapy, recommend considering same agent(s) for adjuvant therapy

Locally advanced unresectable pancreatic cancer: not technically resectable; degree of blood vessel involvement more severe than borderline resectable pancreatic cancer; evaluation of locally advanced pancreatic cancer should take place in multidisciplinary setting with surgeon, radiologist, radiation oncologist, medical oncologist, and other disciplines

Chemotherapy: patients with locally advanced unresectable pancreatic cancer at time of diagnosis can be taken to surgery for exploration with contemporary chemotherapy regimen given in neoadjuvant setting; ≈50% of patients with locally advanced pancreatic cancer explored for surgical resection following neoadjuvant therapy; [different studies conducted at different institutions;] ≈30% of patients overall underwent curative resection with R0 or R1 resection; no consensus on which regimen of chemotherapy should be used as neoadjuvant therapy for locally advanced pancreatic cancer or whether stereotactic body radiation or conventional chemoradiation should be used as neoadjuvant radiation therapy; however, there is consensus that chemotherapy should be given before patient evaluated for radiation therapy; often recommend four to six monthly cycles of neoadjuvant chemotherapy; recommend using chemotherapy regimen used for metastatic pancreatic cancer including gemcitabine/abraxane or folfirinox regimen; patient brought to OR for surgical exploration with resectable disease may receive more chemotherapy as adjuvant therapy following resection or patient may be observed postoperatively; generally recommend total of six monthly cycles of adjuvant therapy given prior to or after surgery; maintenance therapy recommended if tumor remains unresectable following neoadjuvant chemotherapy and radiation therapy; currently waiting for results of phase three study to confirm role of maintenance therapy in patients with locally advanced, unresectable disease

Treatment of metastatic pancreatic cancer: systemic treatment standard of care; single-agent gemcitabine standard of care for several decades; two combination regimens developed as first-line chemotherapy regimen over last decade; folfirinox demonstrated superior to single-agent gemcitabine in progression-free and overall survival in phase three studies; gemcitabine/abraxane second combination chemotherapy regimen; also superior to gemcitabine single-agent in disease-free and overall survival in phase three studies; both folfirinox and gemcitabine/abraxane appropriate first-line chemotherapy options

Toxicities: folfirinox has extensive toxicity; only recommended for patients with good performance status (ECOG 1 or 2); some participants in phase 3 study comparing gemcitabine/abraxane regimen with gemcitabine were of older age and poorer performance status; gemcitabine/abraxane generally considered for patients with relatively poor performance status or older age; gemcitabine/abraxane also associated with extensive toxicity; NCCN guidelines state patients with poor performance status should still consider treatment with single-agent gemcitabine; no formal comparison between folfirinox and gemcitabine/abraxane; improper to compare overall or progression-free survival for either regimen according to different phase three studies; two regimens considered equivalent first-line chemotherapy options

Maintenance therapy: data not available to support using maintenance therapy for metastatic pancreatic cancer despite increasing number of studies demonstrating role of maintenance therapy following first-line chemotherapy for metastatic pancreatic cancer; phase three POLO study recently completed; studied patients with metastatic pancreatic cancer with germline BRCA1 and BRCA2 mutations following at least 4 months of cisplatin-based chemotherapy; patients randomized to receive olaparib PARP (poly [ADP-ribose] polymerase) inhibitor had significantly longer progression-free survival compared to patients who did not receive olaparib as maintenance therapy if disease responded to treatment or remained stable following chemotherapy; olaparib anticipated to become maintenance therapy for metastatic pancreatic cancer patients carrying BRCA1 and BRCA2 mutations; POLO 1 study also highlighted importance of molecular profiling of pancreatic cancer, particularly germline testing of BRCA or mutations in similar pathways

Second-line therapy: multiple regimens considered for metastatic pancreatic cancer; combination of infusion of 5-FU and liposomal irinotecan found superior to infusion of 5-FU in phase three NAPOLI study; liposomal irinotecan and 5-FU has become standard-of-care second-line chemotherapy regimen for patients progressing through gemcitabine-based chemotherapy; gemcitabine/abraxane has been used as second-line chemotherapy after patient has progressed through first line folfirinox chemotherapy; folfirinox can still be used as second-line chemotherapy if patient with good performance status has progressed through gemcitabine/abraxane as first-line chemotherapy

Palliative care: chemotherapy has limited role in treating pancreatic cancer; majority of patients only benefit modestly from chemotherapy; pancreatic cancer associated with significant symptoms; palliative care should always be considered for patients who do not benefit from chemotherapy; consider for all stages of pancreatic cancer

Biliary cancer: not as common as pancreatic cancer in Europe and North America; has become more treatable; increasing evidence available to establish extent of care; biliary tract cancers not single type of malignancy; are at least four types of biliary cancer based on anatomy of cancer origin — gallbladder cancer, perihilar cancer, distal cholangiocarcinoma, and intrahepatic cholangiocarcinoma; perihilar cholangiocarcinoma and distal cholangiocarcinoma often combined as "extrahepatic cholangiocarcinoma;" however, distal cholangiocarcinoma has different origin, biology, and cancer-genetic features from from perihilar cholangiocarcinoma

Treatment:

Surgery: surgical approach different for resectable biliary tract cancers from different origins

Gallbladder cancer: often presents as incidental pathologic finding in cholecystectomy; not common cancer in North America; determine T stage of gallbladder cancer if incidental pathologic finding; often no oncological resection recommended with T1a disease and patient can be observed; oncological resection, often including partial hepatectomy and lymph node dissection, recommended with T1b or above disease; neoadjuvant chemotherapy often recommended with finding of metastasis in cystic duct

lymph node before oncologic resection and lymph node dissection is considered

Intrahepatic cholangiocarcinoma: surgical resection preferred if tumor resectable and without metastasis; upfront surgical resection also preferred treatment for resectable perihilar cholangiocarcinoma and distal cholangiocarcinoma; surgical procedure for distal cholangiocarcinoma is pancreaticoduodenectomy; same procedure used for pancreatic cancer in head and uncinate of pancreas

Neoadjuvant chemotherapy: role has not been established; consider for patients without resectable disease or significant lymphadenopathy

Adjuvant chemotherapy: standard of care following surgical resection; role only recently established; BILCAP phase three study compared capecitabine for eight cycles with observation; capecitabine prolonged median overall survival to 51.1 months compared to 36.4 months in observation group; capecitabine has become standard-of-care treatment option for adjuvant therapy for all types of biliary tract cancers; another phase three study is in progress to compare combination gemcitabine and cisplatin with capecitabine as adjuvant therapy for resected biliary tract cancers

Unresectable locally advanced or metastatic biliary tract cancer: role of systemic chemotherapy well established; phase three ABC-02 study conducted in UK showed combination of gemcitabine and cisplatin superior to single-agent gemcitabine as first-line chemotherapy for advanced biliary cancer; no well-established second-line chemotherapy for biliary tract cancers; ABC-06 study compared folfirinox regimen with active symptom control as second-line treatment for biliary tract cancer progressing through first-line gemcitabine/cisplatin chemotherapy; folfirinox arm met primary endpoint, but only prolonged overall survival from 5.3 months in group with active symptom control to 6.2 months in folfirinox group; still seeking more effective second-line treatments

Molecular profiling of biliary cancer: have been extensive cancer-genomic studies in field of cholangiocarcinoma in past decade; studies show intrahepatic cholangiocarcinoma often associated with IDH1 or IDH2 mutations and FGFR2 fusion changes; molecular therapies have been developed to target these two genetic alterations

IDH1 mutations: IDH1 inhibitor itacitinib approved for treating IDH1-mutated acute myeloid leukemia; recent phase three study compared itacitinib with placebo for IDH1-mutated cholangiocarcinoma after first-line chemotherapy; patients could cross over to receive treatment in other arm if their disease progressed through treatment in assigned arm; results showed itacitinib associated with median progression-free survival of 2.7 months compared to 1.4 months in placebo group; statistically significant; itacitinib associated with 10.8 months overall survival — significant compared to crossover-adjusted placebo group; anticipate itacitinib will become treatment option for IDH1-mutated cholangiocarcinoma

FGFR2 fusion changes: common in intrahepatic cholangiocarcinoma; occur in ≈15 to 20% of intrahepatic cholangiocarcinoma; multiple FGFR inhibitors have been developed; different inhibitors have different spectrums of activity on FGFR receptors; phase three study showed FGFR inhibitors similar in efficacy; demonstrated ≈20 to 40% objective response rate in FGFR2 fusion-change cholangiocarcinoma after disease had progressed through at least one line of therapy; multiple phase three studies currently evaluating FGFR2 inhibitors in cholangiocarcinoma patients with FGFR fusion change as first-line therapy compared to gemcitabine and cisplatin regimen; anticipate FGFR2 inhibitors will become treatment option for patients with FGFR fusion changes; NCCN guidelines recommend considering molecular profiling for all patients with biliary tract cancers; consider referring patients to clinical trials after molecular profiling

Other mutations: HER2, EGF, and ERBB3 mutations associated with gallbladder cancer; distal cholangiocarcinoma associated with BRCA mutations like pancreatic cancer; BRAF mutations also occur in cholangiocarcinoma; BRAF inhibitors demonstrated high objective response rate in small clinical trials for BRAF-mutated cholangiocarcinoma

Microsatellite instability (MSI): in addition to molecular profiling, NCCN guidelines also recommend testing for microsatellite instability in all patients with biliary tract cancer; MSI-high solid tumors have higher response rates to treatment with immune checkpoint inhibitors, particularly anti-PD1 antibodies; approved as treatment for patients who progress following one line of chemotherapy; NCCN guideline recommends considering anti-PD1 antibodies for cholangiocarcinoma as first-line treatment if MSI-high condition is verified; for MSI-low or microsatellite stable (MSS) cholangiocarcinoma, anti-PD1 antibodies also demonstrate modest response; more clinical trial data still needed to support using anti-PD1 antibodies for cholangiocarcinoma treatment

Suggested Reading

Aroldi F, et al: Immunotherapy for pancreatic cancer: present and future. *Immunotherapy.* 2017 Jun;9(7):607-16**; McGuigan A, et al:** Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol.* 2018 Nov;24(43):4846-61; **Squadroni M, et al:** Cholangiocarcinoma. *Crit Rev Oncol Hematol.* 2017 Aug;116:11-31.

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Colorectal Cancer and Management of Localized and Locally Advanced Disease

James Church, MD, *Colorectal Surgeon, Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, OH*

Epidemiology: third most common cancer of solid organs in United States (US); American Cancer Society estimates ~140,000 new cases of colorectal cancer in 2018, cause of ~50,000 deaths; weekly rate of 2700 new cases, 974 deaths; potentially preventable disease; every case arises from premalignant lesion, often takes 10 yrs for benign lesion to become malignant

Pathophysiology: malignant growth beginning in lining of large intestine; arises from dysfunction of genes that control cell growth; lining of large intestine consists of colonocytes, which line crypts, or wells, in epithelium; colonocytes arise from stem cells at base of crypts and move up crypt towards bowel lumen, where they die, shed into stool; process takes 5 to 7 days; colonic stem cells constantly divide to produce colonocytes; sometimes, mistake in DNA replication that does not get repaired persists as mutation, then transmitted into clone of cells that descends from that stem cell; when certain genes called driver genes (*ie*, they drive carcinogenesis) mutated, function abnormally; when these genes help regulate cell growth, their loss allows that clone of cells to grow faster than normal and not die when they should; cells then build up and form visible growth, or polyp

Precancerous lesion: all colorectal cancers start as precancerous lesion; takes ~10 yrs for small precancerous lesion to become malignant; during this time, additional genes develop mutations that cause growth regulation to be further disturbed until affected clone of cells develops capacity to invade and spread to other organs; precancerous lesion now cancer

Histopathology: as precancerous lesions or polyps progress to cancerous lesions, they enlarge and cells look increasingly "wild" under microscope; dysplasia means cells that have lost control of growth; lesions with low-grade dysplasia farther from progression to cancer; high-grade dysplasia cells closer in progression to cancer

Transition to cancer: Bert Vogelstein, famous biologist, described sequence of genetic events associated with transition of adenoma to cancer; stated that, although colorectal cancer cells contain thousands of mutated genes, only few drive progression towards cancer; most mutated genes in cancer result of cancer itself, (*ie*, passenger mutations, not cause of cancer); Vogelstein states that as few as 3 driver gene mutations needed to produce colorectal cancer

Etiology: all cancer genetic, arising through genetic abnormalities that lead to loss of control of cell growth and differentiation; several risk factors; *heredity*– in which genetic abnormality predisposing to colorectal cancer inherited from parent or occurs at conception; colorectal cancer can run in families, either as syndrome, whether dominant or recessive inheritance of specific gene, or in weaker sense, no specific inherited gene, but presence of colorectal cancer in relative increases one's own chance of developing disease; *environmental risk factors* — also play role in colorectal carcinogenesis; best displayed in Japanese migrants to Hawaii; rate of gastric cancer, high in Japan, decreased to American levels in this population; rate of colon cancer, low in Japan, increased dramatically to American levels in this population; population's DNA did not change, but effects of environment did; environmental factors include diet, smoking, exercise, alcohol; Vogelstein also deduced that many cancers arise by chance, through mistakes in DNA during cell division when stem cells divide to populate organ; faster stem cell division rate, higher risk of mistake to become mutation; colonic stem cells among most rapidly dividing of all organs, making colon high risk for cancer; this hypothesis may devalue environmental factor manipulation in effort to reduce risk

Biology of colorectal cancer: ≥2 molecular routes to colorectal cancer

Adenoma-carcinoma sequence: first route, histologically; at molecular level, fueled by chromosomal instability; *first driver gene*– adenomatous polyposis coli (APC) gene, key tumor suppressor gene in Wnt signal transduction pathway; loss of APC function allows β-catenin to enter nucleus and switch on downstream growth-stimulating pathways; germline mutation of APC causes familial adenomatous polyposis, most well-known hereditary polyposis syndrome; APC protein helps stabilize cell growth by combining with other proteins to remove β-catenin from cytoplasm and degrade it; when Wnt pathway switched on, this association of APC and other proteins dissolves, proteins separate, and β-catenin can enter nucleus; when APC mutates, same as turning on Wnt pathway; β-catenin enters nucleus, turns on downstream growth-stimulating pathways, and growth abnormally enhanced; APC mutations also encourage loss of heterozygosity resulting from abnormal chromosome division and separation, creating loss of entire segments of DNA and daughter cells; such cells aneuploid; *second driver gene* — KRAS, proto-oncogene involved in epidermal growth factor (EGF) signal-transduction pathway; *third driver gene* — could be one of many; described by Vogelstein in Vogelgram, SMAD4 and p53; SMAD4 involved in transforming growth factor beta (TGFB) signaling pathway; p53 key

gene that coordinates DNA reproduction, DNA damage checking, and DNA repair

Epithelial serration: second major route to colorectal cancer; underlying DNA hypomethylation; primary driver genes in this route, KRAS and BRAF; BRAF another proto-oncogene in EGF pathway; KRAS and BRAF mutations inhibit apoptosis in colonocytes allowing cells to accumulate in crypt epithelium and form serrations; epithelium of polyps (lesions) appears serrated, like steak knife; also associated with DNA hypomethylation, which cuts out expression of multiple genes and allows neoplasia to develop within burgeoning polyp; if MLH1 (mismatch repair gene) methylated and expression removed, directly linked to development of dysplasia and serrated polyp, advances path to cancer; some methylated cancers referred to as having CpG island methylator phenotype (CIMP); these cancers develop in patients with serrated polyposis, specifically linked to underlying BRAF mutation

Mismatch pathophysiology and Lynch syndrome: when cell divides, DNA replicates into new double-stranded molecules, 1 in each daughter strand; to make new DNA, template strand from original cell used by DNA polymerase to construct new daughter strand exactly matching sequence of nucleotide bases in complementary way; however, DNA has >1 billion nucleotide bases, so mistakes happen; sometimes 1 strand slips on the other, creating DNA mismatch; *DNA mismatch* — mismatches especially likely at DNA microsatellites (*ie*, "slippery" segments of DNA consisting of repeated base pairs); DNA mismatch repair system detects mismatches, excises them, and allows DNA polymerase to restore normal sequence; when DNA mismatch repair not working, resulting cancers have unstable microsatellites; this recognized by comparing length of particular microsatellite in cancer DNA with length of normal DNA; microsatellite instability exists when DNA microsatellites different length in tumor cells than in normal cells; when occurs in ≥2 out of 10 markers, instability level high (MSI-high, MSI-H); MLH1 key gene in this system, also MSH2, MSH6, and PMS2; *Lynch syndrome* — germline mutations in any of these mismatch repair genes will cause Lynch syndrome, dominantly inherited form of colorectal cancer; accounts for ~3% of all colorectal cancers; almost all colorectal cancers in Lynch syndrome MSI-H; ~18%-20% of sporadic cancers MSI-H, mostly due to methylation of MLH1; some sporadic unmethylated cancers MSI-H because of biallelic sporadic mutations and mismatch repair gene

Familial Syndromes

Overview: conditions that can be recognized by 1 of several characteristic clinical or histologic findings; syndromes of hereditary colorectal cancer broadly divided into those with multiple polyps (*ie*, polyposis syndromes) and those without multiple polyps; one biologic characteristic of hereditary syndromes of colorectal cancer, that as result of germline mutation, fundamental disorder of DNA repair; makes cells prone to multiple abnormalities and multiple genes, causes characteristic clinical manifestations of syndromes, such as early age of onset of tumors and multiple neoplasms in multiple organs

Familial adenomatous polyposis (FAP): first syndrome described, late 19th century; germline mutation of APC causes acceleration of typical adenoma-carcinoma sequence via enhanced loss of heterozygosity; as with all colorectal cancer syndromes, causative gene tumor suppressor gene, germline mutation serves as first of 2 issues that lead to loss of function of gene's protein; loss of APC turns on Wnt pathway but never turns it off, leading to constant stimulation of cell growth, ultimately to aplasia; if FAP untreated, not surveyed, develop colorectal cancer at mean age of 39 yrs; generally, patients present with multiple adenomas in colon; by age 18 yrs, ~90% of those susceptible to developing adenomas already have them; perform genetic testing on children of FAP patient when entering puberty and start colonoscopic surveillance of those with parent's germline mutation; start investigating stomach and duodenum at 20 yrs of age, perform surgery when colonic polyps become of such size and number that concern for growth of cancer

MUTYH-associated polyposis: MUTYH, key gene in DNA base excision repair pathway; corrects oxidative damage to DNA; failure of this pathway due to bi-allelic loss of MUTYH allows effect of failed base excision repair to develop in multiple genes; G:C to T:A transversion; signature of MUTYH-associated polyposis similar to microsatellite instability signature of failed DNA mismatch repair; one of genes most affected by biallelic mutation of MUTYH, APC; clinical consequences, mild version of FAP; MUTYH-associated polyposis differs from FAP because recessively inherited; patients have to inherit 1 mutated allele from each parent; usually both parents are carriers with 1 mutant allele each; incidence of carrier genotype in population ~2%; these patients do not have disease but can transmit mutant allele to offspring; if have children with another carrier, 1 in 4 offspring will be affected; FAP and most other syndromes of hereditary colorectal cancer dominantly inherited (only 1 mutant allele needs to be inherited for disease to be transmitted), thus risk 50%

Polymerase proofreading polyposis: recently discovered; elevated neoplasia risk resulting from germline mutation in exonuclease or proofreading demands of 2 DNA polymerases, POLE and POLD1; loss of proofreading capability causes multiple mutations throughout genome; manifests as microsatellite-stable, chromosomal-unstable cancers and large adenomas; dominantly inherited, highly penetrant; characterized by oligopolyposis, early age of diagnosis, colorectal and endometrial cancer

Hamartomatous polyps: group of syndromes; include Peutz-Jeghers syndrome (PJS), juvenile polyposis, and phosphatase and tensin (PTEN) hamartoma tumor syndrome (PHTS); all feature colorectal polyps, but have distinctive extracolonic features

PJS hamartomas: occur mostly in small intestine with few in colon; at risk for small bowel obstruction at early age from intussusception of small-bowel polyps; also at risk for breast, pancreatic, cervical, ovarian, testicular, gastric, small-bowel, and colorectal cancers; feature, especially in young patients, pigmented spots around mouth or on lips; PJS dominantly inherited; due to germline mutation STK11 gene

Juvenile polyposis: dominantly inherited; juvenile polyps develop in large intestine and upper gastrointestinal (GI) tract; germline mutations in SMAD4 or BMPR1A, genes involved in TGFB signal transduction pathway; can be symptomatic when polyps large and numerous; significantly increased risk of colon cancer; in

symptomatic patients or in patients whose polyps not controllable endoscopically, colectomy recommended

PHTS: PTEN important tumor suppressor gene, widely expressed throughout body; loss of PTEN function encourages cell overgrowth; PTEN has important role in regulating cell cycle and preventing cells from dividing too rapidly or growing too fast; PTEN germline mutations cause variety of unusual syndromes, *eg*, Cowden disease and Bannayan-Riley-Ruvalcaba syndrome (BRRS); both syndromes involve growth of multiple histologic types of colorectal polyps, including neurofibromas, hamartomas, adenomas, lipomas, and hypoplastic polyps; also musculoskeletal, facial, dermatologic abnormalities

Hereditary syndromes: account for only ~5% of all colorectal cancers; polyposis syndromes together make up ~2%, whereas Lynch syndrome accounts for ~3%

Lynch syndrome: primary nonpolyposis hereditary colon cancer syndrome; *history* — first reported in 1913 by Aldred Warthin, pathologist in Ann Arbor, Michigan; described large German family with dominant inheritance of colorectal, gastric, and endometrial cancer; 50 yrs later, Henry Lynch, oncologist in Omaha, Nebraska, carried Warthin's observations forward; another 30 yrs before genetic cause discovered; defective DNA mismatch repair due to germline mutations in a mismatch repair gene; syndrome name has changed several times (Lynch-1, Lynch-2, hereditary nonpolyposis colorectal cancer [HNPCC); currently, HNPCC defined as family that meets Amsterdam family history criteria for dominant inheritance, whereas Lynch syndrome defined genetically as presence of germline mutation in mismatch repair gene; distinction important because not every person with HNPCC has Lynch syndrome, not every Lynch patient has HNPCC; *clinical features* — early onset of colorectal, endometrial, biliary, urinary transitional cell, small-intestinal, skin, and ovarian cancer; colorectal cancers most common; with mutations in MSH2 and MLH1, lifetime risk approaches 70%; mutations in MSH6 and PMS2, lower risk of colorectal cancer; MSH6, high risk of endometrial cancer; *screening patients with colorectal and endometrial cancer for Lynch syndrome* — performed by testing tumors for microsatellite instability or presence of mismatch repair proteins by immunohistochemistry; this practice becoming more widespread; in patients without cancer, strong family history of colorectal or other Lynch cancers should lead to referral for genetic testing of germline; family history criteria; *revised Amsterdam criteria*– 3 affected relatives with colorectal or any other Lynch-type cancer; 2 of these relatives first degree of third; ≥1 relative with cancer, aged <51 yrs; polyposis excluded; upon diagnosis, patient undergoes surveillance, possibly surgery

Screening and Prevention of Colorectal Cancer

Prevention: only common cancer that can be prevented; not by primary prevention (refers to prevention or reversal of genetic changes causing neoplasia), but by secondary prevention (*ie*, removing premalignant lesions before become invasive); although all colorectal cancers arise in premalignant lesion, only ~1 out of 100 premalignant lesions become malignant; because most premalignant lesions asymptomatic, detection and removal includes screening, examination of asymptomatic individuals for early detection or prevention; primary prevention clinically relevant; large studies show aspirin, even at low dose, significantly reduce risk of colorectal adenomas and cancer; hormone replacement therapy can reduce risk of colorectal cancer significantly; some evidence that lifestyle changes in general reduce colorectal cancer risk; because no colorectal cancer chemoprevention absolutely effective, no alternative to colonoscopy yet

Screening: well established for routine health maintenance; several options; *gold standard* — well-performed colonoscopy, 95% sensitivity for cancer; ability to detect and remove all sizes and varieties of precancerous polyps; downsides include cost, access, potential complications, variable quality; preferred over all others as individual test; likely reason for overall incidence of colorectal cancer decreasing yearly in US; *flexible sigmoidoscopy* — compromise examination, two-thirds of colon uninspected; as colorectal cancers increasingly right-sided with advancing age, this screening tool increasingly unsatisfactory; decreased cost, greater convenience, but poor sensitivity, so viable option only in very young patients, in whom majority of colorectal cancers left-sided; *fecal DNA testing* — relatively new technique; best noninvasive screening methodology; 92% sensitivity for cancer; 70% sensitivity for adenomas containing high-grade dysplasia, 42% for sessile serrated polyps; better than fecal immunochemical testing (FIT); in patients who decline colonoscopy, fecal DNA testing reasonable alternative; Epi proColon — commercially available blood test for colorectal cancer; uses mSEPT9 methylated marker; 70% sensitivity for cancer, below that of fecal DNA testing, similar to FIT; *approach to screening* — should involve estimation of patient risk by obtaining family history of colorectal polyps and cancer, personal history of polyps, cancer, and inflammatory bowel disease, and other high-risk associations; risk of colorectal cancer increased 2.5-fold if patient has first-degree relative with colorectal cancer and >4-fold if that relative aged <50 yrs at diagnosis; colorectal cancer risk increased 1.8-fold if patient has relative with precancerous polyps

Risk and screening: for screening high-risk patients, colonoscopy starting 10 yrs before youngest family member affected or at age 50 yrs, whichever younger; for average-risk patients, screening starts at age 50 yrs; for African American patients at otherwise average risk, recommended age 45 yrs; some controversy exists about whether age for screening average-risk patients should decrease, given increased incidence of colorectal cancer in patients aged <50 yrs; American Cancer Society recommends screening start at age 45 yrs, but other organizations have not followed suit; in countries with government-funded health service, population screening tends to be via FIT, reserving colonoscopy for those with positive tests

Staging: important because helps determine disease severity and prognosis and helps formulate surgical and other therapeutic strategies; colorectal cancer begins in colorectal epithelium and invades into, then through, bowel wall; when high-grade dysplasia present in epithelium alone, lesion not malignant; when invades below epithelium through muscularis mucosae into submucosa, cells gain access to veins and lymphatics, thus cancer present; histology and cancer location determine prognosis and

treatment strategy, typically done during multidisciplinary tumor board in which pathologists and radiologists describe cancer, and surgeons, medical oncologists, and radiation therapists recommend and decide on course of action; *cancer grade* — usually refers to differentiation of cells; well-differentiated cancers less aggressive, better prognosis; most colorectal cancers moderately differentiated; if poorly differentiated (*ie*, "wild" cells, aggressive), poor prognosis; *cancer stage* — cancer staged according to depth of tumor invasion, presence of cancer in lymph nodes, and spread to other organs; *lymphovascular invasion* — further prognostic factor; indicates cancer cells in lymphatic or venous channels, which provide pathway of spread; worse prognosis

TNM staging system: *T, tumor* — TX, primary tumor cannot be assessed; T0, no evidence of primary tumor; Tis, carcinoma in situ or intramucosal carcinoma or high-grade dysplasia; T1, tumor invaded into submucosa; T2, tumor invaded into muscularis propria of bowel; T3, tumor invaded through muscularis propria into pericolorectal tissues; T4, split into T4a, tumor invaded through visceral peritoneum, and T4b, tumor directly invades or adheres to other adjacent organs or structures; *N, lymph node status* — ≥12 nodes needed for accurate staging; NX, regional lymph node status cannot be assessed; N0, no regional lymph node metastases; N1, metastases in 1 to 3 regional lymph nodes; N2, metastases in ≥4 regional lymph nodes; *M, distant metastasis* — M0, no distant metastasis; M1, positive distant metastasis

Tumor-staging summary: easier way to summarize tumor staging by stages I to IV; stage I, tumor confined to bowel wall, has not gone through it; stage II, tumor through bowel wall but not in regional lymph nodes; stage III, tumor in lymph nodes; stage IV, distant metastases

Presentation and diagnosis: early-stage colorectal cancers can be asymptomatic; if so, usually diagnosed via screening or found serendipitously during tests carried out for other conditions; cancers not detected will ultimately present with symptoms; type of presentation varies with location; *right-sided colorectal cancers* — tend to present late; may be large, sometimes perforate colon; late presentation because right colon has widest part of large bowel; stool is liquid, so obstructive symptoms occur late; most common presentation, occult bleeding, producing anemia; *left-sided colorectal cancers* — tend to present earlier, usually with abdominal pain/cramps or change in bowel habits; left colon narrowest and most muscular part; here, stool formed, thus cancer can easily cause obstruction; passage of formed stool over cancer lesions can produce bleeding, presents as dark bleeding, often mixed in with stool

Rectal cancer: close to anus, thus bleeding often confused with hemorrhoidal bleeding; bleeding tends to be brighter than colonic bleeding, sometimes associated with urge to defecate, or tenesmus (*ie*, feeling that stool present in rectum after defecation); if patient presents with rectal bleeding, significant change in bowel habits, or new abdominal pain consistent with colonic origin, investigation recommended; thorough digital rectal examination important, colonoscopy essential; biopsy if cancer, note location as accurately as possible; full colonoscopy needed to exclude synchronous polyps and cancers; rigid proctoscopy way of determining "lower edge" of cancer accurately; major implications for ability of surgeon to resect cancer with adequate margin while preserving ability to perform restorative resection with anastomosis; digital rectal exam assesses tumor fixity; sometimes examination under anesthesia needed to provide accurate assessment; workup continues with abdominal and pelvic computed tomography (CT) scan for metastatic disease; pelvic magnetic resonance imaging (MRI) with rectal protocol provides accurate staging information upon which to base treatment

Other testing: all cancer patients, baseline carcinoembryonic antigen (CEA) blood level assessed; if patient aged <50 yrs or extensive family history of colorectal cancer, referral to counselor for genetic testing arranged; preoperative clearance also obtained

Treatment: *early-stage disease, malignant polyp* — sometimes cancer found in polyp apparently completely removed; chances of this increase with polyp size, 10% in polyps >2 cm diameter; malignant polyps different from polypoid cancers; polypoid cancers completely cancer but appear as polyp; generally irregular, friable, fixed, and hard to touch; should not be treated endoscopically; malignant polyps basically benign, but some dysplastic cells have penetrated muscularis mucosae and present in submucosa; these can be divided into pedunculated polyps (stalk provides margin of normal tissue) and sessile polyps (no stalk, less margin); most sessile malignant polyps need resection due to difficulty of endoscopic removal, concerns about margin, and lymph node involvement; recent advances in endoscopic polypectomy, such as endoscopic submucosal dissection, allow sessile lesions to be removed more radically, suggesting role for endoscopy in some sessile malignant polyps; rectal malignant polyps can be treated locally by advanced transanal surgery, such as transanal minimally invasive surgery (TAMIS); malignant pedunculated polyps can be treated endoscopically if low risk; risk defined by differentiation (low risk if well or moderately differentiated, high risk of poorly differentiated) and presence or absence of lymphovascular invasion; margin status generally low risk if ≥2 mm normal margin, high risk if <2 mm, although absolute number varies in some studies; malignant polyps with any bad prognostic parameter need formal resection; consider tattooing location of polyps that might be malignant, unless location made obvious by adjacent colorectal landmarks; will help surgeon if laparoscopic resection

Surgery: typical method of treatment, surgical excision; accomplished by oncologic resection; components include high ligation of vessels supplying affected segment of bowel, en bloc removal of affected bowel and any attached organs, and restoration of bowel continuity when appropriate; Cleveland Clinic promulgates concept of minimal manipulation of cancer until isolated by vascular and lymphatic division and section of bowel (prevents spread of cancer cells during surgery); full mesenteric resection, along with high vascular ligation, ensures adequate lymph node harvest; *right colon cancer* — right hemicolectomy and ileocolic anastomosis; closer to cecum, more terminal ileum taken; *transverse colon cancer* — extended right colectomy and ileocolic anastomosis, or segmental colectomy if patient older and

frailer; *descending colon cancer* — either extended right colectomy or extended left colectomy with colorectal anastomosis; *sigmoid colon cancer* — sigmoid colectomy or left colectomy with colorectal anastomosis; percentage of right-sided cancer increases ~20% in young groups to 70% in older age groups (change in biology of cancer with advancing age)

Rectal cancer treatment: rectal cancer accessible through rectal examination on proctoscopy, so early-stage rectal cancers can be treated by transanal techniques; disadvantage of transanal technique, lymph nodes not removed; such techniques appropriate in early-stage cancers; rectal cancers easier to stage preoperatively by ultrasound, MRI, and CT scan

Treatment by cancer stage: *stage I* — can be resected without radiation or chemotherapy; *stage II* — if minimal spread outside bowel and good margin of normal mesentery around cancer, can also be treated with surgery alone; advanced stage II cancer close to fascia surrounding rectum and with danger of positive margin after surgical resection, pretreated with neoadjuvant chemoradiation in hopes of sterilizing margins and reducing local recurrence; *stage III* — with likely positive nodes, neoadjuvant chemoradiation as routine; long-course radiation as usual, takes 6 wks to deliver; then delay of 8 to 10 wks before surgery; during this time, ~16% to 20% of rectal cancers completely disappear both grossly and microscopically, allowing patient to avoid radical surgery ("watch-and-wait" strategy); short-course radiation can be given if surgery needed more immediately, with lower total dose and similar intensity to long-course radiation; *stage IV* — usually presents with liver metastases; if patient asymptomatic from primary tumor, can be treated with full-dose chemotherapy for 3 to 6 mos, then reassessed; if metastases respond, surgery can be considered; symptomatic patients offered either fecal diversion and then chemotherapy and radiation, or proceed to resection

Treatment decisions: best made at multidisciplinary tumor board using patient's history, clinical setting, staging results, and pathology; surgically, dependent on skill and experience needed for successful resection; rectum enclosed by pelvis, limiting access in a way unlike colon cancer; first operation on rectal cancer best chance of cure; *local recurrence* — if local recurrence, cure with additional surgery unlikely; 1 reason for local recurrence after surgery for rectal cancer, viable cells left behind after completion of treatment; 2 reasons viable cells left behind after treatment: poor surgery, in which resectable cells not resected, or bad biology, in which cells irremovable by any surgeon; patient with good-biology cancer, good surgery, can be cured; good biology, bad surgery, high local recurrence rates, but low distant recurrence, local recurrence may be salvaged; bad biology, good surgery, baseline level of unavoidable local recurrence, but high distant metastasis rate; bad biology, bad surgery, high rates of local and distant recurrence; multiple studies showed skill and experience of surgeons makes big difference in outcomes of rectal cancer surgery, surgical technique very important; recently, surgical techniques expanded to include minimally invasive abdominal surgery, or laparoscopy, robotic laparoscopic techniques, and transanal total mesorectal excision

Colorectal cancer surgical technique: majority of surgeries performed using standard techniques while new methods find their place; minimally invasive surgery offers significant advantages and less postoperative pain, quicker recovery, less disability; should not be achieved at expense of oncologic dissection; up to each surgeon to undergo adequate training and to monitor oncologic and surgical outcomes

Postoperative treatment: *stage III cancer* — postoperative adjuvant chemotherapy, generally for 6 mos, followed by CEA blood test every 3 mos for 5 yrs; colonoscopy at 1 yr, then every 3 yrs; abdominal CT scans yearly for 5 yrs; *stage I cancer* — colonoscopy at 1 yr, then every 3 yrs; *stage II cancer* — colonoscopy at 1 yr, then every 3 yrs; CEA every 3 mos for 5 yrs; may need regular CT scans depending on risk; *stage IV cancer* — chemotherapy; first-line chemotherapy usually with oxaliplatin and 5-fluorourocil (5-FU); usually well tolerated, effective in downsizing or holding size of metastases; if first-line chemotherapy fails, second-line treatment often used in combination with targeted therapy

Targeted therapy: *cetuximab* — antibody against EGF receptor, used in patients with "wild-type" KRAS (KRAS-mutant cancers do not respond); KRAS integral part of epidermal growth factor pathway, so if already mutated, further blockade of pathway ineffective; *pembrolizumab* — antibody that blocks programmed cell death-1 (PD-1) protein; PD-1, protein on cell surface, suppresses T-cell activity; blockage activates T cells, allows them to destroy cells that express appropriate antigens; colorectal cancers that possess these antigens microsatellite unstable; unstable microsatellites produce intensely immunogenic short polypeptides; activating T cells in patients with microsatellite-unstable cancers can produce significant response; ~18% to 20% sporadic colorectal cancers MSI-high; such patients candidates for this therapy

Outcomes of colorectal cancer treatment: oncologic outcomes most important aspect of treatment, usually cited according to stage; most important data include rates of local recurrence and rates of disease-free or age-adjusted survival at 5 yrs from surgery; rectal cancer differs because high risk of local recurrence and because use of radiation therapy in rectum but not colon may make difference in outcomes

Cleveland Clinic 2015 colon cancer data: 1013 patients with colon cancer, median age 65 yrs, 55% men; 28% stage I, 38% stage II, 34% stage III; all patients underwent surgery for cure; no stage IV patients included; overall 5-yr cancer-free survival rate 85%; *local recurrence by stage* — stage I, 2%; stage II, 5%; stage III, 8%; distant metastases occurred in 4% of stage I patients, 15% in stage II, 31% in stage III; 5-yr age-standardized survival rates for stage I, 98%; stage II, 91%; stage III, 70%; operative morbidity 14%, mortality 2%; 20 anastomotic leaks out of 1013 cases; average length of stay, 7 days

Rectal cancer outcomes: depend on technique and vary greatly between surgeons; review of 16,425 patients, rectal cancer surgery for cure; data divided by technique and total mesorectal excision vs standard resection; local recurrence rates divided into quartiles, tabulated by stage; *stage I* — total mesorectal excision, 25th percentile of local recurrence, 0%; for standard resection, 3%; *stage II* — 4% for total mesorectal excision; 10% for standard resection; *stage III* — 8% for total mesorectal excision; 19% for standard resection; rectal cancer leak

rates after anastomosis higher than for colon cancer resection; in patients who have, persistent pelvic sepsis, chronic scarring can destroy anastomosis; 10% rectal resection patients have prolonged bladder dysfunction, 30% of previously potent men develop sexual dysfunction

Survivorship issues: cosurvivor, person who cares for loved one with cancer; survivorship means cancer free at 5-yr follow-up, although late recurrence can occur; focus of care switches from cancer treatment to cancer prevention; *physical and psychological effects of surviving cancer*— increased appreciation of life; increased acceptance of patients themselves; general increase in anxiety about health; may be permanent reminders such as permanently altered bowel function, colostomy or other stoma, side effects from chemotherapy or radiation; *3 phases of survivorship*— 1. acute survivorship, starts at diagnosis, goes through end of initial treatment; focus of this phase, cancer treatment; 2. extended survivorship, starts at end of initial treatment, goes through months afterward; focus, effects of cancer and its treatment; 3. permanent survivorship; years have passed, low chance cancer will return; much longer phase; focus, long-term effects of cancer and its treatment; care of patients who have had colorectal cancer gradually adapting to address these issues of survivorship

Suggested Reading

Ahmed S et al: Advances in the management of colorectal cancer: from biology to treatment. *Int J Colorectal Dis*. 2014;29(9):1031-42; **Buccafusca G et al:** Early colorectal cancer: diagnosis, treatment and survivorship care. *Crit Rev Oncol Hematol.* 2019;136:20-30; **Provenzale D et al:** NCCN guidelines insights: colorectal cancer Screening, Version 1.2018. *J Natl Compr Canc Netw*. 2018;16(8):939-49; **Sun Z et al:** Association between neoadjuvant chemoradiation and survival for patients with locally advanced rectal cancer. *Colorectal Dis*. 2017;19(12):1058-66.

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Metastatic Colorectal Carcinoma

Afsaneh Barzi, MD, PhD, *Associate Clinical Professor, Department of Medical Oncology and Therapeutics Research, Director, Employer Strategy, City of Hope Comprehensive Cancer Center, Duarte, CA*

Epidemiology: roughly 145,000 cases of colorectal cancer/y in US; ≈20% to 25% of those patients diagnosed with de novo metastatic disease; another 20% to 25% will develop recurring metastatic disease; ≈50,000 new patients with metastatic disease/y

Staging: identification of patients with curable and potentially curable disease critical to achieving good outcomes; understanding needed of extent of disease and potential for resection at time of diagnosis and later at time of response to treatment to appropriately classify patients into curable and potentially curable groups; single-organ metastatic disease usually involves liver only; low volume of disease — more than one organ but not multisite; patients with single-organ metastatic disease or patients with low volume of disease considered curable; patients with heavier burden of disease confined to one organ also considered curable if response to treatment achieved; discussion of patients in multidisciplinary tumor board critical to achieving good outcomes; surgeons can render opinion regarding resectability of disease; data presented by Nancy You at American Society of Clinical Oncology (ASCO) 2019 demonstrated resection of tumor results in prolongation of survival even when not R0 resection; patients who underwent R0/R1 resection had median overall survival of 6.7 y; those not resected had median overall survival of 1.7 y; those with R2 or incomplete resection had median overall survival of 2.8 y; important to remember that some patients not resectable up front may become resectable later in course of treatment

Treatment: several FDA-approved agents for treatment of colorectal cancer or used frequently in disease management; agents generally classified into three major categories — cytotoxic therapy, targeted therapy, and immune checkpoint inhibitors

Cytotoxic therapies: longest history in disease management; include 5-fluorouracil, capecitabine, irinotecan, oxaliplatin, and TAS-102 (Lonsurf)

Targeted therapies: include VEGF antibody bevacizumab, EGFR antibodies cetuximab and panitumumab; regorafenib, dabrafenib, trametinib, and encorafenib; larotrectinib and entrectinib target NTRK gene fusion but are rarely used

Immune checkpoint inhibitors: include nivolumab, pembrolizumab, and ipilimumab; HER2-targeted agents may be used in future

Molecular data: relevant biomarkers include mutations in RAS gene, such as KRAS, NRAS, or rarely HRAS; mutations in BRAF, specifically BRAF V600; microsatellite instability (MSI) status; other potential biomarkers include NTRK gene fusion — rare but important to consider as treatment is available; HER2 amplification relevant due to future HER2-directed therapies; other biomarkers in development; biomarkers acquired through next generation sequencing, which provides large panel of available mutations in tumor; some used in clinical trial setting but do not have direct relevance in regular patient management

Case example one: 67-year-old otherwise healthy man presents with 3-month history of rectal bleeding and progressive worsening of constipation; no prior history of screening for colorectal cancer; exercises twice weekly; remote history of smoking; quit >30 y prior; denies history of colorectal cancer or any other cancer in first degree relatives; CBC significant for hemoglobin of 9.5; platelets and WBC within normal range with normal differential; chemistry significant for elevation in AST just outside normal range at 40; alkaline phosphatase just outside normal range at 200; all other values within normal limits; referred to gastroenterologist for colonoscopy; found to have mass about 30 cm from anal verge; biopsy of mass reveals well differentiated adenocarcinoma; referred to medical oncology; CT of chest, abdomen, and pelvis reveals three liver lesions within right lobe of liver and evidence of primary sigmoid cancer; patient presents for discussion of treatment options

Considerations: fit patient without significant comorbidities; metastatic disease confined to liver; case discussed at multidisciplinary tumor board; both primary and metastatic disease found to be resectable; primary tumor biopsy submitted for molecular testing; results reveal G12D mutation in KRAS; MSI stable tumor; surgery remains option for management; determine whether patient should receive surgery upfront or chemotherapy prior to surgery; question has not been answered in systematic fashion by clinical trial data; European Organization for Research and Treatment of Cancer (EORTC) clinical trial published in 2008 in *Lancet* by Nordlinger evaluated use of FOLFOX (folinic acid, fluorouracil, and oxaliplatin) prior to surgery, followed by surgery, followed by additional FOLFOX, as opposed to surgery alone; demonstrated trend for improvement of progression-free survival without definitive improvement in overall survival; justifiable for patients with resectable disease to be treated with upfront surgery followed by adjuvant chemotherapy; adjuvant chemotherapy includes FOLFOX or XELOX (oxaliplatin

and capecitabine)administered to high risk/stage III patients; patients should then remain on surveillance due to high risk for recurrence

Treatment of case one patient: patient underwent surgical resection of liver and descending colon with negative surgical margins; received 10 cycles of FOLFOX; placed on surveillance; CT scan 9 months after surgery and 3 months after completion of chemotherapy demonstrated 1.2 cm lesion on left lung; consider surgery *vs* further chemotherapy with post-surgical recurrent disease; short interval between chemotherapy and development of new metastatic disease usually negative prognostic marker; patient treated with surgical resection of lung lesion with no further chemotherapy; although surgery remains mainstay of treatment and mainstay of cure, no data to guide chemotherapy after resection of metastatic site after prior FOLFOX therapy; another CT scan 6 months after resection of lung lesion revealed two additional liver lesions; patient not candidate for further surgical resection; move made to systemic therapy for incurable disease; consideration of single-agent vs combination therapy

Systemic therapy: FOCUS trial provided data for single-agent therapy; evaluated sequential *vs* combination of 5-FU with irinotecan or oxaliplatin; demonstrated no overall survival benefit in sequential *vs* combination use of these agents

Systemic management of case example one: patient proceeded with systemic therapies; FOLFIRI (folinic acid, fluorouracil, and irinotecan) plus bevacizumab decided upon due to patient grade one neuropathy from prior oxaliplatin and rapid development of metastatic disease after exposure to oxaliplatin; bevacizumab targeted therapy offered in combination with FOLFIRI due to patient's KRAS mutation; in modern trials, treatment results in progression-free survival of almost 1 y with overall survival close to 2 y; based on Cremolini publication in *Lancet* in 2015; patient received roughly eight cycles of therapy; CT scan revealed stable disease

Continuing treatment *vs* treatment break: data from trial by Labianca in *Annals of Oncology* in 2011 guides safety of or role for maintenance therapy; demonstrated FOLFIRI on and off roughly equivalent to continuous FOLFIRI in patients with metastatic disease; study published in *Annals of Oncology* in 2014 by Howard Hochster examined FOLFOX at progression *vs* FOLFOX followed by 5-FU and then FOLFOX again at progression; demonstrated maintenance therapy on permanent basis remains viable option; CAIRO trial evaluated induction chemotherapy followed by capecitabine plus bevacizumab *vs* no chemotherapy; revealed capecitabine plus bevacizumab results in better progression-free survival during maintenance phase *vs* no chemotherapy

Continuing therapy for case example one: patient received capecitabine plus bevacizumab roughly 10 months, in range with median progression-free survival; noted to have disease progression in liver and development of retroperitoneal adenopathy; patient re-challenged with FOLFIRI but had progression of disease after only four cycles; treatment options discussed included re-challenge with FOLFOX as patient had not received FOLFOX with presence of metastatic disease *vs* trifluridine-tipiracil (Lonsurf or TAS-102) *vs* regorafenib; regorafenib and TAS-102 two current agents available for treatment in US in advanced setting

Regorafenib: multi-kinase inhibitor; evaluated in CORRECT study against supportive care; 770 patients randomized to best supportive care *vs* regorafenib; overall survival primary endpoint; study met primary endpoint with improvement in overall survival from 5 months in control arm to 6.4 months in treatment arm; 0.77 hazard ratio for improvement; progression-free survival improved from 1.7 months in control arm to 1.9 months in treatment arm; almost no response observed in treatment group; regorafenib FDA approved based on data; drug initially evaluated at dose of 160 mg daily for 21 out of 28 days; drug has significant toxicities; include diarrhea, hand and foot syndrome, rash, and fatigue; ReDOS study in US evaluated different doses of regorafenib for increased tolerability; patients started at 80 mg daily with weekly evaluation; escalated to maximum dose of 160 mg daily in absence of significant toxicity; study demonstrated increasing tolerability with dose escalation; potential for improvement in progression-free survival and overall survival with increased tolerability

TAS-102: evaluated in RECOURSE study; 800 patients randomized to best supportive care *vs* TAS-102; cumbersome dosing; administered days one through five on week one and days eight through 12 on week two with two week break; overall survival primary endpoint; 5.3 month median overall survival in control arm; 7.1 month median overall survival of treatment arm; 0.68 hazard ratio; progression-free survival improved from 1.7 months in control arm to 2 months in treatment arm; cytotoxicity, neutropenia, anemia, and leukopenia major toxicities

Choice of treatment: emphasize toxicities; evaluate prior therapies; more inclined to offer regorafenib antiangiogenic therapy with EGFR antibody use; TAS-102 may be better therapy if patient received prior bevacizumab; monitor patients closely regardless of choice due to significant toxicities of both agents

BRAF mutated colorectal cancer: ≈5% to 10% of patient population; BRAF negative prognostic marker; BRAF v600 mutation results in poorer overall survival and progression-free survival in all retrospective analyses after clinical trials; targeting BRAF seen in other tumor types such as melanoma; single-agent BRAF inhibitors in colorectal cancer do not have activity; combination of dabrafenib BRAF inhibitor and trametinib MEK inhibitor results in 12% overall response rate; going beyond doublet therapy, SWAG trial established combination of irinotecan, cetuximab, and vemurafenib as standard of care in patients with BRAF-mutated colorectal cancer; thus, a noncytotoxic therapy option exists in patient population with negative prognostic marker; BEACON trial published in *New England Journal of Medicine* (*NEJM*) in 2019 examined combination of cetuximab, encorafenib, and binimetinib compared to cetuximab plus encorafenib and irinotecan plus cetuximab; trial enrolled 665 patients; demonstrated improvement in median overall survival in triplet therapy of cetuximab, encorafenib, and binimetinib; improvement with median of >9 months *vs* 5.4 months

in control arm; hazard ratio of 0.52; established triplet therapy as standard of care; FOLFOXIRI (folinic acid, 5-fluourouracil, oxaliplatin, and irinotecan) plus bevacizumab has resulted in best outcomes as first-line therapy in patients with BRAF v600 mutation; triplet therapy with cetuximab, encorafenib, and binimetinib next best option; many BRAF v600-mutated patients have high tumor mutational burden; some are sporadic MSI-high; third-line therapy of immunotherapy; early testing for KRAS and BRAF critical in management of patients with metastatic colorectal cancer to direct appropriate future lines of therapy

Escalation of therapy: doublet cytotoxic therapy paired with biologic therapy normally used depending on patient molecular characteristics and tumor location; treatment continued until disease progression, followed by switching to other doublet chemotherapy not used in first-line setting; KRAS-mutated patients with borderline resectable disease can be converted into surgically curable patients with achieved response; FOLFOXIRI plus bevacizumab *vs* doublet FOLFIRI plus bevacizumab resulted in significantly higher response rate of 66% *vs* 41% in Italian study of chemotherapy triplet

Toxicities: FOLFOXIRI and bevacizumab triplet therapy toxic and difficult to tolerate; STEAM trial compared FOLFOXIRI to FOLFOX and FOLFIRI with switching between regimens and demonstrated response rate in sequential FOLFOXIRI transition between FOLFOX and FOLFIRI equivalent to triplet FOLFOXIRI; TRY-2 trial used FOLFOXIRI plus bevacizumab for 4 months; transitioned to FOLFIRI plus bevacizumab to increase tolerability; strategies allow adequate exposure to all three active cytotoxic therapies in timely manner and evaluate patients for candidacy for potential surgical cure and better long term outcomes

Biological therapies: bevacizumab, cetuximab, and panitumumab most common for colorectal cancer; ramucirumab and ziv-aflibercept less common; cetuximab and panitumumab only indicated in patients with RAS wild-type tumor; testing patients for RAS status critical; chemotherapy plus bevacizumab or chemotherapy plus cetuximab or panitumumab given in first-line setting in RAS wild-type patents; retrospective analysis of multiple trials demonstrates tumor sidedness (right-sided tumors *vs* left-sided tumors) predictive marker of efficacy of cetuximab in population of mutated colorectal cancer patients undergoing first-line therapy

Evidence: all data retrospective; come from analysis of several trials including FIRE-3, CRYSTAL, and PEAK; most relevant data comes from Alliance (Alliance for Clinical Trials in Oncology) trial 80405 examining backbone of chemotherapy FOLFOX or FOLFIRI plus cetuximab and bevacizumab; demonstrated that although bevacizumab results in significant improvement in overall survival of patients with left-sided tumor, magnitude of benefit for patients with right-sided tumor small and not established in comparison to bevacizumab; National Comprehensive Cancer Network (NCCN) panel recommended taking tumor sidedness into account when offering first-line biological therapy, offering cetuximab or panitumumab only to left-sided patients in first-line setting; no data that sidedness has impact on benefit of cetuximab in second-line setting; with certain exceptions, lecturer rarely offers panitumumab or cetuximab in first-line setting; can offer panitumumab or cetuximab in combination with chemotherapy in second-line setting; data regarding lack of efficacy from cetuximab or panitumumab in first-line setting come from retrospective post hoc analysis; if patient has borderline resectable disease and cannot tolerate triple chemotherapy with FOLFOXIRI, can offer cetuximab or panitumumab in hopes of making tumor resectable; discuss limited survival benefit with patient before initiating therapy

Toxicities of biological therapies: bevacizumab well tolerated drug; associated with significant side effects including hypertension, proteinuria, and arterial thromboembolic events, but impact on patient-experienced toxicity minimal; cetuximab, however, has significant patient-perceived toxicities; include rash and diarrhea; discuss toxicity differences with patients prior to initiation of treatment; pay attention to skin toxicities if choosing to offer cetuximab in first, second, or subsequent lines of therapy; data supports preemptive management of skin toxicity

Preemptive management of skin toxicity: start topical hydrocortisone and clindamycin on same day patient starts cetuximab or panitumumab; counsel about use of sunscreen and avoidance of sun exposure; monitor patients closely; offer oral antibiotics including minocycline or doxycycline if patients experience severe rash after first cycle of therapy; shown to significantly reduce skin toxicities

Continuation of bevacizumab beyond first-line therapy: ML18147 study published in *Lancet* randomized 820 patients one-on-one to receive chemotherapy *vs* chemotherapy plus bevacizumab; demonstrated median overall survival in group receiving bevacizumab better than median survival in group receiving chemotherapy; median overall survival 11.2 months for bevacizumab group *vs* 9.8 months for chemotherapy group; translated to hazard ratio of 0.81 with 95% confidence interval of 0.69 to 0.94; significant *P*-value of.0062; based on this trial, bevacizumab can be continued beyond first-line therapy; patients with KRAS wild-type have option of switching biological and chemotherapy in second-line setting; data more relevant to patients in second-line setting where cetuximab and bevacizumab not options

Other biological therapies: less commonly used but FDA approved for colorectal cancer; ziv-aflibercept antiangiogenic therapy; has better binding affinity for vascular endothelial growth factor-A (VEGF-A) and also binds to PDGF (platelet-derived growth factor) and potentially VEGF-C; should theoretically provide better coverage of angiogenesis; 1200 patients randomized to receive FOLFIRI plus ziv-aflibercept *vs* FOLFIRI alone in second-line setting after failure of oxaliplatin chemotherapy in VELOUR phase III study; positive trial; demonstrated improvement in overall survival from 12.06 months to 13.5 months in ziv-aflibercept group; hazard ratio of 0.87 and significant *P* -value of.0032; study also showed improvement in median progression-free survival from 4.7 months to 6.9 months; hazard ratio of 7.6 and *P*-value of <.0001; 19.8% response rate; significant and remarkable response rate; lecturer does

not offer ziv-aflibercept except with KRAS-mutated patient progressing on FOLFOX and bevacizumab and remaining potential candidate for surgery with achieved response; offer FOLFIRI plus ziv-aflibercept due to better response rate than any other antiangiogenic therapy to achieve response and render patient resectable for surgery; ramucirumab another antiangiogenic drug also studied in population of patients with colorectal cancer; in RAISE-OS study, patients received FOLFIRI *vs* FOLFIRI plus ramucirumab in second-line setting and after failure with oxaliplatin regimen; >80% of patients received bevacizumab in first-line setting; positive study; demonstrated 13.3-month median survival in ramucirumab group *vs* 11.7 months in placebo group; 8.4 hazard ratio with significant *P*-value of 0.0219; median progression-free survival also longer in ramucirumab recipients; median progression-free survival of 5.7 *vs* 4.5 months; response rate similar in both groups; 13.4% in ramucirumab group; ramucirumab shown to improve overall survival and progression-free survival but not response rate; selection of ziv-aflibercept in second-line setting for KRAS-mutated patients based on improvement in response rate and not other time-to-event endpoints

Immunotherapy: role in colorectal cancer remains limited; only indication is for MSI-high colorectal cancer after failure of at least one line of chemotherapy; three main pathways result in tumorigenesis in colorectal cancer; most common is chromosomal instability, a gain of alterations or mutations; second is MSI-high; third is CpG island methylator phenotype (CIMP) [Q3

MSI: microsatellites — stretches of DNA with repetitive sequences of nucleotides; four genes, MLH1, MSH2, MSH6 and PMS2, and possibly others, responsible for maintaining microsatellites; microsatellite abnormalities accumulate when genes impaired, resulting in development of colon cancer; MSI represents change in length to insertion or deletion of repeating units of microsatellite within tumor compared to normal tissue; ≈15% of colorectal cancer cases MSI-high; phenotype is stage-dependent; presence in stage IV much less common than in stages II and III; ≈4% to 5% of patients with stage IV have MSI-high cancers; MSI-high patients with stage II do better than microsatellite stable patients with stage II; MSI used as biomarker for prescribing adjuvant therapy in patients with stage II; role in stage IV for selection of immune checkpoint inhibitors or immune therapy

Benefit of immune checkpoint inhibitors in MSI population: Lee and colleagues' publication in *NEJM in* 2015 demonstrated use of single-agent pembrolizumab after failure of chemotherapy results in significant and meaningful prolongation of progression-free and overall survival; significant number of responses in MSI population but not in microsatellite stable population; very small study; only 11 MSI patients; drastic difference played role in approval of immune checkpoint inhibitors for MSI-high population; followed by larger study published by Mike Overman in *Lancet Oncology* in 2017; 74 patients with MSI received nivolumab; 23% response rate; 2.8 month median time to response; pembrolizumab and nivolumab therapeutic options in patients with metastatic MSI-high colorectal cancer after failure of at least one line of therapy; trial with 119 patients published by Mike Overman in *Journal of Clinical Oncology* in 2018 evaluated combination immunotherapy with nivolumab and ipilimumab; showed response rate significantly higher in combination immunotherapy than in single agent immunotherapy; 55% *vs* 23% response rate; those achieving response maintain response for long duration and perhaps achieve cure; 80% of disease controlled >12 weeks; patients with metastatic colorectal cancer should have assessment of MSI and be considered for immune checkpoint inhibitor if MSI or microsatellite unstable

Selection of immune checkpoint inhibitor: individualized; can use single agent pembrolizumab or nivolumab or combination of nivolumab and ipilimumab; combination therapy has more toxicity; choose combination therapy for patients with very high burden of disease requiring response; single-agent adequate for more stable, asymptomatic patients

Determining MSI: many different methods; immunohistochemistry (IHC) easiest method; evaluates expression of four proteins associated with MLH1, MSH2, MSH6, and PMS2; lack of expression of proteins suggests potentially MSI-high patient; can be done in any pathology lab; polymerase chain reaction (PCR) perhaps best method for checking MSI because a percentage of patients with normal IHC will still have MSI-high tumors; ≈10% in colorectal population; next generation sequencing another method

Summary of management of metastatic colorectal cancer: begin with appropriate staging and quantification of metastatic disease status; percentage of patients with metastatic disease have curable disease with surgery; important to identify patients and continue to evaluate for potential candidacy for cure; all patients should receive initial molecular testing; current molecular testing for treatment allocation includes BRAF and MSI status; potentially HER2 status in near future; can offer patients single-agent chemotherapy or combination chemotherapy with two or three chemotherapies and strategy of flipping between two chemotherapies; select appropriate biological therapy based on molecular profile and tumor location; follow patients closely for toxicities, adjustments of dose, and adjustments of course, based on response; remain cognizant about reducing toxicities and appropriate use of maintenance therapy in incurable patient population

Suggested Reading

Chakedis J, et al: Surgical treatment of metastatic colorectal cancer. *Surg Oncol Clin N Am.* 2018 Apr;27(2):377-99; **Ciombor KK, et al:** A comprehensive review of sequencing and combination strategies of targeted agents in metastatic colorectal cancer. *Oncologist.* 2018 Jan;23(1):25-34; **Wrobel P, et al:** Current status of immunotherapy in metastaticcolorectal cancer. *Int J Colorectal Dis.* 2019 Jan;34(1):13-25.

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Lung Cancer: Part 1 — Disease Overview and Patient Workup

Martin J. Edelman, MD, *G. Morris Dorrance Professor and Chair, Department of Hematology/ Oncology, and Deputy Director for Clinical Research, Fox Chase Cancer Center, Philadelphia, PA*

Epidemiology: most common cause of cancer-related death in United States (US); ~220,000 new cases of lung cancer occur each year in US; ~155,000 result in death; in men, deaths from lung cancer exceed those from prostate, colorectal, and pancreatic cancer, and leukemia combined; in women, deaths from lung cancer exceed those from breast and colorectal cancers combined; other malignancies, *eg*, myelogenous leukemia (CML) and Hodgkin lymphoma, account for relatively few patients, though biologically interesting; CML, ~4600 cases per yr; Hodgkin lymphoma, ~8200 cases per yr; ovarian cancer, ~22,000 cases per yr; in contrast, patients who never smoked who develop lung cancer (group that many consider unusual even today) account for 20,000 to 30,000 new cases per yr; therefore, even minor types of lung cancer represent significant problems

Risk factors: well-known risk factors; overwhelmingly occurs in smokers; lung cancer deaths from smoking ~90% of men and ~80% of women; however, lung cancer in never-smokers major disease in and of itself, but clearly dwarfed by number of patients for whom tobacco clear etiologic factor; other environmental exposures can result in lung cancer, also synergistic with tobacco; *asbestos exposure* — most notable environmental risk factor; still common worldwide, though declining in US with the decreasing use of asbestos; important to take careful history from patients to determine if asbestos exposure; found frequently in auto mechanics, plumbers, smelters, jewelers, or in military or navy personnel whose ships sat in yards, or those who handled ammunition; *other potential exposures* — secondhand tobacco smoke, radon, arsenic, and talc; uranium miners also at increased risk; genetic factors; nevertheless, smoking remains overwhelming cause of lung cancer and factor for which intervention possible; clearly evident that higher tobacco taxes result in decreased smoking and lower incidence of lung cancer; paper in *Annals of Internal Medicine* demonstrated clearly that falling rates of lung cancer associated with decreased rates of smoking throughout country; nevertheless, this disease will remain factor well into next several decades

Clinical presentation: vast majority present symptomatically; symptoms can occur at site of primary tumor (*eg*, cough, pneumonia, hemoptysis); symptoms can occur from metastatic disease (*eg*, pain from involvement of enervated organs, fractures); *brain metastases*– common in both small cell and non-small cell lung cancer; can present with headache, seizure, or other central nervous system (CNS) problems; *other organ involvement* — skin nodules, masses; notably, breast masses can occur, can be confused with breast cancer initially; *paraneoplastic syndromes* — syndromes common with both small cell and non-small cell lung cancer; well described and well known in small cell lung cancer; severe syndrome of inappropriate antidiuretic hormone (SIADH), typically in small cell, can result in severe low sodium; many of these same syndromes can occur in non-small cell lung cancer as well; notably, hypercalcemia occurs in non-small cell lung cancer but rarely, if ever, seen in small cell lung cancer; patients frequently present with confusion, fatigue, and other problems; in small cell lung cancer, paraneoplastic neurologic syndromes such as Eaton-Lambert Syndrome also seen

Asymptomatic presentation: fairly frequent; most commonly presents as incidental finding in evaluation of other illnesses; frequently see patient who has gone to emergency department with complaints of abdominal pain; computed tomography (CT) scan of abdomen demonstrates nodule in lung; this results in evaluation for lung nodule, frequently far more significant issue

Screening: increasingly, patients present as result of screening; screening in lung cancer has long history of negative studies before positive National Lung Screening Trial (NLST); chest X-ray screening in 1960s and 1970s demonstrated no benefit; Japanese originally developed screening with low-dose CT scanning; taken up initially by Early Lung Cancer Action Program, uncontrolled study using low-dose CT; some early claims of 80% reduction in lung cancer mortality exaggerated; however, clear demonstration of efficacy of screening in NLST

- **NLST screening trial:** study accrued ~50,000 patients; primary results published in *The New England Journal of Medicine* in 2011; initial screening procedure followed by 2 more screenings with low-dose spiral CT at 1-yr intervals; demonstrated clear benefit in reduction in lung cancer, associated deaths, and overall mortality; number of lung cancer deaths avoided, 1 for every 320 patients screened; that may not seem impressive; however, compared with mammography, in which 570 patients screened for every life saved; therefore, lung cancer screening quite useful and now recommended by all health care authorities
- **NELSON trial:** recently demonstrated validity of NLST; independent, randomized trial in Europe; recruitment from population-based registries, vs US trial (conducted at certain high-volume institutions); central reading of CT scans; demonstrated clear benefit for patients in terms of lung cancer, reduced deaths, and all-cause mortality; greatest benefit seen in women

Screening summary: screening clearly beneficial; should begin in the sixth decade of life for patients at risk (current or former smokers); still significant questions regarding screening (*eg*, how long should it continue? what to do after 2 or 3 negative screenings at 1-yr intervals? should intervals be lengthened?) with screening, important to emphasize smoking cessation in those who continue to smoke; goal to enrich population of patients most likely to develop lung cancer (screened because majority of studies positive); those patients frequently demonstrate suspicious pulmonary nodule; majority (~95%) of those nodules ultimately determined to be benign

Evaluation of pulmonary nodules: common finding and common problem in internal medicine for decades; risk for malignancy in these nodules heavily determined by size of nodules; <~6 mm, very rarely malignant and no routine follow-up recommended in low-risk patient (*ie*, never-smoker with no history of exposures); for higher-risk patients, follow-up indicated, usually with repeat CT scan in 6 to 12 mos; degree of intensity of follow-up and concern increases with increasing size and other nodule characteristics (*eg*, spiculated appearance, part solid or solid as opposed to ground-glass opacities); evaluation of pulmonary nodules well laid out in various guidelines, including National Comprehensive Cancer Network (NCCN) guidelines

Diagnostic workup: once diagnosis of lung cancer made, how to proceed? lung cancer, like other malignancies, needs to be demonstrated pathologically and then staged; pathologic demonstration usually with biopsy; in some instances, definitive procedure (resection) can take place at same time; *eg*, patient with known, growing peripheral nodule, no evidence of mediastinal disease, otherwise fit, at times resection of nodule best procedure; if malignant, proceed to full lobectomy (in this situation, simultaneous diagnosis and treatment); in most instances, initial biopsy, which will demonstrate non-small cell lung cancer; then proceed to staging to determine proper procedure

Stages: basic understanding of lung cancer staging important; 4 stages, as with almost all other solid tumors (stages I-IV), determined by size, location, and other aspects of primary tumor; *tumor (T) component*-presence or absence, location; *node (N) component* — presence or absence, and location of lymph nodes involved; *metastasis (M) component* — presence or absence, characteristics of metastatic disease; currently on 8th version of system and will undoubtedly undergo additional revisions; most important to understand differences in approach and management for localized (stages I and II), locally advanced (stage III), and advanced (stage IV) disease

Localized (stages I and II) disease: no invasion of major structures; no or only peribronchiolar or hilar lymph nodes

Locally advanced (stage III) disease: presence of ipsilateral or contralateral mediastinal lymph nodes, larger tumors, sometimes invasion of nearby major structures (eg, vertebral bodies, major vessels)

Advanced (stage IV, metastatic) disease: disease that has spread to other organs (*eg*, liver, contralateral lung, brain, bone); also characterized by malignant effusions (most commonly pleural, occasionally pericardial); recent subdivision of distant metastases into solitary metastatic lesions elsewhere in body (oligometastases) and more disseminated disease; increasingly important characterization, since some patients with distant metastases (most notably brain) with solitary areas of disease potentially curable and should not be grouped with more widespread disease

Staging procedures: rigorous staging crucial; start with basic history and physical examination; need to recognize that scans do not always show subcutaneous nodules because some areas might be outside scan; also important to find out about patient's smoking status, both for intervention to help in current management and to reduce other risk factors for frequent complications of disease, including cardiopulmonary issues, that impair ability to use therapeutics; *blood testing* — complete blood counts and chemistry panel; LDH has some prognostic value; no role for tumor markers in diagnosis or follow-up of non-small cell lung cancer; carcinoembryonic antigens frequently ordered, but of little value and should not be obtained; *imaging* — positron emission tomography (PET)-CT at time of diagnosis important for limited disease (stages I, II, and III); crucial in making decision whether or not to proceed with definitive treatments (surgical, radiation, or chemoradiation) by excluding metastatic areas; in stage IV disease, to get clear evidence of whether or not disseminated disease; magnetic resonance image (MRI) of brain indicated for most patients, certainly for those with stage II or higher non-small cell lung cancer and basically every patient with small cell lung cancer (brain metastases quite common in both small cell and non-small cell lung cancer); crucial to establish their presence or absence early; brain metastasis from lung cancer most common malignancy in brain and will occur in ≥40% of patients with lung cancer at some point in illness; prior to definitive treatment for those presumed to have stage I or II disease, assessment of mediastinum indicated; previously, performed with mediastinoscopy; recently, endobronchial ultrasound or endoscopic ultrasound have taken its place; allows sampling of mediastinal nodes in outpatient setting without general anesthesia; if mediastinal nodes present, patients most appropriately managed with combined-modality approach

Histology: tissue should be carefully evaluated by pathologist to confirm lung cancer and what type; previously, only important distinction, small cell vs non-small cell lung cancer; however, increasingly determined that specific histology (squamous vs nonsquamous) important in management; also growing importance for molecular analysis; limited panel of immunohistochemical markers sufficient

Markers: most non-small cell lung cancer CK7+, CK20–, but important to recognize that some both CK7+ and CK20+; usually, adenocarcinomas can be determined by positivity for either thyroid transcription factor 1 (TTF1) or napsin A, though TTF1 positivity present in ~75% of non-small cell lung cancers; other diseases, including small cell lung cancer and thyroid carcinoma, may also be TTF1+; patients have been misdiagnosed because they had cancer in lung that, not small cell, and TTF1+, but turned out to be metastatic thyroid cancer; crucial that immunohistochemical information be put together with histologic observations and clinical scenario to arrive at final diagnosis; TTF1– cancer may be adenocarcinoma; in

squamous carcinoma, P40 or P63 positivity usually present; gastrointestinal (GI) tumors can sometimes be confused (test such as CDX2 staining, while most frequently positive in GI tumors, also sometimes seen in lung cancer)

Neuroendocrine markers: should be obtained for specimens with histologic characteristics consistent with neuroendocrine differentiation (*eg*, nuclear molding), and CD56, chromogranin, and/or synaptophysin should be obtained; several types of lung cancer have neuroendocrine differentiation (*eg*, small cell lung cancer, large cell neuroendocrine cancers, carcinoids); important to put together histologic, clinical, and immunohistochemical features; mesothelioma usually characterized by positive staining for mesothelin and calretinin; no single marker absolutely diagnostic; incumbent on anyone involved with diagnosis and evaluation to carefully discuss results of pathologic determination with pathologists, and ideally at tumor board where everything will be discussed with all appropriate specialties represented

Suggested Reading

Aberle DR et al: Reduced lung-cancer mortality with low-dose computed tomographic screening. *New Engl J Med.* 2011;365(5):395-409; **De Koning H et al:** Effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial. *J Thorac Oncol.* 2018;13(10):S185; **Ito M et al:** Management pathways for solitary pulmonary nodules. *J Thorac Dis.* 2018;10(Suppl 7):S860-6; **Jeon J et al:** Smoking and lung cancer mortality in the United States from 2015 to 2065: a comparative modeling approach. *Ann Intern Med.* 2018;169(10):684-93.

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Lung Cancer: Part 2 — Non–Small Cell Cancers

Martin J. Edelman, MD, *G. Morris Dorrance Professor and Chair, Department of Hematology/ Oncology, and Deputy Director for Clinical Research, Fox Chase Cancer Center, Philadelphia, PA*

Resectable stage non–small cell lung cancer: stages I and II; tumor confined to one lobe; not invading any major structures; at most peribronchial or hilar lymph nodes**;** **(**there are some stage IIIa non-small cell lung cancers with a single station, ipsilateral node which might also be considered resectable); note distinction between "resectable" and "operable;" "resectable" means one can obtain anatomic resection of lobe or segment in more compromised patient and not leave residual disease behind; "operability" is physiologic ability of patient to tolerate procedure; many patients have significant cardiovascular and/or pulmonary disease; preoperatively get full evaluation including pulmonary function testing, cardiac evaluation

Resection: preferred approach with limited, stage I and II, disease; lobectomy preferred over larger procedures such as pneumonectomy or bilobar resection; sublobar resections, segmentectomy, wedge resection can be considered for elderly or compromised populations; stereotactic ablative radiotherapy (SABR) can be considered for small lesions (<3 cm) not close to major structures; rate of local control for stereotactic ablative radiotherapy similar to lobectomy; note that with surgical procedure one can obtain key staging information, tumor size, presence or absence and location of lymph nodes — key considerations in deciding whether patient should receive chemotherapy after surgery

Smoking cessation: quitting smoking within 1 to 2 weeks before resection reduces operative complications; evidence it will reduce complications from subsequent therapy; reduces cardiovascular and pulmonary mortality

Nodal evaluation: critical for staging; for patient undergoing surgery, recommended at least six nodes; three from N1 –peribronchial/hilar group; three from N2 — mediastinum; lobectomy specimens should be carefully dissected

Role of oncology: patients often referred after surgical procedure; all but smallest node-negative tumors have substantial possibility of recurrence; prospective, randomized trials demonstrate survival benefit with adjuvant postoperative chemotherapy given to patients with N1 nodal involvement or higher; substantial evidence tumors >4 cm may also benefit from adjuvant chemotherapy even in setting of node negativity; unclear whether smaller node-negative tumors having high-risk features such as poor differentiation or neurovascular invasion will also benefit from chemotherapy

Adjuvant or postoperative chemotherapy: study from International Adjuvant Lung Trials published in *New England Journal of Medicine* (*NEJM*)*,* lead author Lechevalier; cisplatin-based chemotherapy; variety of regimens now considered archaic conveyed absolute improvement in survival of ≈5%; difference between absolute and relative risk survival benefit; oncologists in breast cancer discuss reduction in relative risk; eg, woman with small, node-negative, resected breast cancer with 90% chance of cure post-surgery; means 10% risk of recurrence; additional treatment with chemotherapy or hormonal therapy decreasing risk to 8% is 2% absolute reduction in risk but 20% reduction in relative risk; lung cancer discussed in absolute terms; absolute improvement of 5% led to general acceptance of adjuvant chemotherapy

Adjuvant studies: ANITA trial and Canadian trial demonstrated substantial improvement in 5-year overall survival using cisplatin and vinorelbine regimen; absolute improvement of 15%; hazard ratios of 0.7%; attempts to improve on this result have failed; adjuvant study done by Eastern Cooperative Oncology Group E1505 used bevacizumab in addition to standard chemotherapy; choice of chemotherapy included variety of cisplatin doublets — cisplatin/docetaxel, cisplatin/gemcitabine and cisplatin/ pemetrexed if patients had non-squamous carcinoma; 1500 randomized patients; no difference in overall or disease-free survival; use of bevacizumab clearly not indicated in this situation

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) studies: included EGFR by immunohistochemistry overexpression or elevated copy number by fluorescence in situ hybridization; results negative even in populations subsequently determined to have EGFR mutations; no long-term difference or overall survival difference; progression-free survival advantage lasting as long as patients took TKI; no role for adjuvant EGFR TKI in resected EGFR-mutated lung cancer; currently ongoing ALCHEMIST trial prospectively determined whether patients had EGFR mutations; extended to involve patients with anaplastic lymphoma kinase (ALK) translocations as well as patients with no abnormalities; evaluates use of immunotherapy (nivolumab) after completion of all adjuvant treatments; a number of other trials ongoing of immunotherapy for non-small cell lung cancer

Standard treatment for node-positive non-small cell, resectable lung cancer: cisplatin doublet; cisplatin/ docetaxel for squamous cell carcinoma; cisplatin/ pemetrexed for non-squamous; equivalent regimens include cisplatin/gemcitabine and cisplatin/vinorelbine; cisplatin/vinorelbine has greatest prospective data

Patients who cannot tolerate cisplatin: most will use carboplatin; studies indicate carboplatin regimens give qualitatively similar results; none have clearly demonstrated equivalency in Phase III setting; remains area of controversy

Stage III: now potentially curable

Definition: disease involving ipsilateral or contralateral mediastinal or N2 lymph nodes, or very large tumor, or invasion of major structures; details of staging available from *Journal of Thoracic Oncology*; note that in older literature stage IIIb, now defined by contralateral N2 disease, also included disease with ipsilateral pleural effusion or pericardial effusion, which is now classified as stage IV disease

Evaluation: need pathological confirmation of disease with endobronchial ultrasound (EBUS) or mediastinoscopy; positive PET or enlarged nodes by CT inadequate to make diagnosis; brain imaging critical, as substantial proportion of patients will be found to have asymptomatic CNS metastases

Treatment: curable disease even in patients not resectable

Surgery: not standard treatment for this stage; the single most controversial aspect of treatment; lecturer believes can be indicated in some cases as part of multi-modality treatment

Chemotherapy + radiotherapy: shown to markedly improve survival in study by Cancer and Leukemia Group B (*NEJM*, 1990, Dillman first author); now-obsolete chemotherapy regimen of cisplatin and vinblastine over 5 weeks, followed by radiation at 60 Gy was clearly superior to radiation alone in unresectable stage III disease; subsequent survival analyses published in *Journal of the National Cancer Institute*; later studies, particularly by Radiation Therapy Oncology Group showed that concurrent radiation and chemotherapy further improved outcomes; still controversy about whether to give further chemotherapy following the initial concurrent chemotherapy and radiation, especially if the low-dose carboplatin/paclitaxel regimen has been used (see below)

Controversy about optimal chemotherapy regimen: low-dose weekly regimen with carboplatin and paclitaxel vs. every-three-week regimen with full-dose cisplatin and second drug, usually etoposide; phase 3 studies comparing these never done; meta-analyses have found no difference between them; one by Santana-Davila (*Journal of Clinical Oncology*, 2015) studied >1800 patients, mostly male and with squamous disease, treated at Veterans Administration facilities between 2001 and 2010; showed increased toxicity and no survival advantage with cisplatin-based regimen; second meta-analysis done by Ramalingam at Emory using National Cancer Data Base obtained same result; lecturer feels both regimens acceptable; note that the carboplatin/paclitaxel regimen used in RTOG 0617 (see below) was followed by 2 courses of consolidation chemotherapy; however, Hoosier Group found that docetaxel consolidation therapy following full-dose cisplatin/etoposide did not add benefit; as the relevant controlled trials of consolidation therapy have not been done, issue remains unsettled

Optimal radiation dose: RTOG 0617 study (Bradley, et al.): evaluated 1) increase in radiation dose; and 2) use of cetuximab as radiation sensitizer; control arm received low-dose weekly regimen of carboplatin (AUC 2)/paclitaxel (45mg/m2), radiation dose 60 Gy for 6-week course, followed by consolidation regimen of carboplatin (AUC5)/paclitaxel (200 mg/m2) for 2 cycles; study arm received same chemotherapy regimen but with 74 Gy of radiation; patients were also randomized to receive cetuximab or placebo; results showed no improvement and higher mortality with higher radiation dose; cetuximab conferred no benefit; 20-25% of patients alive at 5 years without progression; 5-year overall survival ~30%; these rates were a marked improvement over those obtained with previous treatments

Addition of immunotherapy:

PACIFIC Trial: results reported 2017; study randomized patients after they had received various strategies of chemoradiation; no standardization of chemotherapy or radiation employed; only requirements were that patients had received more than two cycles of chemotherapy, had not progressed following "definitive platinum-based concurrent chemoradiotherapy," and that they had good performance status; at 1 to 42 days after concurrent chemoradiation, patients were randomized and began receiving either durvalumab — an anti-programmed death ligand 1 (PD-L1) antibody — at 10mg/kg every 2 weeks, up to 12 months/twenty-six doses, or placebo; demonstrated survival advantage overall and progression-free for durvalumab arm; now standard of care; are significant questions about how to employ; best tolerated regimen for stage III patients is low-dose carboplatin/taxol; involves two courses of consolidation; possible in under 42 days; alternative approach is induction course of chemotherapy followed by low-dose chemoradiation — not tested prospectively; considerable heterogeneity in nature of chemoradiation; subsequent trials will control for type of radiation and chemotherapy administered

Other PACIFIC results: reduction in brain recurrence; demonstrates immunotherapy active and preventing CNS metastasis as well as metastasis locally and at all distant sites; toxicity remarkably low; immune-related adverse events but no substantial increase in rate of pneumonitis

Follow-up unplanned analyses of data: can be misleading; for example, reported that patients who received durvalumab as quickly as possible after completion of chemoradiation had better outcomes; interpreted as indicating immunologic issue where proximity of receiving immunotherapy is beneficial; however, lecturer feels effect could be due to fact that patients with larger tumors received larger radiation fields, were sicker to begin with, and had greater delay before treatment; current standard of care is for patients to receive concurrent chemoradiation followed by durvalumab; remaining questions are optimum chemoradiation regimen, rapidity with which immunotherapy needs to follow chemoradiation, and whether immunotherapy should be administered concurrently with chemoradiation; trials are underway

Stage IV disease: metastatic disease; includes distant metastases at presentation and relapsed previous locally

advanced disease; differences in approach between those receiving or not receiving prior systemic therapy

Historical perspective: prior to 2000, emphasis was on demonstrating treatment better than observation alone; controversial — significant toxicities and limited efficacy of agents available at the time; cisplatin first drug demonstrating benefit; trials demonstrated extension of and superior quality of life with platinum as single agent or combined with now-obsolete agents such as mitomycin; even with use of difficult drug like cisplatin and prior to effective antiemetic treatments, treatment with platinum was superior; early 2000s, demonstrated superior two-drug platinum-based regimens; cisplatin or carboplatin combined with paclitaxel, docetaxel, gemcitabine, vinorelbine, and pemetrexed; for first time shown that treatment improved survival; with single-agent platinum or older platinum doublets 1-yr survival was 20% with median survival of 6 months; progressed to 1-yr survivals of 30% and median survivals of 8 months; ECOG 5094 trial examined if there was superiority of platinum-based doublets, specifically cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel or carboplatin/paclitaxel; led by Schiller and published in *NEJM* in 2002; demonstrated agents were roughly equivalent; varied toxicities; early 2000s introduced targeted therapy with bevacizumab, a neutralizing antibody for vascular endothelial growth factor (VEGF), and new cytotoxic, anti-folate agent pemetrexed

Bevacizumab study: by Johnson et al. at Vanderbilt; bevacizumab added to activity of carboplatin and paclitaxel; severe cases of hemoptysis in 6 patients; four were fatal and all occurred in patients with squamous carcinoma; when bevacizumab went forward to definitive testing in ECOG trial (Sandler, 2005), patients with squamous carcinoma were excluded, as were those with history of hemoptysis, anticoagulation, or CNS metastasis

Results: median survival in this group of advanced non-small cell lung cancer patients >1yr; 12.5 *vs* 10 months for control arm carboplatin/paclitaxel; survival at 2 years of 22%; first time achieving >50% 1-yr survival in advanced non-small cell lung cancer; control arm did well because sickest patients, with hemoptysis, CNS metastasis, venous thrombosis, or on anticoagulation, had been excluded; 10.2 month median survival for this group better than prior carboplatin/paclitaxel arm with identical drugs and doses; made histology in non-small cell lung cancer a key consideration and changed how much tissue obtained at time of diagnosis

AVAIL study: results of ECOG trial not completely replicated; used platinum/gemcitabine-based regimens; did not show advantage for bevacizumab; ongoing controversy as to real utility of agent in advanced non-small cell lung cancer; field has moved on with little recent use of bevacizumab

Pemetrexed trial: JMDB trial by Scagliotti; compared cisplatin/pemetrexed to cisplatin/gemcitabine; trial enrolled >1000 patients; evident cisplatin/pemetrexed regimen might be preferentially active in patients with non-squamous *vs* squamous carcinoma; prospectively defined cohort with non-squamous histology evaluated; powered to show noninferiority of cisplatin/pemetrexed *vs* cisplatin/gemcitabine; results would be analyzed by histology if noninferiority shown; commentaries since publication have implied this was not preplanned analysis when it was; demonstrated cisplatin/pemetrexed noninferior to cisplatin/gemcitabine in overall population; showed moderate superiority over cisplatin/gemcitabine in non-squamous population; hazard ratio of 0.81; cisplatin/gemcitabine advantageous over cisplatin/pemetrexed in patients with squamous histology; hazard ratio 1.23; led to pemetrexed license in non-squamous patients; US predominately uses carboplatin *vs* cisplatin; original regimen used cisplatin

Squamous *vs* non-squamous: Grilley-Olson evaluated how well pathologists agreed on histology results based on specimens analyzed without use of immunohistochemistry; poor clinical agreement; unknown how result would compare with modern methods

Targeted treatments: based on cell signaling in cancer cells; first drug was bevacizumab; showed advantage on anti-VEGF antibody but not in targeted population initially; erlotinib/gefitinib — small molecule TKIs directed at EGFR; four randomized trials combined these agents with standard chemotherapy, carboplatin/paclitaxel or gemcitabine/cisplatin; >4000 patients randomized; showed no advantage; knowledge of target missing at time; emerged from observations of Asian, never smoker, younger women with dramatic and sometimes durable responses to EGFR TKIs; led to discovery of EGFR mutations; activating mutations now easily identified; studies prospectively demonstrated EGFR TKIs gefitinib, erlotinib, afatinib, superior to chemotherapy in progression-free survival; trials never demonstrated advantage in overall survival; patients identified with mutations and treated with chemotherapy crossed over and received TKI; led to universal approach that if mutations were identified, treatment would proceed to single-agent EGFR TKI; never answered role of chemotherapy either in addition or in planned sequential fashion before evidence of progression; colored by history of combined chemotherapy and TKIs in untargeted population; recent studies demonstrate superiority adding EGFR TKIs to standard chemotherapy *vs* TKI alone; now being addressed in US prospective trials

Second decade of 21st century: EGFR-targeted therapy for 10% to 15% of non-squamous patients, highly active; cytotoxic chemotherapy based on squamous *vs* non-squamous histology; non-squamous patients received Pemetrexed- or bevacizumab-based regimens; to improve on results with cytotoxic drugs, maintenance therapy introduced predominately with pemetrexed; other studies with taxanes and gemcitabine; pemetrexed still utilized today; four courses of chemotherapy followed by observation compared to four courses of platinum-based doublet therapy followed by single-agent pemetrexed; switch maintenance — initial platinum doublet did not contain pemetrexed; continuation maintenance did; controlled studies demonstrated advantage; criticism of inadequate degree of crossover to active agent on progression; question whether four courses of platinum-based doublet sufficient; four courses *vs* six or more based on results demonstrating four

courses of carboplatin/paclitaxel as good as more courses of carboplatin/paclitaxel; reason for similar result was cumulative taxane neuropathy; not a consideration with pemetrexed; commonly adopted, well-tolerated regimen; basis of current regimens with chemoimmunotherapy; later observed new targetable mutations; ALK translocations activating; crizotinib — mesenchymal to epithelial transition (MET) inhibitor highly active; early-phase results dramatic with remarkable waterfall plots; almost all patients experienced some shrinkage of disease if not partial or complete response and markedly improved progression-free survival; led to rapid approval of crizotinib; confirmed by randomized studies; potential targets include v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation well-treated with dabrafenib/trametinib; c-ros oncogene(ROS) translocations responding to crizotinib; rearranged during transfection (RET) translocations responding to vandetanib; other VEGFR TKIs; most recently MET exon skipping, in which regulatory domain for MET oncogene is missing; leads to uncontrolled activation of MET; also neurotrophic receptor tyrosine kinase (NTRK); represent 1% to 2% of non-squamous population but critical to identify

Smoking: overwhelming number of these gene-mutation patients are never or scant smokers; never smoker — smoked <100 cigarettes in lifetime; scant smoker — <10-pack-years; patients typically smoked from ages 18 to 25 then quit 20+ tears ago; some of these abnormalities now being identified in patients with significant smoking histories; particularly MET exon 14 skipping; perform next-generation sequencing analysis in every patient with advanced non-squamous carcinoma; phenomenal responses to these agents; generally well-tolerated; responses can be sustained for years

Kristen rat sarcoma viral oncogene (K-RAS): most important development in past few months; first oncogene identified in lung cancer; makes up as much as quarter of non-squamous carcinoma; D12C subtype may be targetable with oral agent; data presented at American Society of Clinical Oncology (ASCO) 2019

Other advances in targeted therapy in non-small cell lung cancer: liquid biopsies; evaluate specific mutations; activities of agents specific for mutations; exon 19 deletions and exon 21 missense mutations commonly seen EGFR activating mutations; other mutations such as exon 18 are activating and targetable; insertion mutations in exon 20 do not respond to these agents; not enough to find, eg, EGFR mutation, must identify specific mutation; similar situation seen with BRAF — V600E mutation targetable but other mutations not; with K-RAS, G12C is targetable, but not G12D or others

Other developments in targeted therapy:

EGFR mutations: represent 10 to 15% of non-squamous carcinoma; first-generation agents designed against wild-type receptor; had reversible kinetics; included erlotinib, gefitinib; followed by second-generation irreversible ones — afatinib; not clear second-generation any better; afatinib probably more toxic; hard to compare results of specific agents; all made obsolete by development of osimertinib; osimertinib originally designed to address problem of exon 20 T790M mutations — mechanism of resistance to first two generations of EGFR TKIs; osimertinib designed to inhibit this resistance mutation; also inhibits 19, 21, and other activating mutations; designed against mutated as opposed to native receptor; more active drug hitting all major initial mutations; less toxic because it has no effect on wild-type receptors; far less rash and diarrhea; most common resistance mutation against osimertinib is C797S; other mechanisms of resistance not involving EGFR receptors, such as MET amplification, K-RAS mutations, rare event of small-cell transformation; analyze patients carefully as exact treatments vary

ALK translocations: crizotinib had limited activity in CNS; resistance developed; other agents include ceritinib, alectinib, brigatinib; all have varying degrees of activity; ceritinib had considerable GI toxicity and was supplanted by alectinib and brigatinib; need for data to exactly sequence these drugs; many types of secondary resistance mutations can occur within ALK; varying activities of different drugs; anecdotal reports of using one agent, then different agent, then back again, depending on specific abnormality; reassessing specific mutations is critical; re-biopsy or evaluate for circulating DNA by liquid biopsy techniques

Squamous carcinoma: no real developments in types of targetable mutations; Lung Master Protocol led by Southwest Oncology Group; despite attempts, no identified specific targetable mutations; platform productive in rapidly screening drugs for activity; still ongoing

Status of non-small cell lung cancer to 2010: established that platinum/pemetrexed was preferred regimen in non-squamous cell carcinoma; platinum + taxane, gemcitabine, or vinorelbine used for squamous carcinoma; specific targetable mutations sought in non-squamous

2010-2015: much research on maintenance, oral VEGF antagonists; few significant advances

Immunotherapy: beginning ~2015, major alteration in oncology, non-small cell lung cancer treatment; in 1980s, interleukin-2 (IL-2) and interferons were evaluated in non-small cell and small cell lung cancer; agents substantially toxic and not effective; crucial change was from activating immune system to eliciting immune recognition of tumor; mutations occurring in non-small cell lung cancer result in abnormal cell-surface proteins, antigenic tumor; has altered landscape of therapy

Studies: began as second-line treatment where nivolumab was compared with docetaxel; two separate studies — CheckMate 057 and 017; Merck termed studies Keynote using pembrolizumab; Genentech Roche atezolizumab used BIRCH, POPLAR, OAK and IMPower; AstraZeneca had ATLANTIC, *PACIFIC*, *MYSTIC*, *NEPTUNE*; Merck KGaA with agent avelumab were *JAVELIN* studies

CheckMate studies: compared nivolumab with docetaxel in patients having previous treatment in non-small cell lung cancer; showed remarkable advantages in progression and overall survival; single-agent activity of these drugs; small number had durable responses and were long-term survivors; when used in Phase I refractory population, 15% of patients with advanced

non-small cell lung cancer, heavily pretreated, were alive at 5 years

Pembrolizumab: superiority demonstrated over docetaxel in second line; these drugs moved into first line compared to platinum-doublet chemotherapy

Other trials: not all trials positive; CheckMate 026 study compared nivolumab to platinum doublet to determine by histology; did not find overall survival advantage; Keynote 024 study did find advantage for pembrolizumab compared to platinum doublet; all these studies required patients have varying degrees of positivity for PD-L1 biomarker used to select patients

Chemoimmunotherapy *vs* chemotherapy: initial study in non-squamous carcinoma; Keynote 021 trial compared carboplatin and pemetrexed *vs* carboplatin, pemetrexed and pembrolizumab; demonstrated substantial advantage for chemoimmunotherapy arm; confirmed in Keynote 189 study by Gandhi; substantial advantage in overall and progression-free survival favoring chemoimmunotherapy; similar studies using immunotherapy agents and other platinum doublets such as carboplatin and paclitaxel or carboplatin and nab-paclitaxel with agents such as atezolizumab; chemoimmunotherapy has become front-line standard for substantial population of patients with non-squamous and squamous carcinoma; in non-squamous carcinoma, most commonly employed regimen is carboplatin/pemetrexed and pembrolizumab; all three drugs used for four cycles before dropping down to maintenance of pemetrexed and pembrolizumab; carboplatin/paclitaxel, bevacizumab and atezolizumab is comparable regimen somewhat more cumbersome to use; can be used in non-squamous carcinoma; in squamous disease, combinations of pembrolizumab with carboplatin and paclitaxel have been demonstrated to be advantageous; again drugs carboplatin/paclitaxel used for four courses followed by pembrolizumab as single agent

Ongoing questions: how to best select patients; role for single-agent immunotherapy; when to use chemoimmunotherapy

PD-L1: first biomarker employed; evaluated on tumor cells and expressed as percentage of tumor cells analyzed; 22C3 antibody is most commonly employed antibody; used in Merck-sponsored trials with pembrolizumab; other antibodies comparable; exception of SP142 antibody which appears far less sensitive; used in Genentech Roche studies; variety of somewhat arbitrary cutoffs used; some as detection >1%, sometimes >50%; differences in expression depending on where biopsy taken; recent data indicates assessment on lymph nodes may not be as appropriate as on primary tumor or metastatic lesions; with patients who have high expression of PD-L1 on tumor, use of single-agent immunotherapy with pembrolizumab may be as good as chemoimmunotherapy; does not appear chemotherapy adds in this situation; has not been directly compared

Mutational load or tumor mutational burden: more mutations in tumor, greater incidence of abnormal proteins expressed on cell surface; in lung cancer, published by Rizvi in 2015; increasing tumor mutational burden associated with greater response and benefit in progression-free and overall survival; not been standardization in how test run or cutoff used; has yet to be fully accepted; need for standardization and to prospectively demonstrate this is best way to select patients for treatment; appears use of tumor mutational burden is complementary to PD-L1 expression status; high tumor mutational burden produces antigenic tumor; high PD-L1 expression associated with mechanism antigenic tumor evades immune system; with high PD-L1 and high tumor mutational burden, there is a very antigenic tumor evading immune system by PD-L1; antagonizing PD-L1 with anti-PD1 or anti-PD-L1 antibody is likely to result in success; if tumor mutational burden is low, even if PD-L1 is expressed, not very antigenic tumor and less likely to respond; if tumor mutational burden is high but PD-L1 is low, mechanism of immune escape may be different and might require different approach for benefit

Development: numerous agents currently in development to enhance effects of immunotherapy to lengthen results in majority of patients who get some initial benefit but ultimately have disease progression; significant fraction of patients whose benefit can be quite durable; generally, patient doing well and responding at 6 months will continue to do well at 2 years; substantial number of long-term survivors; not all patients even continue on treatment; some data patients that get significant immune-related adverse events, particularly after several months of treatment, may do better; controversy; may relate to other factors; evidence in emerging database that Keltch-like ECH-associated protein 1 (KEAP1) and serine/threonine kinase 11 (STK11) mutations may be associated with resistance to chemoimmunotherapy; field in rapid evolution; overall remarkable advances in treatment

Immunotherapy toxicities: still learning how to manage and recognize toxicities; median time to develop immune-related adverse events little over a month in some studies; varies and can be anything from hours to 1 year or more; can be quite subtle; patients come in feel very fatigued — not usually remarkable in these patients; check baseline AM cortisol; hypophysitis can occur and be very subtle in onset; thyroid disease very common; patients need monitoring of thyroid stimulating hormone (TSH); if it elevates, monitor free T3 and T4 with replacement thyroid hormone; before replacing thyroid hormone, also assess AM cortisol to make sure patient does not have concomitant hypophysitis or adrenalitis with adrenal insufficiency; could precipitate adrenal crisis by supplementing with Synthroid; severe effects such as colitis and pneumonitis are managed by holding immunotherapeutic agent and treating with steroids; steroid treatment needs to be prolonged, tapering over 6 weeks; re-challenge depends upon severity and nature of actual toxicity; those employing these agents should review specific side effects and management; publications with guidelines from ASCO, National Comprehensive Cancer Network (NCCN)

Oligometastatic disease: advanced by Weichselbaum; published in *Journal of Clinical Oncology*; previously if patient had had one metastasis, assumption there were many others and patients would only benefit from systemic therapy; local modalities such as surgery or radiation would not be of much use; initially proposed for up to five sites of disease; not completely true in other diseases such as sarcoma and in testicular cancer; resecting metastatic lesions is beneficial; resection of metastatic lesions or definitive treatment with stereotactic radiation will produce long-term survivors; commonly seen in lung cancer in brain where patient treated for stage III disease develops

solitary CNS metastasis 6-12 months later; patients can be treated with curative intent with resection of brain metastasis; further use of chemotherapy or radiation is not completely clear; no real prospective studies; other common sites of oligometastatic disease in lung cancer are adrenal, contralateral lung, occasionally bone and liver; recognize and treat patients appropriately; synchronous metastatic disease — patient with otherwise stage I disease and solitary metastatic site elsewhere; metachronous — present down the road with solitary metastasis; prognosis is clearly better; most recent version of staging system breaks out solitary metastatic disease; gives it term of M1B; how best to approach this remains unclear, particularly for synchronous metastatic disease

Oligoprogression: seen frequently in patients with activating mutations treated with various TKIs; most commonly with patients with EGFR-mutated disease; might have individual who had fairly widely metastatic disease, obtained an excellent response to EGFR TKI; 1 year or so down the road follow-up scans show everything good except new growing nodule in one place; previously would have changed systemic treatments; if patient were receiving osimertinib one might go to chemotherapy, or if one identified another activating mutation as the source of resistance; treating with local resection or ablative therapy such as stereotactic radiation and continue initial TKI better approach; can frequently buy months or longer of benefit

Suggested Reading

Akhurst T: Staging of non-small-cell lung cancer. *PET Clin.* 2018 Jan;13(1):1-10; **Gubens MA et al:** NCCN guidelines updates: new immunotherapy strategies for improving outcomes in non-small cell lung cancer. *J Natl Compr Canc Netw.* 2019 May;17(5.5):574-8; **Rafei H et al:** Immune-based therapies for non-small cell lung cancer. *Anticancer Res.* 2017 Feb;37(2):377-87.

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Lung Cancer: Part 3 — Small-Cell Cancer and Rare Thoracic Malignancies

Martin J. Edelman, MD, *G. Morris Dorrance Professor and Chair, Department of Hematology/ Oncology, and Deputy Director for Clinical Research, Fox Chase Cancer Center, Philadelphia, PA*

Epidemiology: small cell lung cancer is the less prevalent type of lung cancer; it comprises 10% to 15% of the 225,000 cases of lung cancer each year in the United States; approximately 25,000 new patients each year

Biology: small cell lung cancer has a distinctive biology compared with non-small cell lung cancer; almost invariably associated with abnormalities in the retinoblastoma and P53 oncogenes; almost all patients, at least in the United States, who present with de novo small cell lung cancer were very active smokers, frequently from a young age; however, there is a small incidence of small cell lung cancer that occurs as a resistance mechanism in patients with epidermal growth factor receptor (EGFR) mutations and perhaps others

Staging system: technically the same as for non-small cell lung cancer, but small cell regarded as limited versus extensive stage; limited stage is everything from stage 1A to 3B in non-small cell lung cancer; patients with disease limited to the hemi-thorax with potentially N3 disease (contralateral mediastinal nodes or even contralateral hilar nodes) without malignant effusions; extensive disease is everything else (metastatic disease); small cell frequently metastasizes, particularly to the brain, but it can metastasize anywhere; limited stage disease historically defined as confined to a hemi-thorax within a tolerable radiation port, but that has never been precisely defined; ideally, when patient is first evaluated, use the same tumor, nodes, and metastases (TNM) system as for non-small cell then divide into limited versus extensive

Limited stage disease: represents about one-third of all patients with small cell lung cancer; these patients may vary enormously within this stage; these can include people who, if they had non-small-cell disease, would be regarded as stage 3 (mediastinal involvement); approach for patients with reasonable performance status is potentially curative using concurrent chemotherapy and radiation; prior to treatment, critical to fully stage; there are clear differences between approach in the United States and Europe; some differences of opinion in use of prophylactic cranial irradiation; for patients with any extent of small cell lung cancer, brain should be imaged, ideally with MRI with contrast; rate of asymptomatic metastasis in brain is extremely high; PET scan is indicated in all patients because it will reveal unsuspected metastatic disease, particularly in bone; this is important to know about before beginning treatment

Therapeutic approach: potentially curative; current standard approach is to use radiation, ideally administered twice a day to a total dose of 45 gray (Gy), with concurrent platinum etoposide (either cisplatin or etoposide); radiation should begin concurrently with either the beginning of the first or second cycle of chemotherapy; chemotherapy administered at full dose and for a total of four cycles; if one uses the twice daily radiation regimen, it will overlap the first and second courses of chemotherapy; chemotherapy with platinum etoposide generally administered over 3 days with platinum etoposide on day 1 and etoposide on day 3, though there are some variations on this theme

Other approaches: studies have looked at the issue of single-day radiation fractions; recent results presented from European groups by Dr. Faivre-Finn used 66 Gy daily versus 45 Gy twice daily; did not show an advantage for 66 Gy; however, this study was powered for superiority, not equivalence; if one looks at the survival curves, it is clear that 45 Gy twice daily is consistently superior to 66 Gy; thus, 45 Gy twice daily remains the standard and should be followed, though there are clear logistical issues; a US trial led by the Alliance for Clinical Trials in Oncology is evaluating 45 Gy twice daily versus 70 Gy daily; it is a CLGB30610 or RGOG0538 that is currently in progress and should complete its accrual in the summer of 2019; results should be available sometime in 2020 or 2021; hopefully they will provide some guidance regarding the optimal radiotherapy for this disease; despite many studies, no chemotherapy regimen has been shown to be superior to platinum etoposide; obvious question is the role of immunotherapy after the results in extensive disease that have recently been presented

Prophylactic cranial irradiation in limited small cell disease: undergoing some reassessment; it is a current standard to administer prophylactic cranial irradiation (PCI) in patients who have had an excellent response to chemo-radiotherapy; however, some questions have been raised, because recommendation is based on meta-analysis published many years ago; though showing an absolute survival advantage of 5% for PCI, this analysis includes some data that predate use of any central nervous system (CNS) imaging, including computed tomography (CT) scans or magnetic resonance imaging (MRI), and therefore is not in line with modern staging; issue will soon be readdressed in a randomized study, which will also address issues in extensive disease; PCI does have some significant morbidity issues, notably cognitive decline and even instances of dementia; at

the very least, it is inconvenient and adds substantially to cost; in practice, can offer PCI to patients who are younger, but discuss pros and cons; PCI in patients older than 70 years should be used sparingly, if at all, because of the risk of cognitive impairment

Extensive disease: many patients present with metastatic disease; may be quite variable; ranges from a patient with some cervical adenopathy to a patient with a kilogram of disease in their liver or extensive CNS metastatic disease; important to recognize that, in a patient who has never been treated for small cell lung cancer, benefits of treatment can be quite substantial, with marked reduction in disease in majority and concomitant improvement in performance status for most patients; some patients in respiratory failure on ventilators as a consequence of small cell disease can receive treatment and within days be discharged from hospital; probably the most important aspect of treating extensive small cell lung cancer is to recognize the rapid development of resistance; after the initial gratifying response, the overwhelming majority experience relapse

Limited disease: though we treat with curative intent, two-thirds or three-quarters of patients will relapse and ultimately die of their disease; how to approach this? the standard regimen, until quite recently, was platinum (cisplatin or carboplatin) etoposide, administered in the same way as in extensive disease, except without radiation; therefore, a substantially less toxic regimen; in both limited and extensive disease, it is important to recognize the significant myelosuppression that can be seen with platinum etoposide; have a very low threshold for using colony stimulating factors or attenuating doses, particularly in the elderly; this is the one regimen in lung cancer where patients predictability develop neutropenic fever; lethal results possible from chemotherapy; important to be cautious with this regimen and to spend considerable time educating the patient and family regarding the potential toxicity

Newer agents: a good deal of time was spent in the 1990s and early 2000s evaluating a host of new agents in small cell lung cancer; included all the other cytotoxics that were evaluated in non-small cell disease and a variety of targeted agents, most particularly those that targeted B-cell lymphoma 2 (BCL2); unfortunately, none demonstrated any advantage in this situation; closest agent was topotecan, which is active as a second-line agent compared with other chemotherapy; however, it did not work as a maintenance strategy after initial treatment with chemotherapy, as demonstrated by the Eastern Cooperative Oncology Group; topotecan, until recently, was the only agent that was licensed for second-line treatment of small cell lung cancer; it is administered on a rather inconvenient schedule of days 1 through 5, either intravenously or orally and is associated with significant risk of myelosuppression; one should have a low threshold for dose reduction or use of growth factors in this population; use of PCI with or without thoracic irradiation as consolidation is controversial; studies from Europe by Dr. Slotman have demonstrated advantages to both approaches

Prophylactic cranial irradiation: a randomized study of PCI versus observation in patients with extensive stage small cell lung cancer who had obtained any type of response to initial chemotherapy was published in *The New England Journal of Medicine* (*NEJM*) in 2007; demonstrated decreased brain metastasis and improvement in overall survival; this led to the adoption of this approach as a recommendation in extensive stage small cell lung cancer; more recently, a Japanese group published a result that was essentially opposite that of the European study, demonstrating no advantage in terms of progression-free survival and some hint of inferior outcomes with PCI; what differed between the two studies was the method of staging; the Europeans only evaluated the CNS in patients with symptoms, whereas the Japanese trial did what would be appropriate staging by United States standards, evaluating the brain with MRI or CT with contrast; PCI not necessarily an established approach in extensive stage disease; the Japanese group did have frequent surveillance of the CNS by MRI; this approach is probably quite reasonable, though others may disagree; there remains a conflict in the various guidelines regarding the role of PCI after extensive disease; as with limited stage disease, this issue is now undergoing testing in a prospective randomized study

Thoracic radiation: studied in Europe with results demonstrating an advantage to thoracic consolidation radiation after treatment with chemotherapy for extensive stage disease; this study was designed as a superiority trial and did not achieve its statistical endpoints; depending on how one wishes to look at it, it could be interpreted as a negative study, though there did appear to be a survival advantage; the basic approaches to staging were somewhat different and there is a conflicting trial that has been presented by the Radiation Therapy Oncology Group; thus, this needs to be evaluated case-by-case; for example, if patient has limited extensive disease with only cervical adenopathy or a small effusion and otherwise relatively limited bulk of disease and gets an excellent response, then consolidation radiation likely has role; the patient who has more widely metastatic disease and a good response may be best left to enjoy what is usually a brief respite until relapse

Immunotherapy: entered scene in the last 1 to 2 years; several uncontrolled single-arm phase 2 studies that demonstrated activity of anti-PD1 agents (nivolumab and pembrolizumab); resulted in approval of nivolumab third-line for small cell lung cancer; much more impressive was a randomized phase 3 trial that evaluated atezolizumab as first-line therapy combined with platinum etoposide; this trial, published by Horn in *NEJM* in 2019, demonstrates advantages for both progression-free and overall survival; led to an FDA approval of atezolizumab in this setting, which is the first advance in extensive small cell lung cancer in decades; there is a clear benefit in this situation; disappointing that the plateaus on the curve appear to be relatively low; given the almost universal exposure to tobacco for these patients, would have expected that these patients would have been the most likely to benefit because of the very high tumor mutational burden; nevertheless, it was clearly a positive study; the CASPIAN study, announced in a news release without any data, evaluated durvalumab in this situation and reported a positive result in combination with platinum etoposide

Special Issues

Very limited small cell lung cancer: identified due to increased screening and use of CT; would otherwise be stage 1 or 2; occasionally patients with solitary pulmonary nodule have resection that shows small cell lung cancer; how does one handle these patients? first, it is crucial to fully stage them, including the CNS; if patient has been completely resected, current guidelines recommend four courses of platinum etoposide chemotherapy; no known role of immunotherapy at this time; four courses of treatment is reasonable; similar to the situation for the more typical limited stage small cell lung cancer, PCI should be considered; these patients do quite well, particularly if they are N0; once there is nodal involvement, the rate of relapse rises markedly; important to recognize these patients and neither overtreat or undertreat; if patients have been completely resected, there is no role for radiotherapy

Immunotherapy: in limited disease, whether to employ it sequentially or concurrently with chemo-radiation is being investigated; role of additional immunotherapy agents and salvage agents in extensive disease is under investigation

Use of prophylactic cranial radiation: under active scrutiny given the antiquity of the results indicating its use in limited disease and issues of trial design and extensive disease; there will likely be substantial developments in this field over the next several years

Other agents: immunotherapy agents and others; some phase 3 trials have closed, and results should become available within next year or so

Extrapulmonary small cell cancer: small cell lung cancer can be associated with organs other than lung; in these situations, it is not associated with tobacco use; most commonly seen in the prostate, cervix, and esophagus; usually these patients initially present with a very poorly differentiated adenocarcinoma; then the disease becomes quite explosive and a rebiopsy shows small cell lung cancer; one time to suspect this is with a patient who has a high Gleason score prostate cancer, whose disease is getting worse while their prostate specific antigen is not changing; treatment for these patients is very similar to that for small cell lung cancer with appropriate adaptation; for patients with metastatic disease, a platinum etoposide-based regimen is appropriate and can frequently be effective; these patients have similar responses initially, usually followed by relapse; for the occasional patient with more limited disease, surgical resection if possible, or use of a concurrent chemo-radiation approach is reasonable; important to note that organ tolerances for radiation differ; for example, 45 Gy twice daily in the esophagus may not be feasible; will need to be adapted to the specific situation and surrounding organs

Rare Thoracic Malignancies

Malignant pleural mesothelioma: relatively uncommon disease; fewer than 10,000 cases per year in United States; usually highly aggressive and lethal; typically diagnosed in later stages; falling incidence in United States with less asbestos exposure, but rising in other areas of the world where the use of asbestos appeared later; more common in men than women (3:1); latency of 20 to 50 years from environmental exposure to asbestos; typically occurs in patients aged 50s, 60s, and beyond

Exposure: asbestos was ubiquitous in the environment until recently; used commonly to wrap hot water pipes and as part of brakes in cars; wherever there was something that was hot, asbestos was used; however, just because a person was in a building where there were asbestos-wrapped pipes does not mean that they had asbestos exposure; the people who actually worked on these pipes and were exposed to aerosolized asbestos are at risk; for example, individuals who did demolition or plumbers or construction workers who worked on older buildings were frequently exposed; military exposure is quite common, particularly in the Navy, where asbestos was used quite commonly throughout the bowels of ships (piping and parts of guns on larger ships); individuals who were in Navy and assigned to vessels that were undergoing refit in shipyards very frequently were exposed; other occupational exposures include smelters, car repairman, jewelers who engaged in soldering; those who engaged in manufacture or mining of asbestos; spouses who may have washed the clothes; other family members may have inhaled asbestos

Biology: malignant pleural mesothelioma starts in mesothelium; most commonly in men and older individuals; frequently associated with the breast cancer-associated protein 1 (BRAC1) gene (BAP1); there may be a familial aspect

Evaluation: patients who present with mesothelioma need rigorous evaluation with chest CT with contrast and biopsy; can be confused with non-small cell lung cancer; crucial to make the distinction; this can usually be done with immunohistochemical stains; mesothelioma typically stains positive for markers such as mesothelin or calretinin; important to make sure that diagnosis is correct; requires more than usual experience by pathology; worth obtaining consultation; management is clearly different from other thoracic malignancies

Presentation: patients typically present with dyspnea or chest pain; although it can metastasize, mesothelioma is usually confined to the thorax and ultimately becomes lethal by gradually encasing lung and causing respiratory failure; can be quite painful, as it involves the chest wall and the intercostal nerves; three major histologic variants are epithelioid variant, sarcomatoid variant, and mixed disease; prognostically, patients with epithelioid disease do somewhat better than those with sarcomatoid or mixed disease; occurs predominantly in chest; can occur in abdomen, occasionally testes, rarely in pericardium

Management: same for all sites; obtain consultation with thoracic surgery and determine if disease is resectable; there has been unending controversy regarding optimal surgical procedure; most radical approach is extrapleural pneumonectomy, which has reports of long-term survivors, but those patients almost exclusively have low-volume disease and the epithelioid subtype; unclear whether even in a more favorable prognostic group there is any superiority to the extensive extrapleural pneumonectomy compared with limited thorectomy, which resects only all the involved areas and is usually followed by radiation; unfortunately, there are no good controlled trials demonstrating the role of surgery nor how to approach this from a multi-modality viewpoint; unfortunately, overwhelming majority of patients will ultimately have disease progression and require systemic therapy

Chemotherapy: the only regimen with clearly demonstrated activity is platinum-pemetrexed; based on comparative trial of platinum-pemetrexed versus platinum (published by Dr. Vogelzang in *Journal of Clinical Oncology* in 2003); study demonstrated advantages in response, symptom improvement, and overall survival for combination with pemetrexed; this regimen is the best available treatment, but it leaves a great deal to be desired; a trial of gemcitabine-cisplatin was combined with bevacizumab, and was negative; a European trial used bevacizumab in addition to platinum-pemetrexed; this therapy was not FDA-approved in the United States, but can be considered; numerous other approaches have been attempted, but usually with negative results; most recently there have been some data about the use of immunotherapy, specifically anti-PD1 treatments, in this setting; there are guidelines that will allow the use of nivolumab or pembrolizumab in this situation, but not FDA approved at this time; a randomized, controlled study of ipilimumab in addition to chemotherapy was completely negative; phase 2 results need to be taken with a grain of salt; there are several active investigations using novel agents including chimeric antigen receptor (CAR)-T cells directed against mesothelin; various agents to deplete arginine in tumor cells; this approach appears to be beneficial; several other approaches; we are awaiting the results of these studies; this remains an extremely difficult disease

Thymic tumors: thymic tumors, particularly thymoma, frequently associated with paraneoplastic syndromes, most notably myasthenia gravis, where resection of the tumor can result in improvement; however, thymoma can be associated with many other paraneoplastic syndromes, including pure red cell aplasia; patients may present with neurologic or other manifestations not directly related to disease; seeing a mediastinal mass on chest imaging should suggest the presence of these diseases; three major thymic malignancies; all are quite unusual but are the most common mediastinal malignancies; basic classification is thymoma, thymic carcinoma, and carcinoid; very important to distinguish between thymoma and thymic carcinoma because they have dramatically different outcomes; crucial to have the pathologist involved, as there are major prognostic differences between those with well-differentiated disease and with certain characteristics; spindle shape, minimal atypia, and minimal lymphocytes characterize WHO class A tumors, versus those with more lymphocytic infiltration, or polygonal cells, or more aggressive degrees of atypia; key differentiation is between thymoma and thymic carcinoma; thymic carcinoma has a very poor outcome

Staging: several staging systems; most commonly used is the Masaoka system; stage 1, tumor completely encapsulated; stage 2, macroscopic invasion into surrounding tissues; stage 3, direct invasion into adjacent organs; stage 4, pleural or pericardial implants; stage 4B, nodal or other hematogenous metastases

Prognosis: varies with staging; this is primarily a surgical disease; attempts at complete surgical resection should be made, including resection of (very frequent) metastases; speak to surgeon first to manage this disease; even quite large tumors can be safely resected

Treatment: no clear role for adjuvant chemotherapy; essentially the solution is resection; good idea for the surgeon to leave some clips in place for radiation to any areas with involved margins; chemotherapy should be restricted to those who have demonstrable disease; for thymic malignancies (carcinoma or thymoma), there are several different regimens; the two major competing regimens are cisplatin, Adriamycin, cyclophosphamide (CAP) and carboplatin/paclitaxel regimen, similar to that used in non-small cell lung cancer; these are clearly very chemotherapy-responsive diseases and one should not hesitate to treat them; probably a role for chemo-radiotherapy, either with induction chemotherapy followed by radiation orS concurrent chemo-radiation for a patient with a locally advanced, unresectable thymoma; these patients, even in advanced stages, can have quite durable responses to chemotherapy; tumors behave somewhat more like lymphoma than non-small cell lung cancer; unfortunately, those with thymic carcinoma tend to do quite poorly; optimal treatment is complete surgical resection and radiation of involved margins; patients with thymic carcinoma respond poorly to chemotherapy; there are a number of regimens available for those who progress; given the rarity of the disease, there is relatively limited knowledge regarding what works

Suggested Reading

Faivre-Finn C et al: Concurrent once-daily versus twice-daily chemo-radiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol.* 2017;18(8):1116-25; **Horn L et al:** First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med.* 2018;379(23):2220-9; **Putora PM et al:** Prophylactic cranial irradiation in stage IV small cell lung cancer: selection of patients amongst European IASLC and ESTRO experts. *Radiother Oncol.* 2019;133:163-6; **Yin X et al:** Prophylactic cranial irradiation in small cell lung cancer: a systematic review and meta-analysis. *BMC Cancer.* 2019;19(1):95.

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Thymic Carcinoma, Mesothelioma, and Anaplastic Thyroid Cancer

Andrea Wolf, MD, *Associate Professor, Thoracic Surgery, Director, New York Mesothelioma Program, Icahn School of Medicine at Mount Sinai, New York, NY*

Thymic Carcinoma

Introduction: rare type of thymic epithelial neoplasm; <10% of 500 new cases of thymic epithelial neoplasm in US each year comprise thymic carcinoma; distinct entity from thymoma; current world health classification for thymic epithelial neoplasms based on morphology of epithelial cells, particularly epithelial cell to lymphocyte ratio; thymic carcinoma represents type C

Epidemiology: more common in men

Presentation: often presents with symptoms due to local invasion from aggressive behavior of tumors; patients may present with cough, chest pain, diaphragmatic elevation due to phrenic nerve involvement, or superior vena cava (SVC) syndrome, manifesting as plethora and facial, head, and neck swelling; paraneoplastic syndromes such as myasthenia gravis extraordinarily rare with thymic carcinoma; their presence should raise suspicion for thymoma instead; fewer than 7% of patients present with metastatic disease; when metastasis seen, kidney, extrathoracic lymph nodes, liver, brain, adrenals, thyroid, and bone most commonly involved

Biology: aggressive; associated with worse prognosis and survival than thymoma; thymoma associated with nearly 100% 5-year survival; thymic carcinoma at best associated with 40% to 60% 5-year survival; 60% seen in most serious cases in which resection possible

Histology: thymic carcinoma pathologically distinct from thymoma; stroma of thymic carcinomas demonstrates B-cells and mature T-cells in contrast to immature T-cells seen with thymoma; thymic carcinoma occasionally seen in combined thymoma-carcinoma tumors; gives rise to theory that thymic carcinoma may rarely develop in longstanding thymomas after 10 or 15 years; squamous cell carcinoma most common histology seen; considered low-grade differentiation; other low-grade differentiated thymic carcinomas include mucoepidermoid and basaloid tumors; high-grade tumors include lymphoepithelioma, clear cell carcinoma, sarcomatoid carcinoma, and adenocarcinoma

Staging: generally begins with chest CT; most patients presenting to oncologist have been diagnosed based on chest CT; MRI may be helpful due to tumors' distinct MRI appearance or signaling patterns, such as necrosis, calcification, cysts, irregular tumor contour, or other characteristic findings; MRI can also be useful in distinguishing thymic carcinoma from thymoma, cysts, and other benign entities; MRI can be helpful in distinguishing additional structure involvement if tumor locally invasive; clinical staging generally done with PET-CT scan; benign entities and thymomas may have no uptake or low-grade uptake in lesion; thymic carcinomas generally associated with high avidity; distant metastases may be assessed with PET-CT; for patients with neurologic, especially central nervous system symptoms, specialized imaging of head with brain MRI or head CT with and without contrast required to fully assess for brain metastases; thymic carcinoma staging based on American Joint Commission on Cancer (AJCC) TNM staging; Masaoka staging system and Koga modification not appropriately used for thymic carcinoma; data on which these systems based included mostly patients with thymoma and few patients with thymic carcinoma; most patients in medical literature presented with stage 3 disease based on AJCC or TNM staging; most studies with higher numbers of thymic carcinoma patients based on registries and international or multicenter retrospective studies; use 8th edition of AJCC TNM staging system; predictive of survival in most series

T stage or tumor size: T1b — tumor encapsulated or invades mediastinal fat within mediastinal pleura; stage T1a — no mediastinal pleural involvement; T[2?]tumor invades pericardium; T3 invades resectable organs; includes segments of lung, innominate vein, SVC, phrenic nerve, portion of chest wall, or pulmonary artery or vein outside pericardium; T4 lesion invades organs considered unresectable; include aorta, arch vessels such as carotid, subclavian, innominate artery, or intrapericardial pulmonary artery, heart, trachea, or esophagus

N staging: divided into two categories; N1 tumors — anterior lymph nodes near thymus; N2 tumors — deep intrathoracic or cervical lymph nodes

M staging: M1a — separate pleural or pericardial nodules distinct from primary lesion; M1b — separate lesions in lung parenchyma or distant metastases

Approach: stages 1 through 3 based on N0 M0; T1 N0 M0 lesion stage 1; T2 N0 M0 lesion stage 2; stage 3 divided into a and b; T3 n0 m0 lesion represents stage 3a; T4 N0 M0 lesion represents stage 3b; any lymph node involvement represents stage 4; stage 4a represents either N1 disease or any M1a disease; any N2 disease or M1b disease represents stage 4b

Treatment:

Surgery: mainstay of treatment for resectable tumors; rate of recurrence very high; many series in literature found benefit to debulking even if R1 or R2 resection performed; R1 — microscopic disease left behind; R2 — gross disease left behind

Adjuvant therapy with radiation: associated with better outcomes in some series; without significant impact in others; most data based on series that combined patients

with thymoma and those with thymic carcinoma; very few have stratified results or had high enough numbers to draw conclusions with regard to benefits of adjuvant therapy in patients with thymic carcinoma; nearly all data come from retrospective series in which R0 or complete resection associated with better survival; when evaluating retrospective data, patients with tumors amenable to R0 or complete resection clearly those with smaller tumors or early stage lesions; results confounded by other favorable prognosticators for better survival

Chemotherapy: may be of benefit; unclear whether to give chemotherapy before or after resection; most regimens include cisplatin with anthracyclines or etoposide; response rates ≈50%; thymic carcinoma has high expression of PDL1; associated with response to PD1 and PDL1 inhibitors in non-small cell lung cancer; too early to understand role of immunotherapy or PD1/PDL1 immunomodulating therapy for thymic carcinoma; trials ongoing

Malignant Pleural Mesothelioma

Overview: 70% of cases associated with asbestos exposure; latency between exposure to asbestos and disease manifestation ≈20 to 40 years

Epidemiology: 3300 cases per year in US; median age at presentation 70; 80% of patients men; median survival without treatment 7 months; ≈12 to 18 months with treatment; 15% 5-yr survival with multi-modality therapy; inherited version of disease associated with BAP1 gene mutation; discovered among Cappadocian residents in Turkey; most patients have sporadic form

Presentation: recurrent pleural effusion causing shortness of breath; sometimes patients present with chest pain, cough, weight loss, or even palpable mass; metastases rare, particularly at time of presentation; can be seen with relapsed aggressive or recurrent disease

Biology: aggressive; progresses locally rather than by hematogenous or lymphatic spread; two main cell types — epithelial and sarcomatoid; may be seen in combination in biphasic or mixed cell type tumor; patients often dichotomized into non-epithelial and epithelial disease; patients with pure sarcomatoid disease carry worst prognosis; mixed cell type somewhere in between; rare subset of patients with pure sarcomatoid malignant pleural mesothelioma with desmoplastic cell type and carrying particularly poor prognosis; well-differentiated papillary tumor more favorable; must be histologically distinguished from epithelial cell type; main differential includes pleural dissemination of other solid malignancies, such as lung, breast, colon, and others; histologically, lung adenocarcinoma most commonly confused with epithelial cell type morphologically; calretinin and WT1 main immunohistochemical markers positive in epithelial cell type malignant pleural mesothelioma; TTF1 positive in lung adenocarcinoma; morphologically, sarcomatoid carcinoma and sarcoma may be similar in appearance to sarcomatoid type malignant pleural mesothelioma; main differential for these tumors; high rate of local recurrence after treatment and resection

Favorable prognostic factors: young age, female gender, epithelial cell type, early stage, and normal hemoglobin, white blood cell, and platelet counts

Poor prognostic factors: non-epithelial cell type, nodal metastasis, male gender, anemia, leukocytosis, and thrombocytosis

Staging: challenging due to poor survival; staging systems designed to stratify patients with disease into distinct groups with separated survival curves; patients with early stages of disease have best survival and those with each higher stage have incrementally worse survival curves; multiple systems developed for mesothelioma; none have stratified patients well; staging systems proposed by Butchart, who published among first series of extrapleural pneumonectomy for malignant pleural mesothelioma in 1976; staging system also proposed by Brigham and Women's Hospital, AJCC, and UICC (Union for International Cancer Control); joint workshop sponsored by the International Association for Study on Lung Cancer and International Mesothelioma Interest Group; formed basis of original AJCC TNM staging system; continues to be updated for modern versions; based on data reported from multiple institutions through international registries; AJCC system currently in 8th edition

T stage: T1 disease limited to pleura; includes visceral, parietal, mediastinal, and diaphragmatic surfaces; T2 tumors involve all four plus diaphragmatic muscle or lung parenchyma; T3 tumors locally advanced but resectable; include all four pleural surfaces in addition to endothoracic fascia, which represents most internal surface of chest wall, mediastinal fat, solitary soft tissue focus in chest wall itself, and tumors invading into but not through pericardium; T4 tumors unresectable; include tumors with diffuse chest wall invasion, tumors invading through diaphragm, contralateral chest invasion by direct extension, and invasion into mediastinum, spine, or through and into pericardium

Nodal stage: N1 nodes — ipsilateral hilar mediastinal nodes; include internal mammary, diaphragmatic, and intercostal nodes; N2 nodes — represent contralateral mediastinal or any supraclavicular node

M stage: any distant metastasis represents M1 disease

Treatment: role of individual components controversial; overall, multi-modality therapy thought to prolong survival; no proven benefit to surgical resection; consensus that surgery recommended with addition of adjuvant therapies

Surgery: two possible operations; extrapleural pneumonectomy — en bloc resection of pleura, lung, diaphragm, and pericardium; pleurectomy decortication — sometimes called radical pleurectomy or extended pleurectomy decortication; involves resection of parietal and visceral pleura with or without pericardium and diaphragm, depending on extent of disease involvement; pleurectomy decortication better in terms of short term outcomes, such as mortality and morbidity, and better long-term survival; no added benefit demonstrated for added morbidity and risk of mortality seen with extrapleural pneumonectomy

Management: surgery alone not enough to treat disease; local recurrence and progression common; adjuvant radiation, chemotherapy, and immunotherapy often used in combination; intraoperative adjuncts have demonstrated promise; heated chemotherapy, betadine irrigation, argon beam or other bipolar coagulation of entire surfaces, and photodynamic therapy; radiation after pleurectomy decortication has also shown promise; represents highly

specialized technique due to remaining lung and toxicities and organs at risk in radiation port, including lung, spine, heart, and esophagus in large field; chemotherapy involves combination of cisplatin and pemetrexed; shown in 2004 publication to be superior to cisplatin alone; other regimens include gemcitabine, vinorelbine, and maintenance pemetrexed; newest systemic therapy includes addition of bevacizumab or pembrolizumab with promising results; role of immunomodulation checkpoint blockade, priming with tumor-targeted vaccines, and more being evaluated in ongoing studies; certain tumors show high rate of mesothelin expression; studies of anti-mesothelin antibodies also ongoing; modern therapies have converted once universally fatal disease into chronic illness with long term survivors

Anaplastic Thyroid Cancer

Overview: extremely rare tumors; aggressive; nearly 100% fatal

Epidemiology: median survival of 3 to 7 months; 5-yr survival of 5% to 14%; 65 average age at presentation; <10% of patients under age 50; stark contrast to well-differentiated thyroid cancers; women 60% to 70% of patients; 20% have prior history of some other differentiated thyroid tumor; 20% to 30% have coexisting differentiated thyroid tumor at time of presentation; up to 50% have history of multinodular goiter; highest incidence of disease in regions of endemic goiter

Presentation: most patients present with symptomatic and often fixed neck mass with pain and tenderness; may be invasion into airway or esophagus; patients present with dyspnea, dysphasia, hoarseness from tracheal compression or recurrent laryngeal nerve involvement, cough, hemoptysis, chest pain, SVC syndrome, and symptoms from metastases depending on organ involved; rapid growth frequent; can sometimes cause hyperthyroidism from thyroiditis; 90% of patients present with at least locally advanced disease at time of presentation; includes perithyroid tissue, nodes, larynx, trachea, esophagus, tonsil, arch vessels in neck or even mediastinum; up to 50% of patients have distant metastases at time of presentation; rarely patients seen with distant metastases and no thyroid primary; metastatic sites include lung and pleura in 90% of patients, bone in 5% to 15% of patients, brain in 5% of patients; can also include skin, liver, kidney, pancreas, heart, or adrenals

Biology: undifferentiated thyroid follicular epithelial neoplasm; morphology characterized by spindle cell, pleomorphic giant cell, and/or squamoid features; tumors have numerous mitotic figures, atypical mitosis, and sometimes extensive necrosis; immunohistochemistry generally shows no staining for TTF1, PAX8, or thyroglobulin except in cases of associated well-differentiated tumor with lesion; 10% of Hürthle cell patients have concomitant anaplastic thyroid cancer within tumor; other tumors have been reported to undergo transformation from differentiated thyroid cancer to anaplastic; theory that well-differentiated thyroid tumors can undergo dedifferentiating events; may involve activating mutations in BRAF and/or RAS pathway; mutations seen in differentiated thyroid cancer and anaplastic thyroid tumors; thought to occur early in causal pathway of transformation; mutations seen in anaplastic thyroid cancer not seen in well-differentiated tumors thought to be further down in causal pathway; include P53, 16B, catenin, beta 1, and PIK3CA

Workup: staging often demonstrates advanced disease; anaplastic thyroid cancer must be distinguished from poorly differentiated thyroid tumors, medullary thyroid cancer, lymphoma, melanoma, and sarcoma; most patients will have had neck ultrasound as part of initial diagnosis; serum thyroglobulin helpful to determine if metastases related to anaplastic thyroid cancer or concomitant differentiated tumor; treatment for these differ; PET-CT will show avidity in primary tumor; can help assess for local and distant spread; hypermetabolic metastatic sites associated with anaplastic thyroid cancer; lower avidity seen with well-differentiated tumors; details of local invasion of structures require CT of neck and chest with contrast; brain MRI required to assess for brain metastases

Staging: 8th edition of AJCC UICC TNM staging system; includes anaplastic thyroid in all T categories; any patient with anaplastic thyroid cancer considered stage 4 within AJCC system; stage 4 divided into 4a, 4b, and 4c; stage 4a — all patients without nodal disease but with anything from T1 to T3a tumor; stage 4b — any patients with T3b tumor and T4 tumors without distant metastases or earlier T stage tumors with N1 node; stage 4c patients have distant metastases

Treatment: consists of multiple therapies with no true standard regimen; surgery recommended in rare case disease resectable and localized; must be followed with chemotherapy, radiation, or both; chemo-radiation used for unresectable disease; salvage resection can be considered with good response to treatment; treatment with high-dose radiation found superior to palliative doses using hyperfractionation for definitive therapy; chemo-radiation for locally advanced disease includes regimens with doxorubicin and/or a taxane; for common situation of patients with metastatic anaplastic thyroid cancer, cisplatin and doxorubicin found more effective than doxorubicin alone; paclitaxel has shown some response; generally none of these regimens have had impact on long-term survival; ongoing studies evaluating tyrosine kinase inhibitors; currently targeted therapies for patients with BRAF, TSC1, TSC2, ALK, and NTRK mutations have shown promise; combination therapy with dabrafenib and trametinib approved by FDA in 2018 for patients with unresectable and/or advanced disease with BRAF mutation, based on favorable results in phase 2 trial and results of earlier studies; palliation of symptoms main goal of treatment; often includes ability to protect airway; sometimes requires stent or tracheostomy; access to nutrition may involve feeding tube placement; very difficult disease to treat; important to manage patient comfort and discuss end of life issues

Suggested Reading

Berghmans T, et al: Systemic treatments for thymoma and thymic carcinoma: a systematic review. *Lung Cancer.* 2018 Dec;126:25-31; **Chintakuntlawar AV, et al:** Diagnosis and management of anaplastic thyroid cancer. *Endocrinol Metab Clin North Am.* 2019 Mar;48(1):269-84; **Kindler HL, et al:** Treatment of malignant pleural mesothelioma: American society of clinical oncology clinical practice guideline. *J Clin Oncol.* 2018 May;36(13):1343-73.

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Kidney Cancer

Brian I. Rini, MD, *Professor of Medicine, Lerner College of Medicine of Case Western Reserve University, and Leader, GU Program, Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Epidemiology: kidney cancer (renal cell carcinoma [RCC]) relatively uncommon; eighth most common cancer in US (~35,000 cases per yr); `170,000 cases globally each yr; ~70% of cases localized, ~30% metastatic disease at presentation; ~25% of localized cases locally advanced (includes extension into renal sinus, perinephric fat, or rarely, involvement of lymph nodes)

Histology: wide range of tumors, not just 1 type of tumor; most common type clear cell RCC (~75%-80%); all others termed non-clear cell, which includes subtypes such as papillary, chromophobe, and medullary cancer; because RCC relatively rare, non-clear cell rare subtype of rare disease; this lecture mostly about clear cell RCC, recognizing that in localized disease, non-clear cell handled same way as clear cell; for metastatic non-clear cell RCC, no specific therapies approved; tend to borrow drugs that have been tested and approved for clear cell and apply to non-clear cell RCC

Risk factors: RCC occurs predominantly in males (2- to 3-fold more common in males than in females); generally occurs in patients in 50s and 60s, although range includes 30s to 80s; few identified risk factors; smoking most commonly identified risk factor, but weak (2-fold risk in smokers compared with nonsmokers); most RCC not inherited; rare syndromes associated with various histologic subtypes; most common inherited form von Hippel-Lindau disease (VHL), which leads to vascular tumors including clear cell RCC; therapeutics in metastatic disease largely based on understanding of VHL biology; other subtypes of RCC can occur in hereditary syndromes including hereditary papillary renal cell and Birt-Hogg-Dubé syndrome, which can lead to chromophobe kidney tumors; these syndromes relatively rare but each has specific genetic association; chemical exposure to benzene and other degreasers used mostly in 1950s and 1960s; most RCC not inherited, most patients do not have identifiable risk factor

Biology: VHL gene on short arm of chromosome 3, can be mutated or methylated in most sporadic kidney-cancer patients; loss of gene function results in loss of ability to degrade transcription factor hypoxia-inducible factor (HIF); mutation results in accumulation of HIF, transcription factor leads to upregulation of various target genes, most notably vascular endothelial growth factor (VEGF); in last decade, drugs designed to inhibit VEGF or block its receptor have become standard of care for this disease

Immune-infiltrated nature of RCC: likely accounts for its responsiveness to immunotherapy; less well understood mechanistically, but immunotherapies have always been part of treatment of RCC

Localized treatment: relatively straightforward; small renal masses may sometimes be observed; more commonly, patients undergo partial or radical nephrectomy, less commonly ablative techniques (*eg*, cryoablation); most patients undergo surgery; risk of recurrence determined by standard histopathologic criteria such as stage and grade; adjuvant therapy in RCC also relatively straightforward

Clinical trials: for decades, no appropriate adjuvant treatment because every trial had proven negative, mainly because agents used largely inactive; VEGF-targeted therapies developed for patients with metastatic disease, but then applied in recent large phase 3 trials in adjuvant setting; of 4 trials reported to date, 3 negative (no advantage in disease-free survival [DFS] or overall survival [OS]); *S-TRAC trial* — randomized patients with T3 or T4 resected localized RCC to either sunitinib (oral VEGF receptor inhibitor) standardly given on schedule of 50 mg/day, 4 wks on, 2 wks off, or placebo; trial showed advantage in median DFS (5.6 yrs in placebo arm and 6.8 yrs in sunitinib arm) with significant hazard ratio (HR) 0.76 (P=0.03); trial criticized based on what was felt to be relatively marginal DFS benefit accompanied by typical toxicities of sunitinib (hypertension, fatigue, diarrhea, hand-foot syndrome, mucositis); no OS benefit; sunitinib approved for use in US (but not elsewhere) for adjuvant therapy of high-risk patients; sunitinib used sparingly in clinical practice, mostly in younger patients with higher-risk disease

Treatment of metastatic disease with debulking nephrectomy: concept of removing primary tumor even when disease has spread to distant organs; practice rooted in trials in 1980s showing improved survival compared with systemic therapy (then low-dose interferon); this practice revisited recently in era of targeted therapy; recent noninferiority trial, CARMENA (reported at American Society of Clinical Oncology [ASCO], published in *New England Journal of Medicine*) randomized patients with de novo metastatic disease to either debulking nephrectomy followed by sunitinib or sunitinib alone; trial had inadequate and slow accrual, but deemed positive because did not show difference; thus, sunitinib alone shown to be noninferior to debulking followed by sunitinib; trial also criticized because many patients poor risk (*ie*, kind of patients who may not have undergone nephrectomy anyway); nonetheless, most experts believe role exists for debulking nephrectomy in carefully selected patients

who have good performance status, do not have multiple adverse risk factors, and have bulk of tumor in their primary site; still questionable

Surgery for metastases: for patient who had nephrectomy for RCC 3 years prior and now has solitary lung nodule, commonly advise resection of metastasis followed by observation; ~10% of patients with RCC get resection of limited metastatic disease, observed, and may have resection of second or even third metastases; type of patient who does better with this approach, those who have longer disease-free interval from nephrectomy to metastatic disease; also good for patients with resectable metastatic disease (*eg*, lung nodule but not pancreatic mass or lymph nodes in abdomen)

Stereotactic radiosurgery: increasingly used for patients with limited metastatic sites; however, traditional surgery has longest track record and most historical data to support

Systemic therapy: if patient not or no longer candidate for further surgical resection (most patients), candidate for systemic therapy; RCC has diverse biology; whereas some patients have indolent, slow-growing disease, others have quite rapid disease; 1 trial and many retrospective series supporting role of observation of patients with metastatic disease; data reported in *Lancet Oncology* few years ago in prospective observational study (mean follow-up, 15 mos) in patients with indolent metastatic disease; generally accepted that not all patients need immediate treatment; emerging role of immunotherapy with potentially curative possibilities might change that paradigm, but important concept to know

VEGF-targeted therapies: in last decade until recently, VEGF targeted therapy standard of care; sunitinib and pazopanib most commonly used initial agents, with objective response (OR) 30%, PFS 10 mos to 12 mos, OS 2 yrs to 2.5 yrs; now changing in era of immunotherapy, although most patients still receive VEGF-targeted therapy as initial therapy

Immunotherapy: *interleukin-2 (IL-2)* — historically, high-dose IL-2 first drug approved for RCC and first immunotherapy (approved in 1992); approved because small fraction of patients (5%-7%) could achieve durable complete response (CR), *ie*, cure; still used today sparingly; never used much because of significant toxicity; used even less today because many other approved agents; still treatment option for young, healthy patients; *nivolumab* — PD-1 inhibitor; first modern immunotherapy approved for refractory disease; showed OS advantage compared with mTOR inhibitor everolimus; very quickly, nivolumab drug moved into frontline treatment in combination with ipilimumab (CTLA-4 inhibitor) because of combination data in melanoma

CheckMate 214: pivotal trial, late 2017; led to approval (April 2018) of ipilimumab plus nivolumab (ipi/nivo) in patients with metastatic RCC; previously untreated patients with advanced RCC randomized to either ipi/nivo (4 combination doses once every 3 wks, then monthly infusion of nivolumab only) compared with standard sunitinib dose; trial unique, focused on intermediate- and poor-risk patients; *risk stratification* — prognostic risk in RCC based on 2 main schemas (Memorial Sloan Kettering and International Metastatic Database Consortium [IMDC]); similar in generally categorized patients, but not identical; IMDC used more commonly, used in CheckMate 214 trial; IMDC looks at 2 clinical factors (performance status and time from diagnosis to metastatic disease) and 4 laboratory factors (calcium, hemoglobin, neutrophil count, and platelet count); depending on number of adverse factors, patients categorized as having favorable, intermediate, or poor risk; patients have different outcomes in various settings and with various drugs; *CheckMate 214 specifics* — enrolled all patients, but primary endpoint just outcomes for intermediate- and poor-risk patients; showed significant advantage in OS both in intermediate-/poor-risk subset and in overall group of patients (intention-to-treat); medians not even been reached in this trial; OS advantage in all patients ~0.7 and in intermediate- and poor-risk patients HR (updated) 0.66; thus, significant and substantial survival advantage to combination immunotherapy upfront in RCC compared to single-agent VEGF-targeted therapy; one quirk of this trial, patients with favorable risk seem to do better with sunitinib, probably because they have more angiogenesis-driven disease (as known from other datasets); this gap has narrowed over time, but most people view these data as supporting sunitinib or similar drug for good-risk patients and ipi/nivo for intermediate- and poor-risk patients (though somewhat debated); however, for intermediate- and poor-risk patients, ipi/nivo would be standard of care based on survival advantage among currently approved agents

PD-L1 expression: PDL-1, protein that can be expressed on both tumor and immune cells; much data in different diseases about usefulness; in RCC, probably prognostic; patients whose tumors express PD-L1 generally have worse outcomes and respond less well to VEGF-targeted therapy; in CheckMate 214, PD-L1-positive patients had somewhat enriched response with higher OR and CR rates; however, PD-L1–negative patients could still have CR, and still showed improved survival compared with sunitinib; *lecturer's opinion* — in clinical practice, PD-L1 expression level not useful in RCC; does not order it because not sure what to do with result (does not impact his treatment)

New therapies: several new therapies emerging for RCC, most notably those that combine 2 main pillars of treatment (*ie*, VEGF-targeted therapy and immunotherapy)

3 phase 3 trials reported to date using various combinations: bevacizumab (VEGF ligand binding agent) plus atezolizumab (PD-L1 inhibitor); axitinib (small-molecule VEGF receptor inhibitor) plus pembrolizumab (PD-L1 inhibitor); axitinib plus avelumab (PD-L1 inhibitor); 3 trials very similar, taking combination regimen and randomizing patients to either that combination regimen or to sunitinib monotherapy; trials accrued over similar time, with similar distribution of patients with respect to risk and where accrued; all data reported within last 6 mos; results differed somewhat by regimen, but all showed advantage in response rate in PFS vs sunitinib

Combination regimens: only axitinib-plus-pembrolizumab combination has shown OS advantage; axitinib combination regimens expected to be approved; benefit from these newer combination

regimens seem to occur across risk groups; unlike ipi/nivo in CheckMate 214, (debated in favorable-risk patients), does not appear to be debate in combinations, probably because VEGF agent included in regimen; in axitinib-plus-pembrolizumab study, benefit appeared regardless of PD-L1 expression (imperfect biomarker in RCC); in next few months, expect axitinib/avelumab and axitinib/pembrolizumab combinations to be approved for frontline treatment of metastatic RCC; then whether to give ipi/nivo or axi/pembro in frontline RCC will be debated; no clear answer because no head-to-head trials and may never be (each has its own pluses and minuses); people discuss things like CR rate and durability of response, ability to treat favorable-risk patients, and toxicity profile; enough differences between regimens that, over time, different patients will get different regimens based on some of those strengths and limitations; over course of next year, vast majority of metastatic RCC patients will get some form of immuno-oncology (IO)–based combination therapy (includes ≤1 IO agent and either another IO agent or VEGF-targeted agent)

Immunotherapy toxicities: important when treating metastatic RCC; cause inflammatory toxicities generally within first several weeks of treatment, but can occur much later; any organ can become inflamed, most commonly skin (rash), gut (diarrhea), and liver (hepatitis); patients need to be recognized and treated promptly with oral or intravenous steroids; patients can get sick quickly; perform appropriate diagnostic testing depending on organ involved; IO/IO regimens and IO/VEGF regimens will have different tolerability and toxicity profiles

Refractory RCC: term "refractory" will change now that frontline treatments changing; for patients who have received combination regimen first-line will get VEGF-targeted monotherapy second-line; emerging retrospective data and prospective trials in progress; several VEGF agents approved and in common use; after initial IO-based regimen, likely empiric sequence of monotherapies would be standard of care; most patients with RCC probably get ~3 therapies on average, even though now 12, and probably soon 14, regimens approved; unfortunately, after 2 or 3 regimens, patients generally worn out and probably not in shape to get more therapies; some IO-based regimens may be curative; CR rate 9% with ipi/nivo, 6% with axi/pembro; additional patients who have partial response may also be cured but still have some radiographic abnormalities; not sure of number, lecturer estimates ≤10%, but maybe 15% or 20% of patients who get one of these IO-based regimens upfront can have long-term disease control and potentially be cured; further follow-up needed

Summary

RCC, disease of men in their 50s and 60s; many people do not present with symptoms, but cancer found incidentally on scan done for another reason; less common to present with symptoms like flank pain and hematuria; patients diagnosed either because they undergo nephrectomy or get biopsy of metastatic site; common metastatic sites include lung and lymph node, but RCC can go anywhere, including to breast, bladder, thyroid, tongue, etc; if you see odd site of metastasis, RCC on differential; patients with localized disease generally undergo surgery to remove primary tumor; sunitinib adjuvant treatment option for higher-risk patients, although not commonly used based on limited data of effectiveness and other trials that have been negative; ongoing trials now of IO agents in adjuvant setting; treatment of patients with metastatic disease, initially consider surgical approach to remove kidney or metastatic sites; observation may be initial approach; many systemic therapies are available; most commonly, anti-angiogenic agents and immunotherapy used, transforming how we treat this disease; median survivals will likely be in range of ≥3.5 yrs to 4 yrs range; median survivals used to be ~1 yr in era of old immunotherapy with IL-2 and interferon; treatment has advanced, but long way to go, since most patients still not cured

Suggested Reading

Lenis AT et al: Adjuvant therapy for high risk localized kidney cancer: emerging evidence and future clinical trials. *J Urol.* 2018;199(1):43-52; **Motzer RJ et al:** Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277-90; **Ravaud A et al:** Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med.* 2016;375(23):2246-54.

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Localized and Locally Advanced Prostate Cancer

Peter C. Albertsen, MD, *Professor of Surgery, Chief and Program Director, Division of Urology, University of Connecticut Health, Farmington, CT*

Background: prostate cancer has risen from relatively rare clinical entity to most commonly diagnosed malignancy in men in past 150 yrs; Thompson reported on 18 cases of prostate cancer in classic monograph published in 1852; microscope improvements in late 1800s resulted in multiple additional case-series reports; by 1891, von Recklinghausen recognized primary lesion in prostate often small and metastatic disease had predilection for bone; no standard way of describing prostate cancer for next 70 yrs; institutions such as Mayo Clinic and Johns Hopkins Hospital had individual grading systems; most pathologists recognized men with firm prostates often had prostate cancer and in many cases, disease progressed slowly, if at all; many men died with, rather than from, prostate cancer; in 1996, Sakr estimated ≤30% of men in 30s and >70% of men in 70s harbored prostate cancer

Gleason score: pathologist Donald Gleason recognized prostate cancer presented in many histologic forms, from minor changes in glandular structure to sheets of cells barely recognizable as arising from prostate; documented 9 different histologic growth patterns; presented schematically in classic diagram as Gleason patterns 1 through 5; classified primary and secondary growth patterns; score highly predictive of subsequent mortality; grading system modified; pathologists no longer utilize Gleason patterns 1 and 2; cribriform artifact associated with Gleason pattern 3 moved to pattern 4; pathologists moving away from Gleason 3+3 to lexicon Gleason grade group; scoring system most powerful predictor of long-term outcomes among men with newly diagnosed localized prostate cancer

Gleason grade groups: now 5 groups; grade group 1 (old Gleason 3+3), well-differentiated disease; grade group 2 (old Gleason 3+4), well- to intermediate disease; grade 3 (old Gleason 4+3), intermediate disease; grade 4 (old Gleason 4+4 patterns), high-grade disease; grade 5, most poorly differentiated cancers, basically any cancer containing Gleason pattern 5

Treatment: fundamentally, 3 treatments; surgery; ablation with radiation or cryosurgery; chemotherapy, *eg*, antiandrogen therapy

Radiation: discovered in 1895; radium discovered in 1898; radium institutes founded in United States and Europe within 10 yrs; men with locally advanced prostate cancers occasionally presented with obstructive urinary symptoms; urologist Barringer implanted radium pellets into periprostatic tissue (basically, inserted glass capillary needles filled with radon gas, first decay product of radium); needles placed via perineum using finger in rectum as guide; needles left in place for 4 hrs to 6 hrs; painful tissue necrosis ensued (glass does not filter beta and soft gamma rays); only 36 of 352 patients receiving radon implants lived for 5 yrs following treatment; subsequently developed gold-encapsulated permanent capillary implant; became known as seeds

Surgery: Hugh Hampton Young described first perineal radical prostatectomy in 1904; developed exaggerated lithotomy position, table, and retractor for procedures; mortality >10%; patients rarely presented with prostate nodules or truly localized disease; operation primarily used to perform prostate biopsies or implant radium seeds

Endocrine therapy: Charles Huggins and colleagues demonstrated in 1941 that metastatic prostate cancer responded to endocrine manipulation; radical orchiectomy became standard of care; evolved into medical use of estrogen, specifically diethylstilbestrol; clinicians argued whether treatment simply palliative or curative; for many men, disease seemed to disappear for several yrs before recurring with widespread bony metastases; men frequently responded for minimum of 3 to 4 yrs before having disease progression; in 1960s, VA Cooperative Urological Oncology Group attempted to identify appropriate treatment for localized and advanced prostate cancer; insufficient number of patients with localized disease to accrue to surgical or radiation studies; established use of diethylstilbestrol 3 mg daily as standard of care; confirmed patients treated with early androgen deprivation therapy did not have survival benefit compared with those receiving it at time of symptom recurrence

Hypothalamic control: control of pituitary function demonstrated by Andrew Schally; characterization of gonadotropin-releasing hormone and analogs paved way for modern medical therapy involving luteinizing hormone-releasing hormone (LHRH) agonists and antagonists; drugs primarily used for men with advanced prostate cancer; also have role in men with locally advanced disease

Halstedian paradigm of cancer progression: cancers arise within target organ, grow for some time, eventually migrate via blood or lymphatics to distant sites; implies cancer can be cured if disease found early enough and removed by surgery or ablated by radiation, cryosurgery, or other technique; paradigm not necessarily true for prostate cancer

Primary radiation: Malcolm Bagshaw challenged paradigm in 1965 by offering definitive radiation therapy as primary treatment for localized prostate cancer; used

360° rotational field, with patient standing within field; prostate localized by placing Foley catheter in bladder and filling bladder with diatrizoate meglumine and diatrizoate sodium solution (Gastrografin); barium placed into rectum; 7000 cGy given over 6-wk period; Bagshaw recognized importance of accurately staging patients prior to treatment; recognized prostate cancer spread to pelvic lymph nodes; employed lymphangiogram or open lymph node dissection to ascertain if patients had positive lymph nodes; whole-pelvis radiation given when nodes positive; original transperitoneal approach with widespread node dissection led to high rate of small-bowel obstruction; technique often resulted in bowel and bladder injury; patients often had radiation cystitis, resulting in bleeding and increased urinary frequency, or radiation proctitis, leading to rectal bleeding, passing mucus, diarrhea; Bagshaw improved on approach and created renewed interest in brachytherapy; offered patients extended pelvic node dissection; allowed for better assessment of extent of tumor within prostate; improved ability to implant radioactive seeds; technique used in 1970s and 1980s; abandoned because of high rate of recurrence

Radical prostatectomy: received attention in mid-1980s; previously described in United Kingdom; not used frequently because of difficulties controlling bleeding; Patrick Walsh (Johns Hopkins Hospital) developed method of controlling dorsal vein complex; allowed for drier, more precise resection; identified neurovascular bundles involved with erectile function and promised patients improvements in postoperative continence and erectile dysfunction; neither Bagshaw, Whitmore, nor Walsh conducted randomized trials to prove efficacy of techniques; uncertain how treatments altered outcome of men with newly diagnosed disease

Prostate-specific antigen (PSA) testing: in 1987, Tom Stamey described serum assay that could measure prostate volume; 4 yrs later, William Catalona proposed using PSA as screening tool; showed use of PSA increased likelihood of identifying prostate cancer compared with traditional digital rectal examination or transrectal ultrasound; greeted with enthusiasm within United States; within 3 yrs of PSA testing, incidence of prostate cancer in United States tripled; most urologists and radiation therapists recommended treatment (prevailing view held prostate cancer uniformly fatal if allowed to progress); perspective not accepted worldwide; skepticism especially in Sweden, where many clinicians recognized prostate cancer appeared to progress slowly in many patients

Clinical Studies

Johansson: recruited consecutive patients in large area within Sweden; patients had early-stage T2 disease; outcomes tracked over time; 223 patients accrued by 1984; followed for 21 yrs; published findings in 2004; found most low- to intermediate-grade prostate cancers diagnosed at early stage have indolent course; local tumor progression and aggressive metastatic disease may develop in long term; half of patients detected following transurethral resection of the prostate (TURP) for benign prostatic enlargement; half detected because of palpable nodule; none identified by PSA testing; two-thirds had well-differentiated tumors, 30% had moderately differentiated disease; only 9 patients had poorly differentiated prostate cancer; of those, 5 died from prostate cancer; median age 72 yrs; *findings* — concluded radical treatment indicated for men with well and moderately differentiated disease with estimated life expectancy of ≥15 yrs

Albertsen: constructed simulation model presented to Jack Wennberg at Dartmouth University Outcomes Group; published markup model documenting surgical or radiation intervention carried at best modest benefit within 10 to 15 yrs of diagnosis; model based on minimal data; proceeded with population-based observational study concerning importance of Gleason scoring; Connecticut has oldest tumor registry in United States; integral part of surveillance system of National Cancer Institute; *study design* — population of 767 men identified from Connecticut Tumor Registry database; Connecticut residents diagnosed with prostate cancer between 1971 and 1984; 717 died before October 2004; median observation 24 yrs; 87% of patients followed for >20 yrs; charts abstracted onsite to confirm date of diagnosis, metastatic evaluations, method of treatment, associated comorbidities; excluded patients undergoing surgery, external beam radiation, brachytherapy, or those with metastatic disease at time of diagnosis; patients with other concomitant cancers and those surviving <6 mos also excluded; study personnel performing chart abstraction blinded to long-term outcome of patients recorded in Connecticut Tumor Registry; *diagnosis and staging* — most original slides did not have scoring system; slides resubmitted to referee pathologist Donald Gleason for rereading (blinded to long-term outcomes); standardized grading performed using original Gleason classification system; active staging information lacking for many men; none had information concerning PSA concentrations; ≈71% diagnosed following TURP or simple open prostatectomy, 26% diagnosed by needle biopsy, 3% diagnosed by other methods

Results: published in 2005; include figure showing competing risk of deaths following diagnosis of prostate cancer; few men with low-grade tumors had disease progression leading to prostate cancer death within 20 yrs of diagnosis; most men with high-grade disease died from prostate cancer regardless of age at diagnosis; among relatively healthy men, 26%, 15%, and 8% survived at 15, 20, and 25 yrs, respectively; study agreed with Johansson that men with well-differentiated prostate cancers rarely die from this disease while men with poorly differentiated tumors frequently die within 5 to 10 yrs of diagnosis, often despite aggressive interventions; men with moderately differentiated tumors (*ie*, Gleason grade group 2, possibly 3) have greatest variation in outcomes; those most at risk of dying have life expectancy >10 to 15 yrs

PSA testing:

Prostate Cancer Prevention Trial (PCPT): phase 3, randomized, double-blind, placebo-controlled study; evaluated whether finasteride could reduce prevalence of prostate cancer during 7-yr period of treatment; *study protocol* — all participants had to undergo end-of-study prostate biopsy; not previously diagnosed with prostate cancer; *study goals and outcomes* — original study powered to detect 25% reduction in prostate cancer; assumed prevalence of disease would be 6% within study population; at conclusion, 24% of men in control arm had been diagnosed with prostate cancer (4 times

expected rate); most had no clinical evidence of disease; biopsied purely because of study protocol; of 449 men identified as having cancer on end-of-study biopsy, 80% had Gleason score 6, 13% had Gleason score 7, <2% had Gleason score 8 or 9; *findings* — study revealed extensive pool of well-differentiated prostate cancer that exists in normal healthy male population; authors demonstrated biopsy-detectable prostate cancer not rare among men with PSA levels of ≤4.0 ng/mL (historically considered normal); >25% of men with PSA values between 3.1 ng/mL and 4.0 ng/mL harbor foci of prostate cancer

Prostate, Lung, Colon, and Ovary (PLCO) Cancer Screening Trial: initiated in 1993 in United Sates; randomized 76,683 men aged 55 to 74 yrs in 10 centers; 50% assigned to intervention arm, 50% assigned to control arm; men in intervention arm received PSA blood test and digital rectal exam at baseline; annual digital rectal exam for ≥3 yrs and annual PSA for 5 yrs more; PSA results classified as abnormal if >4 ng/mL; participants and physicians notified in writing of any suspicious abnormality on screening; diagnostic process following positive screen managed by primary care physician and not dictated by trial; *findings* — extended 15-yr mortality results reported recently; total of 4250 prostate cancers diagnosed in intervention arm, 3815 in control arm; 6.0% died of prostate cancer in intervention arm, 6.4% in control arm; median duration of follow-up 18 yrs; <10% overall likelihood of death from prostate cancer within 13 yrs of diagnosis

Criticisms: men in both control and intervention arms received PSA testing prior to enrollment and frequently during study; many men with elevated serum PSA never underwent transrectal ultrasound and prostate biopsy and did not receive treatment; trial underpowered; conclusion of no difference suspect; study did show that PSA testing clearly identified more prostate cancers than control group, but does not translate into difference in prostate cancer mortality

European Randomized Study of Screening for Prostate Cancer (ERSPC) trial: multicenter randomized screening trial; main aim to compare mortality from prostate cancer in intervention group with screening control group (no intervention); initiated in 1993 in Netherlands and Belgium; Sweden, Finland, Italy, Spain, and Switzerland joined between 1994 and 1998; eligible participants included men aged 50 yrs to 74 yrs at time of randomization; subsequently screened every 4 yrs (every 2 yrs in Sweden); median follow-up from diagnosis of prostate cancer 6.4 yrs in intervention group, 4.3 yrs in control group; *findings* — 41% of screen-detected cases low-volume, low-grade prostate cancers unlikely to result in prostate cancer mortality; at time of last follow-up, clinically significant difference between number of cancers identified in screening vs control arm; 1 patient for every 1000 screened would result in saving prostate cancer life

US Preventive Services Task Force (USPSTF) study: conducted to assess efficacy of PSA testing; evaluated PLCO and ERSPC trials and other trials concerning PSA testing; showed ERSPC trial actually consisted of 6 trials, of which only 2 positive; *findings* — only Swedish trial significantly positive; Finland and Italian sites negative; Netherlands site clinically significant only at last follow-up; concluded that, for every 5 men screened, 1 likely to be spared of prostate cancer death; lowering of prostate cancer mortality from 5 to 4 for every 1000 screened comes at high price; ≥100 of these men would have to undergo procedures such as radical prostatectomy or radiation therapy to effect cure; morbidity associated with those procedures includes risks of bowel, bladder, and sexual dysfunction deemed higher than gain achieved by saving 1 life; recommended against PSA testing

Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP trial): largest of screening trials; published in 2018; consisted of >400,000 men randomized to intervention vs control group; initiated in early 1990s, when prostate cancer testing in United Kingdom infrequent; all subjects received only single PSA test; 189,000 in intervention group, 219,000 in control group; only 75,000 (40%) in intervention group attended PSA testing clinic; only 36% underwent PSA testing; 6857 (≈11%) had PSA level between 3.0 ng/mL and 19.9 ng/mL; 5850 of those had prostate biopsy; after median follow-up of 10 yrs, 549 died of prostate cancer in intervention group, 647 in control group; number of men diagnosed with prostate cancer higher in intervention compared with control group; more prostate cancer tumors with Gleason grade 6 or lower identified in intervention group *vs* control group; *findings* — after 10 yrs of follow-up, no difference in all-cause mortality or prostate cancer–specific mortality between groups; confirmed prostate cancer screening done even once dramatically increases incidence of Gleason 6 disease, causes slight increase in Gleason 7 or grade group 2 disease, and hardly identifies high-grade disease at all; after 12 yrs of follow-up, 4 men for every 1000 screened died from prostate cancer (in both control and intervention groups); confirmed findings estimated earlier by USPSTF and ERSPC trials

Treatment and intervention studies:

Scandinavian Prostate Cancer Group 4 (SPCG-4) trial: between 1989 and 1999, 695 men with early prostate cancer randomly assigned to watchful waiting or radical prostatectomy; followed through 2012; during 23 yrs of follow-up, 200 of 347 assigned to surgery and 247 of 348 assigned to watchful waiting died; of these deaths, 63 in surgical group and 99 in watchful waiting group were from prostate cancer (relative risk reduction 0.56, absolute difference 11 percentage points); 8 needed to treat to prevent 1 death; in radical prostatectomy group, only 1 man died after surgery; *findings* — study also showed androgen deprivation therapy used in fewer patients undergoing prostatectomy (difference of 25 percentage points compared with those in watchful-waiting group); benefit of surgery with respect to death from prostate cancer largest in men aged <65 yrs and in those with intermediate-risk prostate cancer; radical prostatectomy associated with reduced risk of metastasis among older men (relative risk 0.68); authors concluded that extended follow-up confirmed substantial reduction of mortality after radical prostatectomy; number needed to treat to prevent 1 death continued to decrease when treatment modified according to age at diagnosis and

tumor risk; however, large proportion of long-term survivors in watchful-waiting group never required palliative treatment

Prostate Cancer Intervention Vs Observation Trial (PIVOT): enrollment from 1994 to 2002; 731 men recruited from 44 Department of Veterans Affairs sites and 8 National Cancer Institute sites; patients medically fit for radical prostatectomy and had histologically confirmed clinically localized prostate cancer; median follow-up 10 yrs; 171 of 364 men (47%) assigned to radical prostatectomy died, compared with 50% assigned to observation; prostate cancer death in 21 men (5.8%) assigned to radical prostatectomy, compared with 31 (8.4%) assigned to observation; effect of treatment on all-cause and prostate-cancer mortality did not differ among patients according to age, race, coexisting conditions, or patient performance status; closer look at study population shows median age at diagnosis 67 yrs; one-third of patients African American; half diagnosed on basis of elevated serum PSA value; median PSA value 7.8 ng/mL; based on central pathologic review, 52% of patients had Gleason 6 disease or lower; 33% classified as having low-risk disease; *findings* — after 12 yrs of follow-up, radical prostatectomy group associated with nonsignificant absolute reduction in mortality (3 percentage points compared with observation); metastases occurred in 17 men assigned to radical prostatectomy compared with 39 assigned to observation; authors concluded that, among men with localized prostate cancer detected early in era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality compared with observation through ≥12 yrs of follow-up; absolute differences <3 percentage points; trial findings particularly robust for men with PSA value <10 ng/mL; group less well represented in Scandinavian study; authors supported observation for men with localized prostate cancer, especially those with low PSA value and those with low-risk disease

SPCG-7 trial: conducted in Scandinavia; randomized men from 47 centers in Norway, Sweden, and Denmark between 1996 and 2002; 875 patients with locally advanced cancer (*ie*, T3 disease) with PSA <70 ng/mL; centrally randomized by computer to endocrine treatment alone consisting of 3 mos of total androgen blockade followed by continuous endocrine treatment using flutamide or same endocrine treatment combined with radiation therapy; primary endpoint prostate cancer–specific survival; analysis by intention to treat; *findings* — after median follow-up of 7.6 yrs, 79 men in endocrine-alone group and 37 in endocrine + radiation therapy group died from prostate cancer; accumulated incidence at 10 yrs for prostate cancer–specific mortality essentially 24% in endocrine-alone group, 12% in endocrine + radiation therapy group; data offered strong support for use of combined radiation therapy and endocrine management

Michel Bolla parallel study: recruited 415 patients with locally advanced prostate cancer between 1987 and 1995; randomly assigned men to receive radiation therapy alone or radiation therapy + immediate treatment with goserelin; median age 71 yrs; patients in both groups received 5000 cGy radiation to pelvis over period of 5 wks; additional 2000 cGy over additional 2 wks as boost to prostate; patients in combined treatment group received 3.6 mg goserelin subcutaneously every 4 wks starting on first day of radiation, continuing for 3 yrs; patients also received cyproterone acetate during first month of treatment to inhibit transient rise in testosterone associated with administration of goserelin; data available for analysis on 401 patients; median follow-up 45 months; *findings* — Kaplan-Meier estimates of overall survival at 5 yrs 79% in combined treatment group, 62% in radiation therapy group; proportion of surviving patients free of disease at 5 yrs 85% in combined treatment group, 48% in radiation therapy group; statistically significant; strongly supported use of hormonal therapy in conjunction with radiation; subsequently encouraged radiation therapists to use antiandrogen therapy for most men undergoing radiation therapy for localized prostate cancer

ProtecT trial: most recently published randomized trial; combined screening and treatment trial; recruited men between 1999 and 2009; total of 82,429 men aged 50 to 69 yrs underwent single PSA screening; 2664 diagnosed with localized prostate cancer; 1643 (62%) of patients agreed to undergo randomization to 3 arms (active monitoring, radical prostatectomy, and radiation therapy); ≈550 in each; after median 10-yr follow-up, 17 men have died from prostate cancer (8 in active monitoring group, 5 in surgery group, 4 in radiation therapy group);*findings* — no significant differences noted in number of deaths from prostate cancer or from any cause; patients developed metastases more frequently in active-monitoring group (33) compared with surgery group (13) and radiation-therapy group (16); overall, low incidence of prostate cancer deaths and development of metastases at 10 yrs in entire cohort (1% for prostate cancer, 3.8% for metastases)

Differences from SPCG-4 and PIVOT trials: *patient characteristics*– all men recruited to this trial had cancers identified by PSA testing (none presented clinically); most men harbored low-volume, low-grade disease; 77% had Gleason 6 disease, 76% stage T1c, 90% had PSA value of <10.0 ng/mL; men participating in ProtecT trial more typical of contemporary patients diagnosed with localized disease or who might consider active surveillance; *treatment adherence*– differed among study arms; 482 of 545 men (88%) assigned to active monitoring, 391 of 553 (71%) assigned to surgery, 405 of 545 (74%) assigned to radiation received assigned treatment within 9 mos of randomization; after 10 yrs of follow-up, 85% of those assigned to surgery or radiation therapy had received radical intervention; of 545 assigned to active monitoring, 291 (55%) had abandoned monitoring and received radical treatment by end of November 2015; *disease progression and mortality* — 204 men (12%) had disease progression including metastases during 10-yr follow-up; incidence higher in active-monitoring group than in surgery or radiation group; androgen-deprivation therapy initiated in 6.3% of patients, including 47 in active-monitoring group, 26 in surgery group, 30 in radiation-therapy group; all-cause and prostate cancer-specific mortality lower in ProtecT trial compared with SPCG-4 and PIVOT studies; may be related to recruitment of healthier cohort through population-based PSA testing but more likely

because of substantial lead time associated with PSA testing; screening also likely preferentially selected for men with low-grade disease and lower probability of disease progression; almost half of men in active-monitoring arm have received no intervention during 10 yrs of follow-up; *result* — growing interest in active surveillance for men with low-volume, low-grade cancers

Active surveillance: most required patients harbor Gleason 3+3 or Gleason grade group 1 disease or lower; most require PSA value <10 ng/mL and clinical stage T2 or lower; most require <3 biopsy cores positive or <30% of tissues submitted involved with cancer; follow-up in most of these series often <4 yrs; all-cause mortality ranges from 2% to 21%; prostate cancer–specific mortality in all series <1%; *largest active-surveillance case series*– Toronto; has recruited almost 1000 men; most patients have Gleason 6 disease; some patients aged >70 yrs at entry diagnosed with Gleason 7 disease or PSA value >15 ng/mL; 206 patients observed for >10 yrs and 50 patients for >15 yrs; among all 993 patients to date, 149 have died, 819 alive, 25 lost to follow-up; 75% of patients had diagnoses by PSA testing, stage T1c; to date, 15 deaths (1.5%) from prostate cancer; 10- and 15-yr cause-specific survival rates 98.1% and 94.3%, respectively; 13 patients (1.3%) have developed metastatic disease, 9 alive, 4 have died from other causes; at 5, 10, and 15 yrs from entry, 76%, 64%, and 55% of patients remained untreated and on surveillance; *findings* — authors conclude that, for select patients, low-volume, low-risk prostate cancer remains relatively benign disease; during 15 yrs of follow-up, only 3% of patients developed metastatic disease and 1.5% died from prostate cancer

Modalities: *men on active surveillance followed using 3 modalities* — PSA obtained every 3 to 4 mos and monitored to be certain it remains stable; most patients undergo confirmatory prostate biopsy within 1 yr of diagnosis to confirm additional disease not present or missed at initial biopsy; most men now receiving pelvic MRI to evaluate for possible lesions missed at initial biopsy; men with lesions undergo targeted biopsies either 1 yr following diagnosis or repeatedly during follow-up; high-intensity focused ultrasound explored for men who appear to have low-risk disease but do not wish to undergo active surveillance or consider surgery or radiation; ablative technique that treats only small portion of prostate, thereby preserving continence and erectile function; *findings* — outcomes from this treatment will be unavailable for many yrs; any randomized trial would require 15 yrs of follow-up to demonstrate any improvement over active surveillance; unlikely such trials will be conducted

Summary: *treatment*– treatment of localized and locally advanced prostate cancer remains controversial, especially for tumors detected PSA testing; *risk* — lifetime risk of prostate cancer diagnosis ≈17%; risk of dying remains ≈3%; suggests many men unlikely to benefit from treatments; *interventions*– when assessing value of any intervention, men must first understand threat posed by disease before estimating value of different interventions; based upon information gathered from several sources, including population-based studies, randomized trials, and case-series analysis, more accurate picture emerging; *predictors* and prognostic *factors* — most powerful predictor of long-term outcome continues to be Gleason score; men with high-grade disease (Gleason 8 through 10 or Gleason grade groups 4 and 5 have) have high probability of disease progression; those diagnosed clinically often survive 5 to 10 yrs before succumbing to disease depending on whether disease localized or metastatic at diagnosis; men most likely to progress also most likely to benefit from surgical or radiation intervention; men with screen-detected high-grade, localized disease often have additional 5 yrs before experiencing symptoms of disease progression; while they still may have localized disease, micrometastases occur early in natural evolution of high-grade prostate cancer; conversely, men with screen-detected low-volume, low-grade prostate cancers have best prognosis; *survival and mortality* — in absence of intervention, likely to survive at ≥15 to 20 yrs without symptoms or evidence of disease progression; prostate cancer mortality likely <5%; men wishing to consider active surveillance should also recognize evidence supporting treatment efficacy modest; SPCG-4 trial provides strongest support for surgery; based upon study population that had more clinically advanced disease at time of diagnosis compared with contemporary screen-detected patients; ProtecT trial more typical of contemporary patients, therefore, incidence of prostate cancer only 1% at 10 yrs; incidence of progression only 12%; similar results reflect data from population-based cohorts and other randomized trials and case-series analyses of active-surveillance cohorts; high-grade prostate cancer often progresses rapidly and often lethal; natural progression of low-grade, low-volume disease slow and results in disease-specific mortality of 0.1% to 1.5% over 15-yr period; estimates at 20 yrs not much higher; patients with intermediate-risk disease, especially men with small-volume Gleason 3+4 disease, most difficult to counsel; will probably experience disease progression in lifetime, should it exceed 15 to 20 yrs; will probably benefit most from radical intervention with surgery or radiation

Suggested Reading

Albertsen PC: Prostate cancer screening with prostate-specific antigen: where are we going? *Cancer.* 2018;124(3):453-5; **Catto JW et al:** ProtecT study group. Suitability of PSA-detected localised prostate cancers for focal therapy: experience from the ProtecT study. *Br J Cancer.* 2011;105(7):931-7; **Litwin MS et al:** The diagnosis and treatment of prostate cancer: a review. *JAMA.* 2017;317(24):2532-42.

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Advanced Prostate Cancer

Andrew Armstrong, MD, *Professor of Medicine, Surgery, Pharmacology, and Cancer Biology, and Director of Research, Duke Cancer Institute Center for Prostate and Urologic Cancers, Divisions of Medical Oncology and Urology, Duke University, Durham, NC*

Metastatic hormone-sensitive prostate cancer: ≈5% to 10% of US men present with metastatic disease with truncated natural history; between 30% and 50% of patients outside US; dependent on prevalence of prostate cancer screening; other patients have progressed and developed metastatic disease after failure of local therapy and relapse

Standard of care: hormonal dependence of prostate cancer first announced 1941; led to hormonal therapy; lower testosterone and achieve medical castration to same degree as orchiectomy; similar outcomes; has largely replaced orchiectomy, which remains cost effective; agents developed in 1970s and 1980s include LHRH (luteinizing hormone releasing hormone) agonists and first-generation antiandrogens bicalutamide, flutamide, and nilutamide; LHRH agonists leuprolide and zoladex; GnRH antagonist degarelix; androgen-deprivation indicated when metastatic disease diagnosed; start with GnRH agonist or antagonist with or without first-generation antiandrogen; more recently, second-generation antiandrogens, other hormonal agents, or docetaxel have become available and are life-prolonging options

Clinical trial data: early use of chemo-hormonal therapy with docetaxel or potent androgen receptor (AR) inhibitory therapy improves outcomes of men presenting with metastatic hormone-sensitive disease or developing it upon relapse after local therapy; formed basis for NCCN (National Comprehensive Cancer Network) guidelines recommending early use of more potent therapy

CHAARTED US trial: ECOG (Eastern Cooperative Oncology Group) study; showed that docetaxel for six cycles without prednisone led to improvement in overall survival (OS); hazard ratio (HR) of 0.63; median improvement in survival ≈17 months; considerably more than survival benefit in older trials of regimen in castration-resistant setting; survival benefit observed in high-volume patients with presence of visceral metastasis — liver and lung — or at least four bone metastases with at least one lesion outside vertebral column or pelvis; no clear survival benefit in long-term follow-up in low-volume patients with early use of docetaxel and androgen deprivation therapy (ADT); six cycles of docetaxel with ADT led to substantial improvement in OS

STAMPEDE UK study: survival benefit of early docetaxel seen regardless of disease volume; suggests patients largely had de novo disease, while CHAARTED patient population was largely relapsed disease; suggests docetaxel provides survival benefit regardless of disease volume in de novo M1 metastatic hormone-sensitive patients; survival benefit in relapsed disease only seen in high-volume patients

Prognosis: importance of prostate specific antigen (PSA) nadir between 6 and 12 months; PSA declining to undetectable level associated with best OS with ADT alone — 4 to 7 years; with PSA above 4 at 7 months, patient has inferior expected survival — median of 13 months; patients with intermediate PSA of 0.2 to 4 have intermediate endpoint; CHAARTED data demonstrated docetaxel improves survival, particularly in those failing to achieve PSA nadir with ADT alone; PSA nadir important prognostic finding; median survival >5 years; long survival compared with remote history; PSA data and prognosis can be updated based on response to therapy; most important prognostic findings include burden of disease, disease risk factors, Gleason score, and pattern of spread; symptoms not incorporated into multivariate nomogram or model

Docetaxel: generic; most cost-effective option; completed in 18 weeks; provides survival benefit in most patients; not indicated for frail elderly patients with poor functional status or those with significant neuropathy; alternatives to docetaxel include ADT and newer potent AR inhibitors

Abiraterone: LATITUDE and STAMPEDE trials demonstrated similar survival benefit to docetaxel, which confers 1.5-year survival benefit and almost 40% delay in risk of progression or death; choice between abiraterone, enzalutamide, and apalutamide based on availability, costs, and toxicities, not efficacy

LATITUDE trial: global study; patients with metastatic hormone-sensitive prostate cancer, two of three Gleason categories, 8 to 10 disease, greater than three bone lesions or visceral metastases; randomized to ADT with or without abiraterone; OS and progression-free survival (PFS) primary endpoints; improvement in survival similar to docetaxel; ≈17 months at median; HR of 0.66, indicating substantial delay in risk of death over time

STAMPEDE study: included men without metastatic disease and with node-positive disease; survival benefit for patients with node-only metastatic prostate cancer; survival advantage not yet seen for patients in curative-intent but high-risk localized setting; improvements in failure-free survival; substantial HR of 0.21; no data on survival with 2-yr abiraterone course with ADT combined with radiation in nonmetastatic setting; NCCN

recommends abiraterone and docetaxel; level 1 evidence for M1 and N1 patients with metastatic hormone-sensitive prostate cancer

Docetaxel side effects: associated with peripheral neuropathy in ≈6% of patients; fatigue, nausea, hair loss, fluid retention, pneumonitis, and neutropenic fever

Abiraterone side effects: improved quality of life over 6- to 12-month initial period, unlike decreased quality of life with docetaxel; side effects due to mineralocorticoid excess; abiraterone — cytochrome P450 hydroxylase and lyase inhibitor; important enzyme in two-step conversion from cholesterol to mineralocorticoids, glucocorticoids, and androgens; blocking step reduces androgen levels; leads to feedback upregulation of mineralocorticoids; abiraterone commonly given with prednisone; 5 mg of prednisone used in trials to block mineralocorticoid feedback upregulation; significant mineralocorticoid excess observed; hypokalemia, hypertension commonly observed; idiosyncratic hepatotoxicity in 10% to 20% of patients; comprehensive metabolic profile commonly recommended in first few weeks of starting treatment, monthly basis thereafter; home blood pressure monitoring and management of hypertension; patients developing hypertension from abiraterone can be safely treated with anti-hypertensive therapies; agents such as eplerenone block mineralocorticoid excess, which can reverse this effect; potassium-sparing agents like ACE inhibitors, potassium and calcium channel blockers useful

Monitoring: ≈5% to 10% risk of severe hypertension resulting from these agents; follow patients carefully; bone density monitoring important with newer AR therapies such as abiraterone, enzalutamide, or apalutamide; agents can reduce bone density, particularly over long periods; calcium and vitamin D recommended; aerobic exercise and light weight training to maintain muscle mass; home blood pressure monitoring and cardiovascular risk assessment and reduction with primary care doctors recommended; presence of low potassium, hypertension in patients with cardiovascular disease necessitates monitoring and management of potential atrial fibrillation

Secondary benefits of abiraterone: delays time to pain progression, skeletal events, and next therapy when used early; provides more palliation of pain at diagnosis and improves quality of life over period of therapy; median time to progression in LATITUDE study ≈3 years, substantially longer than for ADT alone; patients can be treated for many years with potent AR inhibitors; many studies ongoing with patients still in active follow-up

Following patients: follow patients on abiraterone, enzalutamide, or apalutamide with labs and PSA within ≈1 month; imaging scans for re-baseline assessment between 6 and 12 months; emerging data around benefits of radiation to primary; retrospective SEER (Surveillance, Epidemiology, and End Results program of National Cancer Institute [NCI]) epidemiologic data suggests survival benefit to treating primary with surgery or radiation even with metastatic disease

HORRAD study: randomized 432 patients with metastatic prostate cancer to radiation to primary; no OS benefit; suggestion of survival benefit in men with low burden of metastatic disease — <5 bone metastases; suggests survival benefit to removing source of additional metastatic lesions in presence of small number of bone metastases

Radiation to primary: clear level 1 evidence for radiation to primary from recent STAMPEDE study trial arm; pre-specified analysis; randomized men with metastatic hormone-sensitive disease to radiotherapy to prostate; no OS benefit to entire patient population as in HORRAD study; low-burden patients had survival benefit of ≈30% over no radiation; suggests radiation should be offered to patients with low metastatic burden by standard CT, bone scan, or MRI imaging; no risk stratification based on more sensitive imaging tests like prostate specific PET scans such as fluciclovine, choline, prostate-specific membrane antigen, or sodium fluoride; consultation with radiation oncology after re-baseline imaging to consider treatment of primary in presence of low burden, oligometastatic disease; follow patient every 3 months with labs and scans; however, over time patient will eventually progress

Enzalutamide: pure ligand-binding domain inhibitor of AR, unlike abiraterone, which blocks androgen synthesis but also has some direct AR inhibition; more potent AR blocker than bicalutamide and other first-generation antiandrogens; ENZAMET and ARCHES trials support enzalutamide in hormone-sensitive setting; benefits observed in both trials; dosing 160 mg per day; no prednisone required; treatment generally recommended to start within 3 months of initiation of ADT

Side effects: fatigue, high blood pressure, risk of falls and fractures due to fatigue and loss of muscle mass, rare rate of seizures at 0.3%; 1% to 2% chance of heart disease similar to ADT alone; exercise recommended to reduce risks; bone monitoring and bone density prophylaxis if bone loss observed

ARCHES trial: 1150 patients randomized to ADT alone or ADT plus enzalutamide; primary endpoint of radiographic PFS; low- and high-volume, de novo, and relapsed disease; progression delayed by ≈60%; significant difference with enzalutamide over placebo; significant benefits observed in all subgroups of patients; ≈18% of patients had prior docetaxel; further delay in radiographic progression after completion of docetaxel when enzalutamide was started as maintenance therapy after docetaxel; benefits of enzalutamide regardless of low or high burden of disease; secondary endpoints also met; included freedom from PSA progression, delay of skeletal events, delay of next therapy, and maintenance of high quality of life; mature survival data expected by 2021

ENZAMET trial: enzalutamide trial of >1100 patients; primary endpoint of OS; enzalutamide started during docetaxel, differing from ARCHES; allowed patients with ADT; some data for overlap and safety of giving agents together; ≈45% of patients received early docetaxel for hormone-sensitive disease; ≈50% had high-volume disease; survival benefit of enzalutamide; HR of 0.67; similar to apalutamide, abiraterone, and docetaxel; delays in clinical progression and PSA progression; subset analysis suggests improvements in progression and clinical progression in all subsets; survival benefit not yet observed with apalutamide or triple combination of docetaxel, enzalutamide, and ADT; subsets smaller, more heterogeneous, and less powered, with insufficient follow-up to make definitive statements about survival benefit of docetaxel with enzalutamide; more toxicities

in ENZAMET; neuropathy seen when enzalutamide combined with docetaxel; outside of clinical trials, use enzalutamide with docetaxel sequentially, not concurrently; do not yet have survival advantage for combination; docetaxel followed by enzalutamide could lead to further delay in clinical or radiographic progression; may be reason many patients choose to receive AR inhibitor after completion of ADT and docetaxel in induction of remission

Apalutamide: nearly chemically identical to enzalutamide; differences may lead to decreases in central nervous system (CNS) penetration and differences in side effects; similar hot flashes, fatigue, and hypertension; hypothyroidism — monitor thyroid function; increased risk of rash, ranging from mild to severe; severe rash in ≈25% of patients; discontinue drug if severe; consider resuming at lower dose; often will not recur; mild rashes usually resolve with temporary discontinuation or resumption at lower dose; similar fall risk; ≈1% of patients grade 3 or higher fatigue with apalutamide *vs* 3% with enzalutamide; higher risk of fractures and heart disease; low seizure rate 0.6%

TITAN trial: phase 3 global apalutamide study; 240 mg daily dosing; no steroids required; 1052 patients; some required prior docetaxel; treated with ADT with or without apalutamide; dual primary endpoint of OS and PFS met; OS improved; HR of 0.67; similar to enzalutamide and abiraterone; significant delays in clinical and radiographic progression; all subgroups defined by prior docetaxel use, visceral disease, and disease volume; no survival benefit yet observed in patients with liver metastases or prior docetaxel use; follow-up needed

Agent selection for hormone-sensitive disease: abiraterone requires prednisone; may not be appropriate for patients with metabolic syndrome, obesity, diabetes, cardiovascular risk, given mineralocorticoid excess; requires liver and electrolyte monitoring; now generic; more cost effective; enzalutamide and apalutamide do not require prednisone; no mineralocorticoid excess; no liver or electrolyte monitoring required; blood pressure monitoring required; all agents require bone density monitoring, exercise, and cardiovascular risk reduction strategies for elderly patients; all safely given concurrently with radiotherapy to prostate or to distant metastatic sites if indicated

Bone antiresorptive therapies: no supportive data for use in men with metastatic hormone-sensitive prostate cancer; CALGB 90202 and STAMPEDE trials showed no benefits in OS, PFS, or skeletal-related event-free survival for early use of zoledronic acid; denosumab not expected to provide those benefits either; has no supportive data in hormone-sensitive setting; reserve use of denosumab or zoledronic acid for patients with osteoporosis; less intense schedule such as Prolia or once-yearly zoledronic acid; also use in metastatic castration-resistant prostate cancer (mCRPC) setting

Germline testing: consider early; ≈12% incidence of germline alterations in prostate cancer in familial genes such as BRCA2; may have profound impact on care and need for genetic counseling for family members, especially children or siblings; recommended by NCCN to offer germline genetic testing to all patients with metastatic prostate cancer; includes patients with node-positive disease; prevalence sufficiently high in patients with very high risk or high risk NCCN criteria; prevalence above 5%; testing recommended even in earlier disease or lower risk settings if family history suggestive of hereditary breast, ovarian, prostate, colorectal, or other cancers suggestive of germline mutation

Somatic mutation testing: not yet demonstrated to show clinical utility in general population, but some findings may impact care in castration-resistant setting; homologous repair and mismatch repair deficiencies; improved outcomes with PARP inhibitors, platinum chemotherapy, and pembrolizumab for men with microsatellite unstable (MSI) prostate cancer

Approach: discuss genetic testing with metastatic hormone-sensitive cancer; refer patients with positive tests to genetic counselors; multigene panel of 14 to 18 DNA repair enzymes important for prostate cancer risk; BRCA2, ATM, CHEK2, BRCA1, PALB2, RAD51, ATR, and NBN; HOXB13 gene important for familial prostate cancer but does not yet have implications for treatment

Castration-resistant setting: defined as PSA rise or clinical or radiographic progression with castrate levels of testosterone (<50 ng/dl); determine prior therapies; patients with prior ADT alone may have larger list of agents to consider; patients with prior apalutamide, enzalutamide, abiraterone, or darolutamide in non-metastatic setting face limited options

Non-metastatic castration-resistant prostate cancer (non-mCRPC): evidence of disease progression such as PSA rise in absence of visible radiographic evidence of metastases; patients progressing after treatment with castration hormonal therapy following relapse after local therapy

Prognosis: PSA level and PSA doubling time can predict risk of development of metastases over time; inflection point indicating much higher risk with PSA doubling time <10 months and PSA level >10; consider those at greatest risk of metastasis or death for more aggressive therapy

Management: first-generation antiandrogens have ≈50% response rate; last between 6 and 12 months; can give bicalutamide 50 mg daily if patient has not used it before; observe patients progressing on bicalutamide for antiandrogen withdrawal response caused by ligand-binding domain point mutation in AR; turns bicalutamide from AR antagonist to agonist; occurs in ≈20% of cases; agonistic effect can result in PSA decreases when therapy discontinued; PSA decline can last 3 to 6 months up to years; withdrawal response does not occur if patient did not have good initial response to therapy

Importance of PSA kinetics: patients with slow PSA doubling time may have long natural history; may not need therapy right away; may cause significant toxicities and costs; however, those with rapid PSA kinetics and high PSA may have greater metastasis-free and OS-benefit from treatment; apalutamide, enzalutamide, and darolutamide FDA-approved in non-metastatic setting; all trials required ADT as backbone of all therapies; there are no therapies approved allowing for stopping ADT or replacing it with another approach

Benefits of early use of apalutamide, enzalutamide, darolutamide: 3 trials (see below); none showed OS benefit, but FDA approved them on basis of surrogate

endpoint, metastasis-free survival (MFS); statistical ICECaP (Intermediate Clinical Endpoints in Cancer of the Prostate) data demonstrate clear association between metastasis-free survival and OS; clinically, profound difference over placebo therapy; benefits to patients in delaying metastasis or death; no agents prior to apalutamide had shown efficacy in MFS or OS

SPARTAN study: 1207 men with non-metastatic disease on imaging; allowed to have N1 pelvic adenopathy; randomized 2:1 to apalutamide with ADT continued or ADT alone; led to FDA approval of apalutamide in setting of non-mCRPC; improvements in metastasis-free survival; median MFS of 40.5 months with apalutamide *vs* 16 months for placebo therapy; reduction in risk of metastasis or death of 72%; highly significant; quality of life maintained at high rate; OS not yet improved; HR of 0.7; not yet significant but favorable; risks of rash, hypothyroidism, fatigue, falls, fractures; rare risk of seizures 0.2%; screen patients for history of epilepsy, seizure disorders, and other seizure risk factors; consider alternative agents

PROSPER study: 1401 men randomized 2:1 to ADT with or without enzalutamide; median PSA doubling time ≈3 to 4 months; majority of patients had <6 month PSA doubling times; metastasis-free survival substantially delayed; HR of 0.29; improvement from 14 to nearly 37 months; risk of next therapies also delayed; OS not yet statistically significant; HR of 0.8 in initial report; longer-term follow-up needed; side effects of enzalutamide covered above

Darolutamide: approved in 2019; structurally dissimilar to enzalutamide and apalutamide; favorable side effect profile; less fatigue and falls; no real seizures; does not penetrate blood-brain barrier to cause cognitive difficulties or seizures; can increase risk of muscle loss and fatigue; exercise and cardiovascular risk reduction indicated; initial data suggests safety similar to ADT alone or bicalutamide; no impact on cardiovascular risk or hypertension; long-term data needed

ARAMIS study: 1500 men randomized 2:1 to 600 mg BID of darolutamide with ADT with food or placebo and ADT; MFS primary endpoint; was 40.4 months with darolutamide *vs* 18.4 months with placebo; do not yet see OS benefit; trend favoring darolutamide not yet significant by pre-specified criteria

Selection of agent: all agents expensive; discuss cost proactively with patients; often require copayment assistance, prior authorizations, or foundational assistance; all agents delay metastasis by 2 years on average; patients on studies for 4 to 5 years; remarkable progress; do not have data to support crossing from one therapy to another when patients progress on therapy in M0 setting; cross resistance between these agents; no other life-prolonging or metastasis-delaying therapies in non-mCRPC setting; patients progressing into metastatic CRPC (mCRPC) setting receive next set of available agents

Monitoring: non-mCRPC followed with quarterly PSA; home blood pressure monitoring; program of aerobic exercise and light weights; repeat scans every 6 months; imaging progression can occur in absence of PSA progression; ≈20% of patients treated with AR inhibitor develop radiographic progression over time in absence of working group-defined PSA progression

Metastatic castration-resistant disease: genomic heterogeneity; common features such as AR amplification, upregulation of enzymes regulating androgen production, increases in genes regulating AR biology and androgen signaling; tumor suppressors like P53, loss of RB1 and P10 regulating key oncogenic pathways; most not actionable in castration-resistant setting; ≈20% of men have germline or somatic homologous repair defects such as BRCA2 mutations actionable for further therapy; ≈3% to 6% of patients have MSI or mismatch-repair defects that may respond to PD-1 inhibitor such as pembrolizumab

Treatment: currently FDA-approved agents include enzalutamide, abiraterone, taxanes docetaxel and cabazitaxel, radium-223 radiopharmaceutical, and sipuleucel-T, which is only FDA-approved immunotherapy specifically for prostate cancer; zoledronic acid and denosumab improve bone health; important to maintain ongoing ADT; focus on supportive care; fracture prevention, exercise, sunlight to reduce risk of skeletal events; palliative radiation when indicated; survival time generally shorter than 5 years; may be 1 or 2 years in patients progressing on prior docetaxel, abiraterone, or enzalutamide; survival can be 12 to 15 months in patients receiving cabazitaxel or radium-223; palliative care when indicated; none of these therapies curative in mCRPC setting; clinical trial referral for participation in trials advances care and improves outcomes

Pembrolizumab: immune therapy; approved for prostate cancer in MSI-high disease; not approved for all patients with metastatic castration-resistant prostate cancer; NCCN guidelines recommend MSI testing in all men with metastatic prostate cancer; identifies the ≈3%-6% of patients who may benefit from PD-1 blockade; ≈50% response rate to single-agent pembrolizumab in these patients; responses can be very durable; low response rate, under 5% to 6%, in unselected patients; safe agent with rare risk of autoimmunity, such as hypothyroidism, pneumonitis, and rash; benefits outweigh risks in responding patients; MSI testing often done on tissue with Clinical Laboratory Improvement Amendments (CLIA)- or FDA-approved test, such as Foundation Medicine; cell-free plasma assays now have MSI testing that have been validated against tissue; way to identify patients that may benefit from other-than-traditional therapies for mCRPC

Prognosis of mCRPC: are patient-specific and tumor-specific factors; patient-specific factors — functional status, such as Karnofsky performance status, pain score, and opioid status; tumor-specific factors — cancer spread pattern on imaging; visceral liver metastases have worse prognosis than lung metastases, which have similar prognosis to bone-only spread; lymph node-only disease has best prognosis; abnormal host biomarkers such as albumin, C-reactive protein, neutrophil:lymphocyte ratio, bone markers such as alkaline phosphatase, and hemoglobin associated with poor outcomes; lactate dehydrogenase among strongest pretreatment prognostic markers; PSA levels, PSA kinetics, circulating tumor cells, cell-free DNA concentrations, genomic features such as P53 mutations, RB1 loss, and AR-V7 and AR splice variants associated with worse prognosis; treatment can change prognosis as PSA declines;

confirmed declines associated with improvement in survival, pain, quality of life, circulating tumor cell enumeration, immune response, and bone biomarker turnover; N-telopeptides and alkaline phosphatase changes associated with better outcomes; new multivariable prognostic models for mCRPC include updated Halabi model and PREVAIL enzalutamide model, validated internally; second-line models available; used to update prognosis at single time point or over time; many publications provide prognostic updates

Genotypes and phenotypes: phenotypes — prognostic factors defined by pattern of spread, pain, or differences in biomarkers; genotypes also heterogeneous; some patients with AR-dependent cancers have AR amplification or splice variants; some AR-independent tumors such as small cell prostate cancer and P10 or RB loss; others have variable AR dependence or rapid emergence of resistance regulated by tumor suppressors like RBP10 or P53; as noted, 3%-6% of patients MSI-high — actionable for pembrolizumab; ≈20% have germline or somatic homologous repair deficiencies, for which PARP inhibitors are in development

Sipuleucel-T: autologous cellular therapy; FDA-approved based on improved survival in men with asymptomatic to minimally symptomatic CRPC; autologous cellular manufacturing process involving leukapheresis and pulsing antigen-presenting (CD54-positive) cells with fusion peptide of prostatic acid phosphatase and GM-CSF; these dendritic cells activated and reinfused into patient 3 days later; process repeated twice more; NCCN recommends sipuleucel-T be considered among first therapies in US because of impact in improved survival in men with low disease burden; treatment takes ≈4 weeks

Side effects: infusion reactions include chills, fever, and rigors; before starting therapy, important to rule out patients with high burden of disease who may develop rapid disease progression, spinal cord compression; patients with visceral disease, particularly liver metastasis, may also not be appropriate candidates

IMPACT trial: published in 2010; led to FDA approval of sipuleucel-T; showed median survival improvement of ≈4 months; relative improvement of ≈22% to 23%; favorable safety profile; no real effect on short-term outcomes such as PSA, response rates, or palliative benefits; all patients generally had minimally symptomatic disease; no real delay in time to progression; OS improved; suggests disease-modifying effect long-term

Further analyses: retrospective and subset analyses show greater median survival improvements and relative survival improvements with earlier disease groups defined by PSA; may be greater benefits in men with lower disease burden; recent data has shown greater survival benefit in African American patients in large national PROCEED registry (patient registry maintained by drug company Dendreon); suggests African Americans may clearly benefit from therapy

Pembrolizumab in advanced disease: also immune therapy; generally used only for patients with refractory disease who have exhausted standard-of-care approaches; only effective with MSI instability; MSI testing appropriate in this clinical setting; has quite durable ≈50% response rate in MSI-high patients; low response rate (5%-6%) in others

Enzalutamide: AR antagonist reducing nuclear translocation and AR-mediated DNA binding; efficacy better than bicalutamide in preclinical models; well tolerated; showed improved survival in post-docetaxel mCRPC setting in AFFIRM study; improved survival in chemo-naive setting; improvement in survival ≈40% in post-chemotherapy setting in PREVAIL study; ≈20% in pre-chemotherapy setting despite crossover and delays in radiographic PFS ≈80% along with robust objective, PSA response rates, and maintained quality of life

Bone scan flare/pseudo-progression: associated with potent AR therapies; patient otherwise responding based on PSA or soft tissue response develops new bone lesions on bone scan; may be related to pre-existing lesions not previously visible brought out by response to therapy; bone scan flare seen in ≈20% in patients treated with potent AR inhibitors; not associated with worse outcomes; treat patients through flare phenomenon if patient without symptomatic progression; stop therapy with progression on subsequent bone scans; based on Prostate Cancer Working Group 2 and 3 criteria

Hypertension: side effect of these agents; many penetrate CNS and cause reversible posterior leukoencephalopathy syndrome — rapidly evolving neurologic symptoms including seizures and blindness resulting from untreated hypertension of any cause; discontinue therapy and manage hypertension aggressively

Cougar 301 and Cougar 302 trials: studied abiraterone (Cyp 17 lyase and hydroxylase inhibitor) in post-chemotherapy and chemotherapy-naive mCRPC patients; as with enzalutamide, patients showed improvement in survival and PFS; abiraterone and prednisone at 5 mg BID; associated with improvements in delay and pain progression, functional deterioration, and need for chemotherapy; benefits of abiraterone and enzalutamide observed regardless of prognostic groups; PREVAIL study included patients with visceral metastases while 302 study did not; drugs still active in patients with visceral patterns of spread; abiraterone, unlike enzalutamide, requires concomitant prednisone; can cause mineralocorticoid excess, hypertension, and atrial fibrillation; fluid retention and hypokalemia also seen; follow laboratory studies

Resistance: early use of AR-potent therapies creates concern of developing AR-independent or resistant disease at earlier time point; cross-resistance among AR-related therapies appears despite drugs acting through different mechanisms — one for androgen-synthesis inhibition, one acting on AR itself; mechanisms of resistance often shared, eg, AR splice variants with emergence of lineage plasticity in small-cell carcinoma, other oncogenes and tumor suppressors; create cross-resistance; some mutations do not confer cross-resistance, such as point mutations in AR ligand binding domain; may allow sensitivity; sensitivity to crossover therapy observed in ≈20% to 30% of patients with second-line AR-directed therapies; consider taxane chemotherapy standard-of-care when patient progresses rapidly on AR therapy; radium-223 option with bone pattern of spread; docetaxel or cabazitaxel reasonable for soft tissue or visceral patterns of spread depending on prior exposure to taxane

Docetaxel: first FDA-approved life-prolonging therapy in mCRPC setting; based on TAX 327 study; ≈2.5-month improvement in OS in mCRPC; global phase 3 trial compared docetaxel to prednisone and mitoxantrone; up to 10 cycles of agents given every 3 weeks; docetaxel 75 mg/m^2 with prednisone 5 mg BID; ADT and bone health agents continued; response rates and quality of life improved with docetaxel; acceptable toxicity; neutropenic fever rate of 2% to 3%; some sensory neuropathy; well tolerated regimen; benefits of docetaxel observed in all subgroups defined by functional status, age, PSA levels, and pattern of spread

Cabazitaxel: unique to prostate cancer; synthetically derived from docetaxel; FDA-approved in second-line setting after progression on docetaxel

2019 CARD trial: showed cabazitaxel improved survival compared to second-line AR therapy in mCRPC patients who had received prior abiraterone or enzalutamide and progressed within 12 months; many patients had also received prior docetaxel; cabazitaxel group showed improvement in PFS and OS; better response rate; suggested cabazitaxel should be third-line standard of care rather than another oral agent

TROPIC study: original cabazitaxel study; randomized, phase 3 trial; led to FDA approval; compared cabazitaxel every 3 weeks with prednisone to mitoxantrone and prednisone for up to 10 cycles; showed better response rate, PFS, and OS by ≈30%; all subgroups benefited from cabazitaxel, even those who had not benefited from docetaxel; suggested cabazitaxel not substrate for multidrug-resistant efflux pump on prostate cells; may sensitize prostate cancer cells resistant to parental docetaxel compound

Side effects: febrile neutropenia; use of growth factors encouraged; incidence of hematuria ≈17%; diarrhea, fatigue, other notable side effects; neuropathy less common with cabazitaxel than with docetaxel

Radium-223: radium bone tropism in prostate cancer; prostate cancer tends to cause osteoblastic bone metastases; number of bone metastases measured with bone scan index or by counting number of lesions; associated with worse survival; radium — calcimimetic; particularly taken up by osteoblastic bone metastases; emits alpha particles — small helium molecules decay and cause delivery of radiation directly to bone; does not target cancer outside bone — its main limitation; men with symptomatic bone metastases who have failed abiraterone, enzalutamide, or chemotherapy, or those not candidates for docetaxel with bone-predominant pattern of spread best candidates for radium; should lack visceral metastases or bulky adenopathy >3 to 4 cm; provides survival and palliative benefit; not much PSA decline

ALSYMPCA trial: led to FDA approval of radium-223; phase 3 trial of 922 men with symptomatic CRPC and two or more bone metastases with no visceral metastases; many post-docetaxel or unfit for docetaxel; randomized to radium up to six doses at 4-week intervals and best supportive care or best supportive care with placebo; 30% improvement in survival; median improvement of ≈3 months; quality of life benefits; declines in alkaline phosphatase; prevention of spinal cord compression; acceptable safety profile allows for repeat dosing; mild anemia, neutropenia, and thrombocytopenia; greater benefit in patients with high alkaline phosphatase or more bone metastases; has not demonstrated benefit in earlier disease; combination with abiraterone should not be given in earlier disease settings because of increased risk of death and fracture; used after abiraterone or enzalutamide progression; can be given before or after docetaxel chemotherapy

Small cell/neuroendocrine prostate cancer: among most difficult to treat; behaves like small cell lung cancer; does not produce PSA; characterized by loss of tumor suppressors like P10, P53, and RB1; platinum sensitivity, visceral pattern of spread, bulky disease, and absence of high PSA; some patients may have components of typical prostate adenocarcinoma and neuroendocrine prostate cancer simultaneously; can make characterization difficult; recent biopsy studies suggest ≈20% of men have neuroendocrine prostate cancer not anticipated at time of clinical assessment; consider biopsy in patients with disease progression; opportunities for platinum therapy or clinical trial eligibility; evolving standard of care involves platinum-based chemotherapy doublet; typically carboplatin/etoposide or docetaxel/carboplatin based on reasonable response rates and PFS; research studies exploring immunotherapy, antibody drug conjugates, and combination approaches; unmet need

Suggested Reading

Damodaran S, et al: Newly diagnosed metastatic prostate cancer: has the paradigm changed? *Urol Clin North Am.* 2017 Nov;44(4):611-21; **Hossain MK, et al:** Immune-based therapies for metastatic prostate cancer: an update. *Immunotherapy* 2018 Feb;10(4):283-98; **Metcalfe MJ, et al:** Role of radical prostatectomy in metastatic prostate cancer: A review. *Urol Oncol.* 2017 Apr;35(4):125-34.

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Bladder Cancer and Upper Urinary Tract Cancers

Matthew I. Milowsky, MD, *George Gabriel Villere Distinguished Professor of Bladder and Genitourinary Cancer Research, University of North Carolina (UNC), Chapel Hill, Section Chief, Genitourinary Oncology, and Co-Director, Urologic Oncology Program, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Epidemiology of bladder cancer: not uncommon; estimated ~80,500 new cases and ~ 17,700 bladder cancer–related deaths in US in 2019; median age at diagnosis 73 yrs; incidence 3 to 4 times higher in men than in women;
- Major risk factors: tobacco use, occupational exposures, urinary tract diseases, and certain medications (*eg*, cyclophosphamide); cigarette smoking most significant risk factor for bladder cancer; occupational exposure to aromatic amines as well as in specific occupations, (*eg*, dye-stuff manufacturing, rubber and aluminum industries) also at increased risk; infection with *Schistosoma haematobium* in other parts of the world (*eg*, northern Africa) leads to increased risk of both squamous and urothelial carcinomas; other chronic urinary tract infections (UTIs) leading to chronic inflammation may also increase risk; *hereditary nonpolyposis colon cancer (HNPCC), aka Lynch syndrome* — bladder, and specifically upper tract, urothelial cancers may be associated with HNPCC, or Lynch syndrome; important to take family history for other Lynch syndrome–related cancers (*eg*, colon, endometrial, ovarian, small bowel, others); Lynch syndrome associated with mutations or loss of mismatch repair genes
- Characteristics: bladder cancer characterized by field effect such that patients with bladder tumors at risk for development of recurrent tumors throughout urinary tract (polychronotropism); 3 general categories of disease: non-muscle invasive, muscle invasive, metastatic

Pathology and biology: >90% of urothelial carcinomas originate in bladder; however, any structure lined by urothelium may be at risk for tumor development; upper urinary tract tumors, which include renal pelvis and ureter, account for 5% to 7% of urothelial carcinomas; in US, ~92% of bladder cancers urothelial carcinomas, 5% squamous cell carcinomas, 2% adenocarcinomas, ≤1% small-cell carcinomas; in Northern Africa and other parts of world with high prevalence of schistosomiasis, ≤75% of tumors pure squamous cell carcinomas; lesions of mixed histology occur commonly, generally variants of urothelial carcinoma with divergent differentiation (*eg*, squamous, adenocarcinoma, plasmacytoid, signet ring cell, micropapillary variant, others); subset of adenocarcinomas, urachal origin occurring at dome of the bladder
- Pathways of tumorigenesis: urothelial tumors evolve through divergent pathways of tumorigenesis; Ras signaling pathway has major role in low-grade noninvasive tumors, including 70% with mutations in fibroblast growth factor receptor 3 (FGFR3), upstream tyrosine kinase receptor involved in cellular proliferation and angiogenesis; although 70% of these low-grade lesions recur, only 10% to 15% progress to muscle invasion; progression to muscle-invasive disease, or in those 20% to 30% of patients who present with muscle-invasive disease, additional molecular alterations occur in tumor suppressor genes, including tumor protein p53 (TP53) and retinoblastoma (RB); muscle-invasive bladder cancer potentially lethal phenotype with ~50% of muscle-invasive tumors progressing to metastatic disease
- Potential therapeutic targets: Cancer Genome Atlas Research Network Comprehensive Molecular Characterization of Urothelial Bladder Carcinoma identified potential therapeutic targets, including targets in PI3-kinase/AKT/mTOR pathway and RTK/MAP kinase pathways; researchers have identified molecular subtypes of bladder cancer based on RNA sequencing that may have implications on both prognosis and prediction of response to different therapies; in addition, bladder cancer has high mutational burden; this, coupled with results from clinical trials of anti-programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) antibodies in patients with metastatic bladder cancer, suggests high mutational burden may enhance ability of immune system to recognize tumor cells, thus making metastatic bladder cancer potentially excellent target for novel immunotherapy approaches

Screening and prevention: no studies to date with sufficient evidence to support screening for bladder cancer, including hematuria testing, urine cytology, or other urine biomarker tests in asymptomatic individuals; primary prevention strategies target exposures linked to bladder cancer, including smoking with tobacco cessation, and occupational exposures

Presentation and diagnosis: hematuria most common presenting symptom; patients may also have irritative urinary symptoms (*eg*, frequency, urgency, dysuria); diagnosis established by cystoscopy and biopsy

T staging: Ta tumors, noninvasive papillary lesions; Tis, carcinoma in situ, precursor lesion for more aggressive invasive variant; T1 tumors invade subepithelial connective tissue (*ie*, lamina propria or muscularis mucosa); T2 tumors invade muscularis propria; T3 tumors invade perivesical tissue; T4 tumors invade prostate,

seminal vesicles, uterus, vagina, pelvic and/or abdominal wall

N staging: N0, no regional lymph nodes detected; N1, single regional node in true pelvis (*ie*, perivesical, obturator, internal and external iliac, or sacral lymph nodes); N2, multiple regional lymph nodes in true pelvis; N3, lymph node metastases to common iliac lymph nodes

M staging: M1a, distant metastasis limited to lymph nodes beyond common iliac; M1b are non-lymph node distant metastases

Staging: historically, any regional or distant lymph node involvement considered stage IV disease; staging system revised such that N1 incorporated into stage IIIA and N2 and N3 included in stage IIIB; major problem with staging relates to suboptimal correlation of depth of tumor invasion determined by cystoscopy and biopsy resulting in cystectomy; for staging, computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate for extravesical or nodal disease; F-18 fluorodeoxyglucose positron emission/computed tomography scan (FDG PET/CT scan) may have role in staging of muscle-invasive disease and in detection of metastatic bladder cancer

Non-muscle-invasive bladder cancer: ~70% of patients with newly diagnosed bladder cancer present with non-muscle-invasive disease, 70% confined to mucosa (*ie*, Ta or Tis), 30% involving submucosa (*ie*, T1), with involvement of lamina propria

Management: transurethral resection (TUR) to completely remove tumor, followed by regular surveillance with cystoscopy and urine cytology to evaluate for recurrence or progression; ~70% of patients with non-muscle-invasive bladder cancer will have recurrence or new occurrence within 5 yrs, ~15% will progress to more advanced stage; when urine cytology positive but cystoscopy reveals no visible lesions in bladder or urethra, selective catheterization and visualization of upper urinary tracts warranted due to potential for upper-tract urothelial cancer; in addition to complete TUR, management generally involves use of intravesical therapy (*ie*, therapy instilled into bladder); *intravesical therapy* — single dose of intravesical mitomycin (Mitomycin C, Mutamycin) after TUR for non-muscle-invasive bladder cancer associated with significant reduction in tumor recurrence; low-grade Ta disease managed with TUR followed by regular surveillance; intravesical therapy generally recommended for multifocal or recurrent Ta lesions, carcinoma in situ, and T1 disease; randomized trials have established intravesical Bacillus Calmette-Guerin (BCG immunotherapy weekly for 6 wks, including maintenance schedule (intravesical treatment of choice to decrease recurrence and reduce risk of progression); salvage intravesical therapies, including gemcitabine and mitomycin, may be considered if patient progresses after BCG; however, cystectomy often indicated

Muscle-invasive bladder cancer: potentially lethal phenotype; ~50% of muscle-invasive tumors progress to metastatic disease; standard surgical treatment, radical cystectomy with bilateral pelvic lymphadenectomy; lymph node dissection necessary component of surgery (more extended lymph node dissection associated with improved outcome); radical cystectomy includes removal of bladder, prostate, seminal vesicles, and proximal urethra in men; removal of bladder, urethra, uterus, bilateral salpingo-oophorectomy, and excision of portion of anterior vaginal wall for women; *3 main types of urinary diversion* — ileal conduit (which drains to appliance on anterior abdominal wall), continent cutaneous reservoir, and orthotopic neobladder

Perioperative adjuvant chemotherapy for muscle-invasive and locally-advanced bladder cancer: level I evidence not available (underpowered trials); several small historical trials demonstrated mixed results (some showed benefit, others no benefit); more modern studies evaluating adjuvant chemotherapy include the following: *Italian multicenter randomized phase 3 trial* — compared adjuvant chemotherapy with gemcitabine (Gemzar, Infugen)and cisplatin (Platinol, Platinol-AQ) to chemotherapy at time of relapse for patients with muscle-invasive bladder cancer after radical cystectomy; did not demonstrate significant difference in disease-free survival (DFS) and overall survival (OS) between groups; however, study underpowered, did not meet accrual goal; *Spanish Oncology Genitourinary Group randomized phase 3 trial* — compared adjuvant paclitaxel (Onxol, Taxol), gemcitabine, and cisplatin (PGC) to observation in patients with resected high-risk bladder cancer (*ie*, pT3-4 and/or node-positive disease); demonstrated improvement in DFS and OS; however, trial prematurely closed, underpowered, limiting conclusion; *EORTC-30994 phase 3 study* — largest adjuvant trial published to date; randomized patients with pT3-4 or node-positive bladder cancer after radical cystectomy to immediate chemotherapy with either 4 cycles of gemcitabine and cisplatin, combination of high-dose methotrexate (MTX; Otrexup, Rasuvo, Trexall), vinblastine (Velban), doxorubicin (Adriamycin), and cisplatin (MVAC), vs 6 cycles of chemotherapy at time of relapse; trial closed after only 284 of planned 660 patients; although no statistically significant improvement in OS with immediate treatment compared with deferred treatment, 5-year progression-free survival (PFS) 47.6% vs 31.8%; median PFS 3.11 yrs vs 0.99 yrs; hazard ratio (HR) 0.54, $P<0.0001$; 2013 updated systematic review and meta-analysis of randomized trials of adjuvant chemotherapy, including 945 patients from 9 trials, revealed pooled HR 0.77 for OS and 0.66 for DFS; *comparative effectiveness study* — also demonstrated improvement in survival for adjuvant chemotherapy compared with observation in patients with ≥pT3 and/or node-positive bladder cancer; although level of evidence represents barrier to formal recommendation, based on available data, adjuvant cisplatin-based chemotherapy may be considered for patients with high-risk features after radical cystectomy, including those with pT3-4, and/or node-positive disease; no clear role for use of adjuvant chemotherapy in patients who received preoperative or neoadjuvant chemotherapy; *immune checkpoint research* — ongoing

Perioperative neoadjuvant chemotherapy for muscle-invasive and locally advanced bladder cancer: largest phase 3 randomized neoadjuvant chemotherapy trial randomly assigned 976 patients with T2, Grade 3, T3, or T4a N0 bladder cancer undergoing cystectomy, radiotherapy, or both to 3 cycles of neoadjuvant chemotherapy with cisplatin, MTX, and vinblastine compared with no chemotherapy; median follow-up at 8 yrs, statistically significant (16%) reduction in risk of death, HR 0.84, $P=0.037$, corresponded to increase in 10-yr survival from 30% to 36% with neoadjuvant

chemotherapy; chemotherapy regimen associated with higher pathologic complete response (CR)rate in bladder; *US phase 3 randomized intergroup trial* — assigned 307 patients with T2-T4a N0 bladder cancer to neoadjuvant MVAC plus cystectomy or to cystectomy alone; at median follow-up of 8.7 yrs, estimated risk of death reduced by 25% for patients who received MVAC and cystectomy; median survival of patients assigned to surgery, 46 mos compared with 77 mos among patients assigned to MVAC plus cystectomy; survival benefit of neoadjuvant MVAC associated with tumor downstaging to pathologic CR (*ie*, pT0), seen in 38% of patients who received MVAC compared with 15% who received cystectomy; 85% 5-yr survival in patients with pathologic complete response; *meta-analysis of neoadjuvant chemotherapy in muscle-invasive bladder cancer* — performed with data from 3005 patients enrolled in 11 randomized trials showed significant OS benefit for platinum-based chemotherapy, with 14% reduction in risk of death, 5% absolute survival benefit at 5 yrs; OS increased from 45% to 50%; based on these data, neoadjuvant cisplatin combination chemotherapy represents standard of care in management of muscle-invasive bladder cancer, with level I evidence to support use; *most commonly used regimen gemcitabine and cisplatin* — retrospective data suggest similar pT0 rates compared with standard MVAC; *2 more recent phase 2 studies utilizing dose-dense MVAC with pegfilgrastim (Fulphila, Neulasta, Udenyca) support* — promising pathologic response rates in patients with clinical T2-T4a, including patients with regional nodal involvement; *other studies* — insufficient data for non-cisplatin-based chemotherapy use in perioperative setting; 2 recent studies have demonstrated promising pathologic response rates for single-agent immune checkpoint inhibitors in patients with muscle-invasive bladder cancer; further research needed to understand whether or not role for immune checkpoint inhibitors in this setting

Organ preservation: potential alternative to surgery in appropriately selected patients with muscle-invasive disease trimodality bladder-sparing approach; treatment consists of maximal TUR, as complete as safely possible, together with chemotherapy plus radiation; results in long-term DFS and OS rates approaching those seen in radical cystectomy series; majority of trimodality protocols use cisplatin-based chemotherapy; in largest randomized study to compare chemoradiotherapy using 5-fluorouracil (5FU; Efudex) and mitomycin with radiotherapy alone in muscle-invasive bladder cancer, chemotherapy-plus-radiation therapy arm associated with 32% reduction in risk of local regional recurrence, median follow-up of ~70 mos; another non-cisplatin-based regimen includes twice-weekly low-dose gemcitabine combined with radiation therapy; in Radiation Therapy Oncology Group (RTOG) 0712 study, this regimen demonstrated similar rate of freedom from distant metastases at 3 yrs to regimen of 5FU and cisplatin; important to review with patients that approximately one-third of patients will ultimately require cystectomy for less than CR or for recurrent muscle-invasive tumors; patients require continued surveillance with cystoscopy, urine cytology, and periodic imaging of upper urinary tracts

Management of metastatic disease: based on early randomized trials comparing MVAC with single-agent cisplatin and with combination of doxorubicin, cyclophosphamide (Cytoxan, Neosar), and cisplatin, MVAC associated with survival benefit, standard of care for treatment of metastatic disease; increasing dose intensity of MVAC with growth factor support compared with standard MVAC on a 4-wk schedule led to borderline statistically significant relative reduction in risk of progression and death compared with MVAC; however, median survival 15.1 mos with high-dose-intensity MVAC and 14.9 mos with MVAC; gemcitabine and cisplatin standard of care and most commonly used cisplatin-based regimen based on randomized trial comparing MVAC with gemcitabine and cisplatin in patients with locally advanced or metastatic urothelial carcinoma; although trial not designed as noninferiority study, results demonstrated similar response rate, PFS, and median survival for gemcitabine and cisplatin at 14 mos and MVAC at 15.2 mos, as well as less toxicity for gemcitabine and cisplatin compared with MVAC; triplet chemotherapy with paclitaxel, cisplatin, and gemcitabine compared with gemcitabine and cisplatin showed no improvement in survival for 3-drug combination

Eligibility for cisplatin-based chemotherapy: bladder cancer frequently disease of older individuals with coexisting medical problems, including kidney dysfunction, so ~40% to 50% of patients with advanced bladder cancer ineligible for cisplatin-based chemotherapy; criteria to determine ineligibility include 1 of the following: Eastern Cooperative Oncology Group (ECOG) performance status of 2, creatinine clearance <60 mL/min, grade 2 or greater hearing loss, grade 2 or greater neuropathy, and/or a New York Heart Association Class III heart failure

Management when ineligible for cisplatin-based therapy: phase 2/3 trial of gemcitabine and carboplatin compared with combination of MTX, vinblastine, and carboplatin (Carboplatin Novaplus, Paraplatin) (M-CAVI) in patients with metastatic urothelial cancer ineligible for cisplatin-based chemotherapy based on World Health Organization performance status 2 and/or creatinine clearance 30 mL/min to 60 mL/min demonstrated no difference in outcome and less toxicity for gemcitabine and carboplatin compared with M-CAVI; provides level I evidence for use of gemcitabine and carboplatin in patients unable to receive cisplatin-based chemotherapy

Prognosis: prognostic factors predicting long-term survival in patients with metastatic urothelial cancer receiving cisplatin-based chemotherapy include Karnofsky Performance Scale score less than or greater than 80% and presence or absence of visceral metastases (specifically lung, liver, or bone); median survival times for patients with 0, 1, or 2 risk factors 33 mos, 13.4 mos, and 9.3 mos, respectively; more recently, 2 nomograms for predicting survival in patients with metastatic urothelial cancer also published

Second-line treatment: until recently, no US Food and Drug Administration (FDA) approved second-line treatments in advanced bladder cancer; evaluations of single agents such as ifosfamide (Ifex), docetaxel (Docefrez, Taxotere), gemcitabine, paclitaxel, and pemetrexed (Alimta) demonstrated response rates 9% to 27%, PFS 2 mos to 3 mos, and no documented improvement in OS; in patients with metastatic disease who experienced treatment failure after platinum-based regimen, 3 adverse risk factors (ECOG performance status >0, hemoglobin <10 g/dL, and

presence of liver metastases) have been shown to predict OS

New role for immune checkpoint inhibitors in advanced urothelial cancer: no major advances in management of metastatic urothelial cancer over past 30 yrs until recently; immune checkpoint inhibitors have revolutionized treatment of patients with advanced disease; between May 2016 and May 2017, 5 immune checkpoint inhibitors targeting PD-L1 and PD-1, including pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo), durvalumab (Imfinzi), and avelumab (Bavencio), received FDA accelerated approvals for patients with advanced disease

KEYNOTE-045 study — provided first level I evidence to support use of immune checkpoint inhibitors in patients with metastatic urothelial cancer that progressed after first-line therapy; 542 patients with metastatic urothelial cancer who progressed after platinum-based chemotherapy for advanced disease or recurred within 12 mos after receipt of either adjuvant or neoadjuvant therapy for localized muscle-invasive disease randomized to pembrolizumab targeting PD-1 administered every 3 wks vs investigators' choice chemotherapy with paclitaxel, docetaxel, or vinflunine (Javlor); primary endpoints PFS and OS; pembrolizumab associated with improvement in OS with median survival of 10.3 mos vs 7.4 mos in chemotherapy group, HR 0.73; no difference in PFS; fewer treatment-related adverse events (AEs) in pembrolizumab group than in chemotherapy group; this trial established role for pembrolizumab in patients with advanced urothelial cancer who progressed after platinum-based chemotherapy

Two phase 2 studies (KEYNOTE-052 with pembrolizumab and IMvigor210 with atezolizumab): included patients with metastatic urothelial cancer ineligible for cisplatin-based chemotherapy in first-line setting; both trials demonstrated promising outcomes; *KEYNOTE-052 study (pembrolizumab)* — 370 patients with cisplatin-ineligible metastatic urothelial cancer, objective response rate (ORR) 24%; *IMvigor210 study (atezolizumab)* — 119 patients with cisplatin-ineligible disease, ORR 23%, median OS 15.9 mos; based on durable responses, promising survival outcomes, and tolerability, both agents received FDA accelerated approval for patients with metastatic urothelial cancer ineligible for cisplatin-based chemotherapy; *updated indication* — after initial accelerated approval, FDA restricted use of pembrolizumab and atezolizumab to patients with locally advanced or metastatic urothelial cancer ineligible for cisplatin-containing chemotherapy, based on decreased survival with use of these agents as monotherapy compared with platinum-based chemotherapy in 2 clinical trials treating patients with metastatic urothelial cancer who had not received prior therapy and who had low expression of PD-L1; thus, updated indication in first-line metastatic setting includes patients with locally advanced or metastatic urothelial carcinoma ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 by immunohistochemistry or in patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status; different assays and cutoffs used for PD-L1 positivity; for pembrolizumab, combined positive score, including tumor and immune cells ≥10; atezolizumab, tumor-infiltrating immune cells covering ≥5% of tumor area

Predictive biomarkers for response to immune checkpoint inhibitors needed: both PD-1 and PD-L1 imperfect; ongoing research evaluating additional potential biomarkers, including tumor mutational burden and number of predicted neoantigens, RNA subtypes, immune gene–expression profiling, T-cell receptor clonality, many others

AEs: immune-related AEs, including but not limited to rashes, include thyroid dysfunction, adrenal insufficiency, hypophysitis, diabetes, colitis, nephritis, pneumonitis, myocarditis, myositis, and neurologic disorders; patients monitored closely for signs and symptoms consistent with these immune-related AEs; American Society of Clinical Oncology and other organizations developed guidelines for management of immune-related AEs, predominantly corticosteroids and other immunomodulatory agents (*eg*, infliximab [Remicade])

Targeted therapies: first targeted therapy, erdafitinib (Balversa), in patients with locally advanced or metastatic urothelial cancer with FGFR3 or FGFR2 alteration that has progressed on platinum-containing chemotherapy, recently received FDA accelerated approval; approval based on phase 2 trial in which erdafitinib demonstrated 32% OR in patients with FGFR2- or FGFR3-positive, locally advanced or metastatic urothelial cancer; responses seen in patients previously treated with immune checkpoint inhibitors; common AEs include hyperphosphatemia, stomatitis, fatigue, elevated creatinine, diarrhea, dry mouth, onycholysis, and elevated transaminases; other additional studies evaluating novel targeted therapies in patients with specific genetic alterations

Radiation therapy: can have significant palliative effects in patients with metastatic disease, including in patients with bone involvement and locally advanced, nonresectable primary tumors; in highly selected patients with metastatic urothelial carcinoma, resection of metastatic disease can result in long-term disease control

Management for cancers arising in urothelial tract outside of bladder: urothelial carcinomas arising in renal pelvis, ureter, and proximal urethra managed similarly to urothelial carcinomas arising in bladder; however, role of perioperative chemotherapy less clear because of difficulty in adequately staging patient (*ie*, determining muscle invasion)

Nonurothelial histologies within urothelial tract: divergent or variant histologies commonly seen in patients with urothelial carcinoma (*eg*, squamous and glandular features); generally managed as urothelial carcinoma; chemotherapy used for urothelial carcinoma considered less effective in pure nonurothelial histology tumors; for patients with pure small cell or adenocarcinoma, use of chemotherapy regimens demonstrating activity in other sites with similar histology generally used (*eg*, etoposide [Etopophos, Toposar, VePesid] and cisplatin in lung small cell carcinoma may be used for management of small cell carcinoma of bladder; 5FU-based regimes in patients with pure adenocarcinomas); micropapillary bladder cancer, rare variant of urothelial carcinoma, associated with more aggressive course and worse prognosis

Important survivorship issues: in older patient population, often many coexisting medical problems (*eg*, heart

disease, chronic obstructive pulmonary disease, chronic renal insufficiency); treatment and posttreatment care can be complicated; good coordination between urologist, medical oncologist, and primary care physician necessary; lifelong surveillance often needed, including cystoscopic evaluations and periodic imaging; for patients with muscle-invasive disease, radical cystectomy requires urinary diversion procedure that patients must learn to manage; can be complicated by comorbidities such as peripheral neuropathy; in those receiving perioperative chemotherapy, short- and long-term chemotherapy-related side effects not inconsequential (*eg*, hearing loss, peripheral neuropathy, renal insufficiency); in metastatic disease, chemotherapy-related side effects can have significant impact on quality of life as well

Suggested Reading

Martinez Rodriguez RH et al: Bladder cancer: present and future. *Med Clin (Barc).* 2017;149(10):449-55; **National Institute for Health and Care Excellence:** Bladder cancer: diagnosis and management of bladder cancer. *BJU Int*. 2017;120(6):755-65; **Smith AB et al:** Impact of bladder cancer on health-related quality of life. *BJU Int.* 2018;121(4):549-57.

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Testicular Cancer

Timothy Gilligan, MD, *Associate Professor of Medicine, Department of Hematology and Medical Oncology, Cleveland, and Vice-Chair for Education, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Introduction: testicular cancers most common form of germ cell tumors (GCTs); almost all testicular cancers GCTs; extragonadal GCTs in adults can occur in anterior mediastinum, retroperitoneum, or elsewhere, managed similarly to testicular GCTs; testicular cancer curable even when widely metastatic; affects young people, so failure to cure results in many lost decades of life; overly aggressive treatment causes unnecessary side effects or complications and loss of much quality of life; treatment based on strong data

- **Categorization:** 2 main categories, seminomas and nonseminomas; managed somewhat differently; any mixed GCT, nonseminoma; seminomas pure seminomas; if tumor 99% seminoma and 1% embryonal carcinoma, considered nonseminoma because mixed tumor
- **Staging:** stage I, stage II, and stage III; no stage IV because curable at any stage; stage I limited to testis; stage II has spread to regional (retroperitoneal) lymph nodes; stage III has spread to distant lymph nodes (*eg*, pelvic) or other organs (lungs, liver, or bones)
- **Risk categories:** disseminated disease classified as good, intermediate, or poor risk; important to assign correct risk group to choose appropriate chemotherapy
- **Serum tumor markers:** important, particularly alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (beta-hCG), and, to a lesser extent, lactic dehydrogenase (LDH)
- **Treatment:** important to know how to manage early-stage (stage I and II) disease and how to choose chemotherapy for early-stage or disseminated disease; how many cycles, which regimen; how to manage residual disease (mass); how to manage seminomas and nonseminomas
- **Early and late toxicity:** young patients will live for many years; consequences to chemotherapy, radiation therapy, surgery; important to be aware of those effects

Epidemiology: most common cancer in men aged 20 to 35 yrs; appears after puberty (age 15 yrs) and decreases after age 50 yrs; rare before puberty; not just cancer just of 20s and 30s; significant incidence in 40s and even 50s, but rare afterward; incidence rising, likely from unknown environmental causes; mortality has declined significantly due to more effective treatments and earlier diagnosis; 5-year relative survival, 97%; most patients cured

Risk factors: cryptorchidism (undescended testicle) one of biggest risk factors; relative risk, 10% to 15%; absolute lifetime risk of germ cell tumor, 2% to 3%; orchidectomy (lowering of testis) prior to puberty lowers cancer risk, but not to that of general population; family history in father or brother raises risk; brother with testicular cancer raises risk twice as much as having father with it, possibly because of shared mother, development in same womb, probably in same region of world, and in same era, thus similar exposure to environmental factors; no personal behaviors linked to testicular cancer; thought to be related to chemicals in environment; personal history of testicular cancer increases risk of second primary in other side (2% or 3% during lifetime); 97% do not have second cancer; monthly self-exam recommended for those with previous cancer; very rare for men not to notice lump in testis, but may fail to seek medical attention; message, if you notice something, see doctor; infertility another risk; possible common pathway in that abnormalities in male sexual development lead to infertility and testicular GCTs, but incompletely understood

Biology: testicular cancers almost always GCTs; in adults, testicular all GCTs have extra copies of short arm of chromosome 12; isochromosome 12p or detectable using fluorescence in situ hybridization (FISH) or cytogenetics; in children, biology different; for carcinoma of unknown primary with genetic testing that shows extra copies of short arm of 12p, treat as GCT; in clinical practice, uncommonly used

GCTs: 5 main categories, plus sixth category in older men; *5 main categories* — seminomas, embryonal carcinoma, choriocarcinoma, yolk sac tumors (formerly called endodermal sinus tumor), and teratomas (cancers in adult males, but may be benign in children); mature teratomas (ovarian GCTs) in women often benign; in adult men, teratomas considered malignant even though less likely to spread than other GCTs; *sixth category* — spermatocytic tumor (formerly called spermatocytic seminoma; renamed to clarify that not seminoma); spermatocytic tumors have different biology than other GCTs, with minimal potential to metastasize

Non-GCTs of testis: Leydig cell tumors, Sertoli cell tumors, and granulosis cell tumors; very rare; recommend referral to someone with more expertise or experience; lymphomas also occur in testis

Germ cell neoplasia in situ: term for carcinoma in situ for GCT; pediatric GCTs do not arise from that background

Choriocarcinoma in adults: should be distinguished from gestational trophoblastic choriocarcinoma because treated differently; gestational type does not occur in men, but choriocarcinoma in women can be GCT arising from ovary or can be gestational trophoblastic disease

Teratomas: differ biologically in men vs children vs women; higher malignant potential in men; different biology and

genetics; respond to pathology report differently based on sex and age of patient

Serum tumor markers: AFP, beta-hCG, and LDH; AFP and beta-hCG more important for diagnosis, staging, judging response to treatment, and surveillance for relapse

AFP: not produced by seminomas; if patient has orchiectomy and pathology report describes pure seminoma but elevated AFP, nonseminoma; AFP has half-life of ~1 wk; if AFP elevated prior to orchiectomy, should fall by 50% every 7 days after orchiectomy; if AFP not falling, concern for residual or metastatic disease; AFP associated with hepatocellular carcinoma, gastric carcinoma, and other cancers; tricky if carcinoma of unknown primary; if highly elevated, increased suspicion of hepatocellular carcinoma or GCT, but not pathognomonic; generally ignore AFP levels <20 ng/mL; normal cutoff varies widely (may be 7 ng/dL, 9 ng/dL, or 12 ng/dL); very mildly elevated AFP rarely significant; reasonable to do surveillance and recheck if concerned, but generally do not treat based on AFP level if <20 ng/dL or even <30 ng/dL; need to verify if real problem; well documented that some people have chronically mildly elevated AFP levels; do not want to give chemotherapy for that; liver disease and hepatotoxicity also raise AFP levels

Beta-hCG: can be made by any type of GCT; shorter half-life than AFP; should decline by ≥50% every 3 days (2 half-lives per wk, twice as fast as AFP); very high levels (70,000 mIU/mL or 100,000 mIU/mL) suggest choriocarcinoma; false positives can occur; can cross-react with luteinizing hormone, so test by administrating supplemental testosterone; for someone postorchiectomy with beta-hCG mildly elevated afterwards, how do you figure it out? one legitimate thing to do, give supplemental testosterone and see if number goes down; pituitary makes hCG in response to hypogonadism; so not just cross-reactivity with assay, but may be elevation of hCG in response to hypogonadism; reports that marijuana consumption leads to hCG elevation, but never proven; beta-hCG and AFP useful for diagnosis, staging, response, and surveillance; elevation of AFP or hCG common first sign of relapse, so important

LDH: less useful; only situation in which clearly useful, when deciding how much chemotherapy to give for disseminated disease; if LDH highly elevated, more chemotherapy should be given; use value of LDH on day 1 of cycle 1 of first-line chemotherapy; problem with LDH, so many different diseases cause elevation; if used for surveillance, get many false positives, so some guidelines have stopped recommending surveillance with LDH; not very specific, so not very useful for confirming diagnosis of GCT

Tumor marker value cutoffs: AFP and beta-hCG have high cutoffs; risk categories for AFP, <1000 ng/dL good, 1000 ng/dL to 10,000 ng/dL intermediate, >10,000 ng/dL poor; use values on day 1 of cycle 1 of first-line chemotherapy, not preorchiectomy; risk categories for beta-hCG, <5000 mIU/mL good, 5000 mIU/mL to 50,000 mIU/mL intermediate, >50,000 mIU/mL poor; decision about how much chemotherapy to give based on risk classification; serum tumor marker level one thing that dictates risk classification; LDH slightly more complicated; risk categories for LDH <1.5 times upper limit of normal (ULN) good; 1.5 to 10 times ULN is intermediate, and >10 times ULN poor; however, guidelines often recommend using 3 times ULN because of false positives; on board exams, if LDH >1.5-times ULN, give more chemotherapy; if treating actual patient, recommend using 3 times ULN

Clinical presentation: patients typically present with painful or painless testicular mass; presence of pain does not mean benign, just more likely to be infection; gynecomastia (breast enlargement) or gynecodynia (breast pain) can also be presenting signs; young man with these symptoms should be assessed for testicular cancer; testicular atrophy can be sign of GCT because testis may shrink around tumor and overall size of testis gets smaller; possibly infertility; metastatic disease with back pain, abdominal mass, supraclavicular lymphadenopathy; thromboembolic event, shortness of breath, other respiratory symptoms; testicular mass by far most common presentation

Surgical approach: do not biopsy testis; never pass needle through scrotum or remove testis through scrotum; testis removed through inguinal approach (inguinal orchiectomy or radical orchiectomy); management depends to some extent on predictable drainage pattern of testicular cancers to retroperitoneal lymph nodes, as lymphatic vessels pass up along with spermatic cord; sticking needle or cutting through scrotum can create alternative drainage that throws off surveillance and management strategies

Urgency: testicular tumors rapidly growing and aggressive; should be treated early; if man presents with testicular mass, it should be assessed by ultrasound and orchiectomy, both performed within 1 wk

Key steps in evaluation: physical examination, transscrotal ultrasound of testis to look for mass, check serum beta-hCG, AFP, and LDH for baseline values; if ultrasound shows suspicious mass, inguinal orchiectomy next step; computed tomography (CT) scan of chest, abdomen, and pelvis for staging if cancer confirmed; consider sperm banking

Staging: stage I, limited to testis, scrotum, or spermatic cord; stage II, metastases to retroperitoneal lymph nodes only; serum tumor markers can be only mildly elevated to be stage II; if tumor markers in intermediate- or poor-risk category, patient stage III, even if only retroperitoneal lymph node metastases; stage III, disseminated disease with distant metastases (pelvic and mediastinal lymph nodes, lungs, liver, bone, anywhere outside testis and retroperitoneal lymph nodes); retroperitoneal adenopathy plus highly elevated tumor markers, stage III; if radiographically stage I (no evidence of metastasis) but tumor markers do not decline to normal after orchiectomy, stage IS but treated same as stage III with respect to chemotherapy

T stages: T1, testis only, including invasion of tunica albuginea (the membrane immediately surrounding testis); T2, lymphovascular, tunica vaginalis, epididymis, or hilar soft tissue invasion; T3, invasion of spermatic cord; T4, invasion of scrotum; rarely see T3 or T4; lymphovascular invasion indicates higher relapse risk for those with early-stage disease

Stage II: lymph nodes ≤2 cm, stage IIA; 2 cm to 5 cm, stage IIB; >5 cm, stage IIC

Stage III: disseminated disease; stages IIIA, IIIB, and IIIC correlate with good, intermediate, and poor risk;

different for seminomas and nonseminomas; metastatic seminomas only good or intermediate risk; only important distinguishing factor location of metastases

Seminoma: good risk if metastases limited to lungs and/or any lymph nodes; intermediate risk if spread to liver, bone, brain, or any organ other than lungs; no poor risk; do not care so much about tumor marker levels as location of cancer; limited to lungs and lymph nodes or has it spread elsewhere?

Nonseminomas: poor risk if cancer has spread to liver, bones, brain, any organ other than lungs; good risk if limited to lungs and lymph nodes; different from seminomas in that tumor marker levels important; if tumor markers normal or good risk, patient has good risk; if intermediate risk markers, patient stage IIIB, or intermediate risk (AFP between 1000 ng/dL and 10,000 ng/dL, beta-hCG between 5000 mIU/mL and 50,000 mIU/mL, or LDH is between 1.5 times and 10 times ULN; poor risk if AFP >10,000 ng/dL, beta-hCG >50,000 mIU/mL, or LDH >10 times ULN; risk classification goes with whichever category worse; if patient meets any criteria for poor risk (*eg*, liver, bone, or brain metastases, high markers), considered poor risk; all men with mediastinal primary nonseminoma GCTs considered poor risk

Treatment for stage I seminoma: 3 options include surveillance, chemotherapy with single-agent carboplatin, or radiation to retroperitoneum; all result in nearly 100% 5-yr disease-free survival (DFS) but relapse rate differs; relapse rates ~17% for surveillance, ~1.6% for 2 cycles of carboplatin, ~5% for 1 cycle of carboplatin, ~4% for radiation; can lower risk of relapse with radiation or carboplatin chemotherapy, but not likelihood of 5-yr DFS; key issues to risk stratify, tumor size and presence of lymphovascular invasion; as tumor gets bigger, risk of relapse increases for stage I disease; ≤3 cm favorable; ≥3 cm unfavorable; *eg*, 1-cm tumor has relapse risk of ~10% and 8-cm tumor has relapse risk of ~25%; if lymphovascular invasion present, risk slightly higher (15% for 1-cm tumor and 35% for 8-cm tumor)

Surveillance: even for high-risk disease, two-thirds or more cured with orchiectomy alone, so surveillance generally preferred for stage I seminoma; almost all guidelines agree with that recommendation; some men uncomfortable with 20% relapse risk and want to lower that risk, even though we can cure them with chemotherapy if they relapse

Carboplatin: 2 cycles associated with fewest relapses, but never tested in randomized controlled trial; data from single-arm series; use controversial; if giving carboplatin for stage I seminoma, dose using measured glomerular filtration rate (GFR), not calculated creatinine clearance using Cockcroft-Gault; carboplatin well-tolerated; main toxicity is mild thrombocytopenia; febrile neutropenia and treatment-related bleeding rare; late effects unknown; one randomized trial showed 5% or 6% relapse rate for 1 cycle of carboplatin compared with 4% to 5% relapse rate for radiation therapy; subsequent series from clinical practice shows that risk reduction from 1 cycle of carboplatin unsatisfactory; if give carboplatin, recommend 2 cycles to get 98% relapse-free survival; carboplatin linked to second cancers; platinum-based chemotherapy linked to cardiovascular disease; some experts argue against using it

Radiation: controversial; clear increased risk of second cancers and death from gastrointestinal disease; increased cardiovascular mortality; lecturer reluctant to give radiation to patients with 99%+ 5-year disease-specific survival (DSS) if on surveillance; recommend surveillance; for men comfortable with that, give 2 cycles of carboplatin; on board exams, 1 cycle of carboplatin will likely be option but radiation, surveillance, and carboplatin all have excellent outcomes and none preferred; those 3 legitimate options; bleomycin/etoposide/cisplatin (BEP) chemotherapy not used

Treatment for stage II seminoma: higher nodal volume or larger diameter confers higher risk of relapse after radiation therapy; for nodes <2 cm, radiation therapy and chemotherapy equally effective; for this disseminated disease, give 3 cycles BEP or 4 cycles etoposide/cisplatin (EP); when nodes bigger, radiation less effective; hard cutoff at 5 cm; some recommend chemotherapy if >2 or 3 cm, but not standardized; in clinical practice, early stage II treated with either radiation or chemo; for stage IIB or IIC, prefer chemotherapy; role of retroperitoneal lymph node dissection being explored but no standard role at this time

Treatment for stage I nonseminoma: 3 options; surveillance preferred; if chemo, 1 cycle BEP recommended; retroperitoneal lymph node dissection (RPLND) also option; historical studies used 2 cycles BEP, but 1 cycle now preferred; 5-year DSS 99% for surveillance, RPLND, or BEP chemotherapy; relapse rates differ; surveillance relapse rate ~25%; RPLND relapse rate ~10%; 1 cycle BEP chemotherapy relapse rate ~2%; surveillance preferred approach because most men cured with orchiectomy alone; avoid treating men who do not need it if we can cure them at relapse; risk factors for relapse include lymphovascular invasion and high proportion of embryonal carcinoma; if both present, most patients relapse, so they may be uncomfortable with surveillance; downside of surveillance, needing serum tumor markers measured at least every 2 mos, if not every mo

How to choose: some advocate surveillance for all; some recommend risk-adapted approach (if no lymphovascular invasion, do surveillance; if lymphovascular invasion, give 1 cycle BEP); RPLND, option for all patients, but limited number of surgeons who do this complicated procedure; advantage of surveillance, most men spared postorchiectomy treatment; downside, many doctor visits and, if relapse 1 yr later, life completely disrupted because now going through chemotherapy for 2 mos or 3 mos and possibly postchemotherapy surgery to remove residual masses; chemotherapy up front gives lowest risk of relapse and peace of mind but early and potential late toxicity of chemotherapy; RPLND lowers risks of relapse, ever getting chemotherapy, of late relapse; RPLND leaves big scar, possible perioperative surgical complications, 10% risk of relapse (higher than risk after BEP chemotherapy), need to find skilled and experienced urologist; all 3 options relevant; carboplatin used only for seminomas

Treatment for stage II nonseminoma: volume or size of lymph nodes matters; for early-stage disease IIA (≤2 cm lymph node volume), RPLND good option; allows pathologic confirmation whether or not metastases present because false positives possible on CT scans; alternative, 3 cycles BEP; if confident that metastatic disease exists, 3 cycles BEP legitimate approach; RPLND valid if not sure about metastases; if nodes ≤2 cm but tumor markers elevated (mildly elevated AFP or hCG), prefer chemotherapy with 3 cycles BEP or 4 cycles EP; if markers highly elevated, indicates stage III, this does not apply; give more chemotherapy for intermediate- or poor-risk marker levels; do not use RPLND if markers elevated because higher risk of relapse after surgery compared with chemotherapy

First-line chemotherapy for disseminated germ cell tumors: BEP, EP, or etoposide, ifosfamide, and cisplatin plus mesna (VIP)

Second-line chemotherapy for relapsed disease: vinblastine, ifosfamide, cisplatin (VEIP);, paclitaxel, ifosfamide, and cisplatin (TIP); or high-dose chemotherapy with carboplatin and etoposide

How much chemotherapy and which regimen to choose: *stage I seminoma*- single-agent carboplatin only chemotherapy used as 1 or 2 doses; *stage I nonseminoma* — 1 cycle BEP standard; *stage I or stage II nonseminoma and RPLND shows pathologic stage II disease (positive nodes)* — 2 cycles BEP or EP only valid options; *disseminated disease* — for good-risk disease, 3 cycles BEP or 4 cycles EP only correct options; *intermediate- or poor-risk disease* — 4 cycles BEP or 4 cycles VIP only standard first-line regimens; *relapsed disease* — second- or third-line setting; 4 cycles VEIP, 4 cycles TIP, or 2 cycles high-dose chemotherapy using carboplatin and etoposide standard options

Bleomycin pneumonitis: important toxicity because patients at risk of progressing to fatal pulmonary fibrosis; important to diagnose early; looking for it only way to diagnose early; patients tend to present with dry cough and may have bilateral basilar rales and shortness of breath; no medical testing helps confirm; no pulmonary function tests to monitor because neither sensitive nor specific; when in doubt, discontinue bleomycin

Good-risk disease: if patient on BEP and develop signs or symptoms of bleomycin pneumonitis, stop bleomycin and switch to EP alone; make sure total of 4 cycles given but does not matter how many included bleomycin; so, if they got 2 cycles of BEP and then concern exists at beginning of cycle 3, drop bleomycin and give cycles 3 and 4 with EP

Intermediate- or poor-risk disease: if patient on 4 cycles BEP, substitute ifosfamide and mesna for bleomycin and give remaining cycles with VIP instead of BEP

Monitor for bleomycin pneumonitis: talk to patient to see if having symptoms; auscultate for rales; recommended precautions for patients after bleomycin to avoid high partial-pressure oxygen in hospital or during surgery; should not be induced for anesthesia with 100% oxygen, only as much oxygen as necessary to maintain safe blood saturation level; minimize perioperative (particularly intraoperative) intravenous (IV) fluids

Bleomycin pseudonodules in lungs: if patient has normal chest CT or chest x-ray prior to treatment and postchemotherapy imaging shows new fluffy lung nodules, probably inflammation from bleomycin; rare to present with new lung metastases in that setting; important not to overreact to new lung nodules, especially if inflammatory appearance and develop after chemotherapy

Other toxicities: cisplatin causes renal toxicity, ototoxicity, peripheral neuropathy in fingers and toes; etoposide, cisplatin, and carboplatin all associated with increased risk of secondary leukemia; all GCT chemotherapy associated with increased risk of infertility

Disseminated disease: patients with good-risk disease have option of 3 cycles BEP or 4 cycles EP; most evidence supports 3 cycles BEP in most patients; however, for older patients with declining renal function, prefer 4 cycles EP because bleomycin cleared by kidneys and patients more likely to get bleomycin pneumonitis; many recommend that patients aged >50 yrs be given 4 cycles EP and other patients be given 3 cycles BEP; if compromised renal function, prefer 4 cycles EP, regardless of age

Intermediate- or poor-risk disease: should they be given 4 cycles BEP or 4 cycles VIP? give VIP if specific contraindication to bleomycin (older patients, compromised renal function, or massive pulmonary metastases and concern about pulmonary function, prefer not to give lung-toxic drug)

Criteria for giving more chemotherapy: does patient need 3 cycles BEP, 4 cycles BEP, or 4 cycles EP? any patient who can have 3 cycles BEP can have 4 cycles EP; give more chemotherapy if AFP >1000 ng/mL, beta-hCG >5000 mIU/mL, or LDH >1.5-times ULN, if metastases to organs other than lungs, or if mediastinal primary nonseminoma GCT; 4 cycles BEP and 4 cycles VIP preferred in those situations; to choose between 4 cycles BEP and 4 cycles VIP consider 2 things; if patient healthy and no lung issues, prefer 4 cycles BEP because less toxic than VIP; if specific contraindication to bleomycin, prefer VIP; in clinical practice, prefer BEP for patients who can tolerate it; VIP causes more myelosuppression and febrile neutropenia

Growing teratoma syndrome: rare; patient getting chemotherapy for disseminated disease has markers going down but mass growing; typical scenario would be patient with stage III testicular nonseminoma, doing well but complaining of increasing back pain; imaging shows retroperitoneal mass growth during chemotherapy as beta-hCG went down; cancer shrinking but teratoma growing; teratomas less responsive to chemotherapy and typically require surgical removal; stop chemotherapy, resect teratoma, and do RPLND; not very common in clinical practice

Residual masses: *seminomas*- pure, with no teratoma component (*eg*, if mixed GCT, nonseminoma); for pure seminomas, most residual masses benign; if mass <3 cm, fewer than 5% have residual disease, so typically just surveillance; if mass <cm, surveillance or positron-emission tomography (PET) scan (only reason to consider PET scan for GCT; PETs can identify residual cancer but have high false-positive rate that leads to unneeded surgery); surveillance always option, but reasonable to get PET scan if >3 cm; wait ≥6 wks after chemotherapy to get PET to let inflammation subside or will have higher false-positive rate; *nonseminomas* — multimodality therapy and resection of residual masses whenever possible standards of care; removal of residual

masses may involve RPLND and surgery on lungs and/or liver to remove all residual tumor and render patient no evidence of disease (NED) at end of chemotherapy; may require surgical expertise only available at academic centers; postchemotherapy RPLNDs more difficult, with higher complication rate; worthwhile to send patients to surgeon who does those procedures regularly; for patients undergoing surgery for residual masses after chemotherapy, viable cancer present in ~10%, teratoma in ~40%, and fibrosis and necrosis in ~50%; if residual cancer found, often give 2 more cycles chemotherapy (based on retrospective studies of clinical experience)

Second-line chemotherapy: VEIP, TIP, or high-dose carboplatin and etoposide; no evidence favors one of them; if give VEIP but patient relapses, can give high-dose chemotherapy third-line

Late relapse: can often be cured; surgery key because often have teratomatous elements and at risk for subsequent relapse; may give chemotherapy up front, but resecting residual masses particularly important; sometimes resect everything up front, if possible; if markers elevated, prefer chemotherapy

Late effects of chemotherapy: increased risk of cardiovascular disease, secondary malignancies, infectious diseases, Raynaud phenomenon, peripheral neuropathy, hearing loss, and reduced pulmonary and renal function; predictable outcomes; treatment highly curative but quality of life can be compromised

Suggested Reading

Dieckmann KP et al: Serum tumour markers in testicular germ cell tumours: frequencies of elevated levels and extents of marker elevation are significantly associated with clinical parameters and with response to treatment. *Biomed Res Int.* 2019;2019:5030349; **Fukawa T et al:** Current knowledge of risk factors for testicular germ cell tumours. *Int J Urol.* 2018;25(4):337-44; **Ghandour RA et al:** Management of stage II germ cell tumors. *Urol Clin North Am.* 2019;46(3):363-76; **Ghodoussipour S et al:** Postchemotherapy resection of residual mass in nonseminomatous germ cell tumor. *Urol Clin North Am.* 2019;46(3):389-98; **Roth BJ:** Management of clinical stage I germ cell tumors. *Urol Clin North Am.* 2019;46(3):353-62; **Thomas LJ et al:** The role of imaging in the diagnosis, staging, response to treatment, and surveillance of patients with germ cell tumors of the testis. *Urol Clin North Am.* 2019;46(3):315-31.

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Penile and Adrenal Cancers

Tanya Dorff, MD, *Associate Professor of Medicine, Department of Medical Oncology and Developmental Therapeutics, and Head of Genitourinary Cancers, City of Hope Comprehensive Cancer Center, Duarte, CA*

Penile cancer: penile squamous cancer rare tumor; affects only 2320 men in US annually; ~26,000 cases globally, highest rates in less-developed countries; median age at diagnosis 50 to 70 yrs

Risk factors: 2 major driving risk factors, human papillomavirus (HPV) and chronic inflammation; for group affected with HPV, tends to be same high-risk genotypes as those seen in cervical cancer, particularly strain 16; HPV accounts for 45% to 80% (median 50%) of cases; preliminary data suggest penile cancer related to HPV may have more favorable prognosis; other group of patients, risk factors include lack of circumcision, balanitis, phimosis, or trauma; less known about related specific biology

Presentation: squamous cancers; can present with paraneoplastic syndromes (*eg*, hypercalcemia) when disseminated; most common presentation, lesion on penis (erythematous plaque or nodule); in locally advanced cases, spread to inguinal lymph nodes, occasionally disseminated cutaneous lesions

Staging: penile cancer follows orderly progression for metastases; staging consists of computed tomography (CT) of abdomen and pelvis; if no pelvic lymph node involvement, no chest metastasis; histology can have various patterns, including verrucas, associated with low malignant potential, papillary, "warty," or basaloid; sometimes described as keratinizing or not; grade more relevant than histologic features; poorly, moderately, or well differentiated, may have implications for behavior; *staging begins with T stage* — Tis (*ie*, tumor in situ) or Ta (*ie*, noninvasive); T1 involves glans, invading lamina propria or foreskin, invading dermis, lamina propria, or dartos fascia; T1 broken down into T1a if absence of lymphovascular or perineural invasion and absence of high-grade differentiation; T1b, minimally invasive, has any higher-risk features; T2, tumor invades corpus spongiosum, with or without urethral invasion; T3, tumor invades corpora cavernosa, including tunica albuginea with or without urethral invasion; T4, tumor invades adjacent structures, including scrotum, prostate, or pubic bone; *lymph node staging begins with clinical staging* — N1, palpable, mobile, unilateral lymph nodes; clinical N2, palpable and mobile nodes, ≥2 unilateral or bilateral; clinical N3, nodes fixed or CT reveals pelvic node involvement; *pathologic staging* — N1, similarly, ≤2 unilateral; pN2 ≥3 unilateral without extranodal extension; pN3, pelvic lymph nodes involved or extranodal extension; T1a, stage I tumor; T1b and T2, stage IIA; T3 tumors, stage IIB; node involvement, stage IIIA; 2-level node involvement, stage IIIB; T4 tumors, those with N3 status or distant metastases, stage IV; because understanding nodal stage important, sometimes necessary to perform needle biopsy of inguinal lymph nodes (can be inflammatory or reactive); will help with surgical planning for inguinal lymph node dissection

Prognosis: localized disease can typically be cured; surgery plays biggest role; nodal involvement important prognostic factor; without nodal metastases, 5-yr cancer-specific survival 85% to 100%; decreases to 79% to 89% if nodal involvement; if multiple or bilateral nodal metastases (*ie*, stage N2 or N3), 5-yr survival 17% to 60%; N3 with pelvic node involvement, 5-yr survival <17%

Localized and early-stage treatment: for localized disease, typically surgical, although early-stage disease and/or very superficial disease can be treated, in some cases, with topical therapy using 5-fluorouracil (5-FU) or imiquimod; with earlier-stage disease, important to consider organ sparing; rather than partial penectomy, consider wide local excision; Mohs surgery; radiation sometimes used for organ sparing

Advanced tumor treatment: lymph node dissection frequently indicated (*ie*, T2 tumor with high-risk features, *eg*, poorly differentiated histology, grading, or vascular invasion) to stage inguinal lymph nodes; sentinel lymph node techniques not associated with adequate sensitivity, so not utilized; if ≥2 inguinal lymph nodes involved, indication for pelvic lymph node dissection; if ≥4 lymph nodes involved, bilateral pelvic lymph node dissection

Role of systemic therapy in locally advanced disease: controversy, lack of level 1 evidence regarding whether neoadjuvant chemotherapy should be employed; neoadjuvant refers to inguinal lymph node dissection; most commonly, primary lymph node resected first, then consider chemotherapy prior to nodal dissection; consensus, no controversy for locally advanced case involves ulcerated lesions, bulky lymph nodes, or pelvic lymph nodes

Pagliaro et al, *Journal of Clinical Oncology* (2010): prospective study of neoadjuvant paclitaxel, ifosfamide, cisplatin (TIP) chemotherapy for stage N2 or N3 penile cancer without distant metastases; administered 4 cycles of modified TIP regimen, paclitaxel 175 mg/m^2 day 1, ifosfamide 1200 mg/m^2 days 1-3, cisplatin 25 mg/m^2 days 1 to 3 for 4 cycles; although no randomization or control group aside from historic performance, results compelling; 50% of patients had objective response,

some with pathologic complete response (pCR); conclusion, median overall survival (OS) 17 mos far exceeded historical comparison, and together with observed clinical responses, this regimen became new standard of care

- Surgery remains critical: important to note that surgery remains critical, and any patient treated with neoadjuvant chemotherapy still needs lymph node dissection; also, if clinical progression during neoadjuvant chemotherapy, discontinue and proceed to surgery
- Cisplatin, 5-FU (TPF): several studies have shown pCR in ~15% of patients with overall response rates approaching 40%
- Adjuvant chemotherapy: while neoadjuvant chemotherapy preferred approach, patient who undergoes inguinal lymph node dissection and has findings of more lymph node involvement than expected can be offered adjuvant chemotherapy (but level of evidence not high); older regimens, including bleomycin, no longer typically used in penile cancer because of toxicity; lack of data complicates rational treatment planning (*eg*, how to incorporate radiation in locally advanced penile cancer); International Penile Advanced Cancer Trial (InPACT) will seek to answer several unanswered questions for penile cancer patients; these include patients not receiving adjuvant or neoadjuvant chemotherapy to receive chemoradiation using cisplatin, and also questions about pelvic lymph node dissection
- Platinum chemotherapy failure: little evidence for what treatment should be selected; multiple case series using epidermal growth factor receptor (EGFR)–targeted therapy due to nearly ubiquitous high expression of EGFR in penile squamous cancers; series of studies showing responses with cetuximab or panitumumab, sometimes combined with either taxane or platinum chemotherapy, or used together with radiation for refractory pelvic masses or local regional disease

- Genomic profiling: could be used to try to find rational target for patients with limited treatment options; programmed death ligand-1 (PD-L1) expressed strongly in up to half of penile cancer patients, primarily HPV-negative cases, but limited data so far regarding use of immune checkpoint inhibitors in this group of patients

Adrenal cancer: rare tumor; many benign, or metastatic deposits from other primary cancers; with larger adrenal tumors, greater possibility of malignancy; women more commonly affected than men; symptoms of hormone secretion might indicate adrenal tumor with malignancy

- Workup: first aspect of investigation includes assessing for hormonal secretion, particularly for evidence of pheochromocytoma which requires special management; general workup includes checking urine for metanephrines, plasma cortisol, and adrenocorticotropic hormone (ACTH), plasma renin and aldosterone, testosterone, dehydroepiandrosterone sulfate (DHEAS), and estradiol; adrenal tumors can secrete 1 or multiple hormones, most commonly cortisol and androgens
- Pheochromocytoma: highly associated with hereditary syndromes, so genetic consultation mandatory; 20% demonstrate aggressive behavior, more commonly in older men or patients who present with large primary synchronous metastases or elevated dopamine levels
- Pheochromocytoma presentation: headaches, heart palpitations, diaphoresis; tend not to be present in other types of adrenal tumors; new hypertension, labile hypertension also suspicious for pheochromocytoma; if suspected, 24-hr urine collection necessary to measure secreted hormones; extra-adrenal pheochromocytomas (*ie*, paragangliomas) present with similar symptoms
- Hereditary pheochromocytomas: neurofibromatosis; multiple endocrine neoplasia (MEN)1 and MEN2; von Hippel-Lindau disease; familial paraganglioma syndromes
- Pheochromocytoma diagnosis: either urine or plasma levels can be measured; certain medications can cause false-positive results in plasma testing for dopamine and metanephrines, including tricyclic antidepressants, beta blockers, levodopa, caffeine, monoamine oxidase (MAO) inhibitors, withdrawal from clonidine and alcohol; drugs that can interfere with testing and urinary assays include beta blockers, tricyclic antidepressants, buspirone, and nicotine; plasma metanephrines highly sensitive; 24-hr urine total metanephrines and catecholamines valuable in making diagnosis; typically, pheochromocytoma can be seen on standard imaging such as CT; occasionally, suspicion for pheochromocytoma based on symptoms present but tumor not clearly visualized; in these cases, iodine-131-meta-iodobenzylguanidineiodine (MIBG) scan can help find tumor location with greater sensitivity, also highly specific; patients need to discontinue certain medications (*eg*, beta blockers, tricyclic antidepressants, prochlorperazine) for 48 to 72 hrs before, and must block thyroid uptake using iodine preparation; fluorodeoxyglucose-positron emission tomography (FDG-PET) scan also has some utility in these cases, although typically utilized after MIBG if results inconclusive
- Pheochromocytoma surgery: risk during surgery for blood pressure (BP) fluctuations resulting from secretions by pheochromocytomas; alpha- and beta-adrenergic blockade critical before surgical intervention or can perform preoperative tumor embolization
- Surgical planning: control alpha- and beta-adrenergic axis to avoid tachycardia and BP fluctuations intraoperatively as well as risk of arrhythmias; *alpha-adrenergic blockade* — phenoxybenzamine most commonly utilized alpha-adrenergic blocker, typically started for at least 1 to 3 weeks before surgery, titrated to BP and symptom control during that period; some side effects, so alternatives include doxazosin or terazosin (more selective); liberal salt and fluid intake also important in perioperative period; *beta blockade* — after alpha-adrenergic blockade established, begin beta blockers, which should never be used alone in these patients; most commonly, atenolol and metoprolol preferred over nonselective beta blockers such as propranolol; calcium channel blockers may be used as alternative if difficulty tolerating other agents, but not as first line; metyrosine also shown to be helpful; blocks rate-limiting step in catecholamine synthesis, in which tyrosine converted

to L-dopa; some trials positive and some negative for using this agent alone or in combination with phenoxybenzamine; currently should be reserved for cases with large tumor burden or if lack of effect of other agents; *surgical team* — experienced surgical team including experienced anesthesiologist critical to manage potential intraoperative complications that can occur despite preoperative alpha and beta blockade; if acute hypertensive moments intraoperatively, sodium nitroprusside and phentolamine or nicardipine favored

Postoperative: risk of hypotension or hypoglycemia; careful postoperative monitoring not only of BP but also glucose levels critical for success

Systemic therapy: rare tumor, so no level 1 evidence in terms of systemic therapy for advanced cases; most common chemotherapy regimen cyclophosphamide, vincristine, and dacarbazine (CVD), associated with response and symptom relief in up to 50% of patients; can also be palliation of secretion-related symptoms; overall, regardless, prognosis poor, median survival 3 yrs; *newer agents* — some case reports assessing sunitinib show some evidence for response but again, no large randomized trials available; radioactive agent 177-Lu-[DOTA 0, Tyr 3] octreotate (177-Lu-DOTATATE), primarily used in gastrointestinal (GI) or endocrine tumors, has shown promise for treating paragangliomas; case report documenting some response; also could be used in von Hippel-Lindau–related pheochromocytomas, showing some reductions in tumor burden and improvement in symptoms; also some case reports with temozolomide inducing partial responses; in future, more prospective data coming from trial with vascular endothelial growth factor (VEGF) therapy, and trial from Canada with sunitinib; *epigenetic therapy* — succinate dehydrogenase (SDH) mutation leads to accumulation of metabolites and hypermethylation, so guadecitabine being studied

Adrenocortical carcinoma (ACC): also very rare; can occur at any age, but 2 peaks in incidence, one in first decade of life, second 40 to 50 yrs of age; women more frequently affected than men

Familial syndromes: Li-Fraumeni syndrome, from tumor suppressor gene TP53 mutations; Beckwith-Wiedemann syndrome, from alterations in insulin-like growth factor (IGF); also many other gene alterations, not necessarily hereditary, can also occur as part of etiology

Assessment of hormonal secretion: once pheochromocytoma ruled out, assessment for hormonal secretion by adrenal tumors includes checking cortisol, ACTH, DHEAS, 17-hydroxyprogesterone, testosterone, androstenedione, and estradiol; recommended to perform dexamethasone suppression test and to measure free urinary cortisol

CT scans and other imaging: many adrenal tumors benign; tumors ≤10 Hounsfield units (HU) in unenhanced CT most commonly benign; if >10 HU, using contrast for enhancement can be helpful based on enhancement pattern and washout; utility of PET scan not established (currently being evaluated in ongoing studies)

Weiss score: pathologically, Weiss score used to determine tumor aggressiveness; factors include nuclear grade using grade 3 or 4 based on Fuhrman criteria, mitotic grade, mitotic rate (specifically, >5 per 50 high-power fields), atypical mitotic figures, presence of ≤25% clear or vacuolated cytoplasm, diffuse architecture (*ie*, greater than one-third of tumor forms patternless sheets), necrosis, venous invasion, sinusoid invasion, and invasion of tumor capsule; each of these 9 Weiss criteria score 1 point; score of ≤3 represents adenoma, ≥4 classified as adrenocortical carcinoma

Ki67: greater emphasis on Ki67 (mitotic index) in terms of prognostication; ≥5% cutoff; >20 mitoses per 50 high-power field, high-grade ACC; low-grade ACC ≤20 mitoses per 50 high-power field

TNM staging: T1 tumors, ≤5 cm; T2 tumors, >5 cm; T3 tumors, invasion of surrounding tissue; T4 tumors, invasion of adjacent organs or demonstrate venous tumor thrombus in vena cava or renal vein; node staging dichotomous, N0, negative lymph node involvement; N1 positive lymph nodes; same for M, or metastatic, staging; stage I tumor, T1, N0, M0; stage II, T2, N0, M0; stage III, T3 or T4 or nodal involvement; stage IV, distant metastatic tumors

Prognosis: surgery mainstay of management for adrenal tumors including adrenocortical carcinoma; some experiences using radiofrequency ablation as less-invasive approach; ~20% of patients have metastatic disease at time of presentation; these patients or those who later relapse after adrenalectomy have poor prognosis, with 5-yr survival rate close to 0

Mitotane: adrenolytic drug; extensively studied in adrenocortical carcinoma; toxicity major limitation; GI and constitutional symptoms common; *The New England Journal of Medicine* (2007) — for patients whose tumor has been resected, adjuvant mitotane after adrenalectomy associated with prolonged survival in, not randomized study; patients in study received 1 g to 5 g daily based on titration and toleration of symptoms; median duration of treatment 29 mos; study performed in Italy and Germany; *ADIUVO* — ongoing study; will test mitotane vs observation after surgery in low- or intermediate-risk adrenocortical carcinoma (*ie*, Ki67 ≤10%); *ADIUVO-2* — patients randomized to mitotane vs mitotane plus combination chemotherapy using etoposide and cisplatin for high-risk patients with Ki67 >10%; mitotane also used in advanced disease, can be used as single agent; Fassnacht et al, *The New England Journal of Medicine (2012)* — suggested chemotherapy did have role combined with mitotane; in this study, progression-free survival 5 mos compared with 2 mos; OS improved by addition of chemotherapy; hazard ratio 0.79; objective responses seen in 23% of patients with combination of etoposide, doxorubicin, cisplatin (EDP) chemotherapy with mitotane; 58% of patients experienced disease control; toxicity major concern, given difficulty for patients to tolerate mitotane on its own; 58% of patients experienced serious adverse events, most commonly myelosuppression; ~ 7% of patients had cardiovascular or thromboembolic events; also cases of severe fatigue, GI difficulties, neurologic and respiratory toxicities

Other treatment approaches: approaches to leverage underpinning of hormonal secretion and molecular changes found in adrenocortical cancers (*eg*,

figitumumab and linsitinib, target IGF signaling, some evidence of activity); VEGF-targeted therapy, including studies of bevacizumab with capecitabine, sorafenib with paclitaxel, and sunitinib as single agent; everolimus has been tested but interacts with mitotane; *linsitinib trials* — in phase 1 trial with linsitinib, 11 adrenocortical cancer patients treated for 12 mos; 1 patient had positive response, 4 had stable disease; however, placebo-controlled study published by Fassnacht et al in *The Lancet: Oncology* (2015) did not find survival advantage; mutational load high in adrenocortical cancers; PD-L1 expression modest, but no strong evidence for efficacy of immune checkpoint inhibitors in this disease

- Metastasectomy: due to few treatment options, consider metastasectomy when patient has limited amount of spread; several studies published suggesting excellent long-term survival with metastasectomy; study from National Cancer Institute showed median survival of 40 mos in 23 patients with median 6 lesions resected; Memorial Sloan Kettering study of 83 patients found that patients with complete resection of metastases had median survival of 74 mos, whereas those with incomplete resection had median survival of 16 mos; German study in 24 patients showed median survival of 50 mos
- Immunotherapy: immunotherapy with pembrolizumab tested in limited number of patients; 3 of 12 patients showed evidence of response, more common in patients with nonfunctioning tumors; more studies needed; ongoing trials will seek to answer role of immune checkpoint inhibitors in adrenal cancer, including studies of nivolumab and pembrolizumab as single agents and study of nivolumab plus ipilimumab; additional VEGF tyrosine kinase inhibitors (TKIs) actively being studied, including cabozantinib, because of interest in MET signaling as part of pathogenesis of adrenocortical carcinoma; lenvatinib also being studied; referral for clinical trial likely best option for metastatic adrenocortical cancer patient

- Cushing syndrome: ~10% of Cushing syndrome cases arise from adrenal tumors; manifest as glucose intolerance and hypertension; symptoms can include proximal muscle weakness, facial flushing, increased fat deposition, Cushingoid facies, fat deposition around abdomen, striae (*ie*, purplish markings primarily on abdomen); can also have impact on sex hormones, may lead to menstrual irregularities or androgen excess, virilization
- Hyperaldosteronism: another syndrome that adrenocortical carcinoma patients may have; manifests primarily as hypertension and hypokalemia
- Androgen secretion: in patients whose tumors secrete androgens, can see virilization, including hair growth, acne eruptions, increased libido; estrogen-secreting tumors can present as feminization in males, including gynecomastia, decreased libido, and testicular atrophy; for women, breast tenderness or dysfunctional uterine bleeding
- Management after adrenalectomy: algorithm in E*uropean Journal of Endocrinology* (2013); for patients with R0 resection (*ie*, negative surgical margins), stage I to III, Ki67 ≤10%, observation or mitotane can be considered; if Ki67 >10%, mitotane adjuvant recommended; for patients with positive surgical margin, Ki67 ≤10%, mitotane recommended, can consider radiation (albeit limited evidence); if Ki67 >10%, mitotane offered, consider additional chemotherapy; if gross residual disease or recurrence, repeat surgery considered; radiotherapy can be considered for unresectable lesions, mitotane plus chemotherapy can lead to response and potentially make some tumors resectable
- Mitotane dosing: start at low dose, 500 mg to 1 g twice daily, titrate upward, aiming for therapeutic range of 14 mg/L to 20 mg/L; when mitotane combined with chemotherapy, dose 1 to 3 g divided into 3 doses daily, again targeting adequate serum level; chemotherapy typically consists of etoposide 100 mg/m^2 days 2 to 4, cisplatin 75 mg/m^2 day 1, and doxorubicin 40 mg/m^2 day 1; cycles administered every 3 to 4 wks; regimen based on Berruti et al trial in *Endocrine-Related Cancer* (2005)

Suggested Reading

Kamel MH et al: Organ sparing surgery for penile cancer: a systematic review. *J Urol*. 2017;198(4):770-9; **O'Brien JS et al:** Penile cancer: contemporary lymph node management. *J Urol.* 2017;197(6):1387-95; **Sautter AE et al:** Laparoscopic adrenalectomy for adrenal cancer-a systematic review. *Am Surg*. 2016;82(5):420-6; **Spartalis E et al:** Metastatic carcinomas of the adrenal glands: from diagnosis to treatment. *Anticancer Res.* 2019;39(6):2699-710.

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Ovarian Cancer

Jenna Z. Marcus, MD, *Assistant Professor, Division of Gynecologic Oncology, and Director, Robotic Surgery, Rutgers New Jersey Medical School, Newark, NJ*

Ovarian cancer: the ovary is divided into different compartments, with cellular functions representing each; ovarian cancers can be subdivided into nonepithelial and epithelial subtypes; epithelial ovarian cancers include high-grade serous carcinoma, low-grade serous carcinoma, mucinous carcinoma, clear cell carcinoma, and endometrioid carcinoma; nonepithelial subtypes are further divided into sex cord-stromal tumors and germ cell tumors; additional category represents metastatic disease to the ovary

Epithelial compared to non-epithelial tumors: the majority of ovarian cancers fall into the epithelial group; ~7% of diagnosed malignancies are sex cord-stromal tumors and 2-3% are germ cell tumors; tumors also occur in a different age range in patients, have a different biology, and a different prognosis from epithelial cancers

Epithelial ovarian cancer: leading cause of death from a gynecologic malignancy in the US and Europe; fifth most common cause of cancer death in women; ~1 in 70 will be diagnosed with an epithelial ovarian cancer and 1 in 100 will die of this disease; in 2019, there will be ~22,530 new diagnoses and 13,980 deaths; disease attributed to differences in genetic predisposition, as well as hormonal and reproductive factors; higher incidence rates are seen in North America and Europe vs Asian and African countries; biology is not well understood

Tumor types: epithelial ovarian cancers include cancer arising in the peritoneum, fallopian tube, and ovary; extreme variations in histologic structure and biologic behavior; a recent dualistic pathogenesis model suggests that tumor types can be subdivided into type 1 and 2 tumors

Type 1 vs type 2 tumors: type 1 tumors tend to follow a more indolent course and have precursor lesions; include carcinomas that are low-grade serous, mucinous, endometrioid, and clear cell; mutations in these tumors are often BRAF, KRAS, Pi3 kinase, and ERBB2, as well as additional signaling molecules; type 2 tumors often have mutations in p53 and develop into high-grade serous carcinomas; mutations within the tumor suppressor BRCA1 and BRCA2 genes also can lead to high-grade serous ovarian cancer because the BRCA genes participate in cell cycle checkpoint, gene expression, and DNA repair via homologous recombination or double-stranded DNA repair; BRCA-mutated cells cannot repair double-stranded breaks and have increased genomic instability, which may be subject to malignant transformation

Type 1 tumors: the precursor lesion often resembles the carcinoma that develops; eg, borderline tumors are thought to be responsible for the development of low-grade serous ovarian cancers, endometrioid cancers, and mucinous cancers; another example is that the malignant transformation of endometriosis is thought to be responsible for the development of both clear cell and endometrioid ovarian carcinomas; the risk of malignant transformation is low in this population, but studies have demonstrated molecular alterations and chromosomal aneuploidy in these lesions

Type 2 tumors: thought to arise de novo from intraepithelial carcinomas; classic thinking was that they developed from surface dysplasia of the ovarian surface or ovarian surface disruption, commonly referred to as the incessant ovulation theory, where post-ovulatory repair was thought to generate dysplastic cells within the ovarian surface epithelium; more recent evaluation of intraepithelial carcinomas has led to the finding of lesions in the fallopian tube fimbriated end containing p53 on immunohistochemistry ("p53 signature"); theory that a portion of ovarian cancer arises at the fimbriated end of the fallopian tube and can be seen in a precursor lesion known as serous tubal intraepithelial carcinoma (STIC); there can also rarely be malignant transformation from a type 1 into a type 2 tumor

Screening: given the low incidence of ovarian cancer and the lack of a clear pre-invasive lesion or feasible screening, screening is difficult; Society for Gynecologic Oncology, American College of Obstetrics and Gynecology, and the United States Preventative Services Task Force do not recommend screening in women that are low-risk and asymptomatic, as screening in these women with either CA-125 (cancer antigen-125) levels or pelvic ultrasounds often results in false-positive tests that can lead to unnecessary procedures; screening has not led to increased diagnosis and detection of ovarian cancer in earlier stages to reduce ovarian cancer mortality

Subset of patients recommended to undergo screening: those who have a BRCA family germline mutation in either BRCA1, BRCA2, or other genes associated with ovarian cancer; includes patients with mismatch repair or Lynch-associated syndrome germline mutations and genes within the Fanconi anemia pathway; often identified in panel testing performed in high-risk women; women with a strong family history but negative testing should also be considered for screening

Risk factors: include the long-term use of estrogen alone, a first- or second-degree relative with a history of ovarian cancer, older age, a personal history of infertility,

residence within North America, nulligravidity (never being pregnant), higher levels of education and income, talc exposure, late age at natural menopause, Caucasian race, and early age of menarche; factors that decrease the risk of ovarian cancer include a history of hysterectomy with tubal ligation or a history of tubal interruption and use of oral contraceptives; women who use oral contraceptives for ≥5 years have a 50% decreased risk; risk reduction strategies in the general population include chemoprevention with a combined oral contraceptive pill for ≥5 years, and surgical strategies, such as tubal interruption or tubal removal (salpingectomy), if the patient has completed childbearing and is undergoing hysterectomy for benign disease; although most cases are sporadic, ~15-20% are the result of a germline mutation in BRCA1, BRCA2, or other genes associated with hereditary breast and ovarian cancer; cumulative lifetime risk by age 70 in a female with the BRCA1 gene is ~40%; in BRCA2, just under 20%

Testing: identification of patients with a [family?] history of breast or ovarian cancer can suggest those who may benefit from novel therapeutic agents and those who are at risk and may benefit from a risk-reducing, bilateral, salpingo-oophorectomy; also offers the potential to include extended genetic testing to biological relatives, known as cascade testing; cascade testing can lead to early intervention and employment of cancer risk-reduction strategies in families affected by BRCA mutations

Risk reduction for women known to be at higher risk: in prospective studies, risk-reducing salpingo-oophorectomy decreased the risk of developing ovarian, fallopian tube, or primary peritoneal carcinoma by 80%; the National Comprehensive Cancer Network (NCCN) recommends risk-reducing salpingo-oophorectomy at age 35-40 after the completion of childbearing; it is possible to delay this surgical procedure until age 40-45 in patients harboring a BRCA2 mutation; for patients who have not elected to undergo surgical intervention by removing the tubes and ovaries, transvaginal ultrasound combined with CA-125 serum levels for ovarian cancer screening can be considered at age 30-35, although this is of uncertain clinical benefit; patients undergoing risk-reducing salpingo-oophorectomy should have their specimens submitted to identify occult tumors at the distal end of the fallopian tubes; known as the SEE-FIM protocol (sectioning and extensively examining the fimbriated end of the fallopian tube); amputation and longitudinal sectioning of the infundibulum and fimbrial segment (distal 2 cm) to allow maximal exposure of the tubes; cut transversely at smaller intervals

FIGO (International Federation of Obstetrics and Gynecology) ovarian cancer staging: updated most recently in 2014; mainly based on location of tumor

Stage I disease: tumor confined to ovaries or fallopian tubes; there is no stage I primary peritoneal carcinoma; stage IA — limited to 1 ovary and requires an intact capsule or fallopian tube; stage IB involves both ovaries, with an intact capsule or contained within the fallopian tube; stage IC is tumor limited to 1 or both ovaries or fallopian tubes; stage IC1 — surgical spill occurs intraoperatively; stage IC2 — capsule is ruptured before surgery or tumor on ovarian surface or fallopian tube surface is present; stage IC3 — malignant cells in the ascites or peritoneal washings; ascites or peritoneal washings are commonly collected at the start of the procedure for surgical staging

Stage II: tumor present on 1 or both ovaries or fallopian tubes with pelvic extension; stage IIA — extension or implants on the gynecologic structures, the uterus, or fallopian tubes; stage IIB — extension to other pelvic intraperitoneal tissues

Stage III: tumor involves 1 or both ovaries or fallopian tubes or primary peritoneal cancer, which is confirmed to have spread to the peritoneum located outside the pelvis and/or metastases in the retroperitoneal lymph nodes; IIIA1 — positive retroperitoneal lymph nodes only; further divided into metastases ≤1 cm or >1 cm; stage IIIA2 — microscopic extrapelvic peritoneal involvement with or without positive retroperitoneal lymph nodes; stage IIIB — macroscopic extrapelvic peritoneal metastases measuring ≤2 cm, with or without the presence of positive retroperitoneal lymph nodes; can include extension to the capsule of the liver or the spleen; stage IIIC — macroscopic extrapelvic peritoneal metastases >2 cm, with or without the presence of positive retroperitoneal lymph nodes; also includes extension to the capsule of the liver or spleen; parenchymal involvement is not included

Stage IV: distant metastases, excluding peritoneal metastases; stage IVA — positive pleural effusion where cytology is positive for tumor; stage IVB — hepatic and/or splenic parenchymal metastases or metastases to extra-abdominal organs, including the inguinal lymph nodes and lymph nodes outside the abdominal cavity; bowel infiltration may be present if there is transmural spread with mucosal involvement and/or an umbilical deposit

Clinical presentation: wide range; patients presenting with early-stage disease and small pelvic or adnexal masses range from completely asymptomatic to mild pressure or pelvic/abdominal pain; more advanced cancers may present with vague clinical symptoms such as abdominal distension, early satiety, abdominal or pelvic pain, change in bladder or bowel function, nausea, vomiting, anorexia, fatigue

Physical examination: includes examination of the lymph nodes, including supraclavicular lymph nodes, paying attention to the left side, which is the side of the drainage of the thoracic duct, axillary, and inguinal lymph nodes; abdominal exam may reveal presence of a fluid wave, indicating ascites; veins crossing over the abdomen that appear engorged and consistent with caput medusae may be an indicator of venous obstruction; presence of an umbilical nodule positive for carcinoma is termed the Sister Mary Joseph nodule and indicates more advanced disease; pelvic exam is performed to assess the size, mobility, and location of a pelvic mass; a rectovaginal exam can be performed to assess the rectovaginal space for nodularity, obliteration, presence of tumor, and parametrial involvement, which may indicate the need for a larger surgical procedure

Laboratory examination: in advanced ovarian cancer, a CBC may demonstrate hemoconcentration and the presence of thrombocytosis, which is a poor clinical marker; CA-125 testing can indicate many false positives in premenopausal women; in stage I

ovarian cancer, ~50% of CA-125 values are elevated; in postmenopausal patients with ovarian cancer, 80% of CA-125 levels are elevated; additional markers examining ovarian cancer are HE4 (human epididymis 4) and OVA1, which is a combination test of CA-125, pre-albumin, apolipoprotein A1, beta-2 microglobulin, and transferrin

Additional tumor markers: may be checked, depending on suspected tumor histology; the serum marker for epithelial ovarian cancer is CA-125; when suspecting a mucinous cystadenocarcinoma, CEA (carcinoembryonic antigen) may be elevated; AFP (alpha fetoprotein) is often elevated in endodermal sinus tumors; human chorionic gonadotropin (HCG) and AFP may be elevated in embryonal cell carcinomas; elevated HCG typically seen in choriocarcinomas; elevated lactate dehydrogenase (LDH) may indicate disgerminoma ovarian tumors; inhibin may be a marker of granulosis cell tumors; markers plus patient age at presentation may give clues to tumor histology prior to surgery

False positive CA-125: gynecologic conditions that can falsely give an elevated CA-125 include acute pelvic inflammatory disease, benign ovarian neoplasms, endometriosis, menstruation, Meigs syndrome, ovarian hyperstimulation, and uterine fibroids; nongynecologic conditions that can elevate CA-125 concentrations include hepatitis, pancreatitis, chronic liver disease, cirrhosis, colitis, congestive heart failure (CHF), diabetes, diverticulitis, nonmalignant ascites, pneumonia, postoperative conditions, renal disease, and autoimmune conditions, such as lupus

Imaging: sonogram of the abdomen and pelvis, depending on the location of the mass; adnexal mass can be described as simple, complex, containing solid or heterogeneous elements, septations, papillary projections, mural nodularity, and/or the presence of ascites; other than a simple-appearing structure, these factors increase concern for malignant disease; ultrasound sensitivity is ~84% with a specificity of 80%; if ultrasound reveals an indeterminate lesion, a contrast-enhanced MRI with T2-weighted imaging may be able to evaluate septations, solid areas, and papillary projections, and can increase the sensitivity and specificity for a cancerous nodule; CT scan, MRI, and/or PET CT are often not recommended for the initial evaluation of adnexal masses; CT scan can be performed when cancer is not adnexal or when additional pathology is suspected throughout abdomen; MRI can distinguish subtle differences in tissue signals, enhance anatomic detail, and assist in evaluating indeterminate lesions on ultrasound; PET CT following abnormal ultrasound has good sensitivity and specificity; more effectively used when disease recurrence is suspected; sensitivity in recurrent disease is 82% with a specificity of 87%

Differential diagnosis of an abdominal or pelvic mass: may include other intraabdominal malignancies (eg, colon, gastric, or pancreatic cancers); may include hematologic and other malignancies; Krukenberg tumor is a metastatic lesion from a gastric cancer to the ovary; when suspecting a colon or colorectal cancer in the differential, a CA-125/CEA ratio >25 indicates the likelihood of an ovarian cancer primary

Surgical staging/cytoreductive procedure: includes surface inspection of all pelvic organs, the small and large intestine, mesentery, appendix, stomach, liver, gallbladder, spleen, omentum, both diaphragms, and the entire peritoneum, with possible biopsies, excision, or resection; should include abdominopelvic and upper abdominal washings, removal of the affected ovary, total hysterectomy with bilateral salpingo-oophorectomy in patients not undergoing fertility preservation, infracolic or infragastric omentectomy, pelvic and periaortic lymph node dissection; appendectomy may be indicated; if no peritoneal disease, random biopsies of the peritoneum are indicated to rule out micrometastases

Fertility preservation: in early-stage disease, fertility preservation procedures may be considered and would omit the removal of the contralateral tube, ovary, uterus, and cervix; if these procedures are not performed in a suspected early ovarian cancer, surgical staging should be done within 3 weeks of diagnosis; 20%-30% risk of an undiagnosed higher stage in these patients; 5%-25% of unstaged early cancers have positive lymph nodes, which would up-stage the patient to microscopic advanced disease and would require adjuvant chemotherapy

Advanced ovarian cancer: may require more radical procedures to achieve maximal resection or optimal cytoreduction; may include multiple bowel resections, complete peritonectomy or peritoneal stripping, splenectomy, distal pancreatectomy, cholecystectomy, full-thickness resection of the diaphragm, liver wedge resection, and low-anterior resections in the pelvis; in advanced ovarian cancers, systematic pelvic and periaortic lymph node dissection may be omitted with the caveat that any clinically suspicious nodes or nodes >1 cm in size, which would impact optimal cytoreduction, should be removed; a recent randomized, controlled trial (RCT) demonstrated no improvement in progression-free survival (PFS) or overall survival (OS) in the presence of systemic lymphadenectomy for advanced-stage ovarian cancer

Cytoreduction: R0 resection — complete resection with no gross residual or microscopic status; R1 — removal of all tumor to <1 cm in size; R2 — remaining visible tumor >1 cm in size; these are suboptimal resections; patients with R0 and R1 resections have improved outcomes vs patients who are suboptimal at the initial debulking surgery; perform maximal surgical cytoreduction if possible at the initial debulking procedure; serum cancer antigen testing, such as CA-125, and imaging tests are not predictive as to which patients will undergo a successful optimal cytoreduction

Scope and score approach: entails taking a patient to the operating room to perform a diagnostic laparoscopy and evaluate the patient's abdominal disease for presence of features that would require more radical resection; scoring system initiated by Fagotti et al. to determine the rate of exploratory laparotomy with suboptimal results; for scores >8, the probability of an optimal resection was 0; this laparoscopic approach should be considered in any patient with suspicion for more advanced disease than would be optimally debulked with initial surgery; patients have improved

outcomes when they have less tumor burden and optimal cytoreduction at up-front surgery

Patients with contraindications to maximal cytoreduction: include those with intraparenchymal liver metastases, lung metastases, presence of disease that is unresectable at the porta hepatis or root of the mesentery; these are candidates for primary neoadjuvant chemotherapy; survival is inversely related to the volume of disease at the conclusion of the procedure; a phase 3 study in advanced stage IIIC and IV disease found less blood loss, decreased rate of infection and thrombotic complications, and shorter operating time in patients undergoing neoadjuvant chemotherapy followed by interval cytoreduction; 80% of patients undergoing neoadjuvant chemotherapy had tumors <1 cm at interval debulking vs 46% in the up-front surgical cytoreductive setting; no differences in PFS or OS; results from the phase 3 CHORUS trial agreed; proponents favoring surgical cytoreduction argue that optimal debulking rates approach 40%-80%, with 50% as an acceptable rate for optimal cytoreduction, and that these rates were not reached in patients in these studies; this remains open question; interval debulking, an initial attempt at surgery, followed by chemotherapy for 3-4 cycles and an attempted debulking should be performed in patients without maximal initial surgery; these patients are most likely to benefit from interval surgery

Hyperthermic intraperitoneal chemotherapy (HIPEC): recent data suggest the use of HIPEC in the interval debulking setting; a recent RCT published in the *New England Journal of Medicine* (*NEJM*) demonstrated improvements in recurrence-free and overall survival by ~12 months; approach should be considered in any patient undergoing interval cytoreductive surgery

Chemotherapy: not required for the treatment of all early-stage ovarian cancer but indicated in certain subpopulations; early studies performed by the Gynecologic Oncology Group (GOG) demonstrated the need for chemotherapy; GOG-157 and -175 looked at 3 vs 6 cycles of carboplatin/paclitaxel; in GOG-175, maintenance paclitaxel was continued; in both studies, patients with stages IA and IB grade 3, clear cell IC and stage II completely resected cancers were examined; in GOG-157, there was no difference in 5-year OS between groups; recurrence rate was decreased in the 6-cycle group, but this result was not statistically significant and the use of 6 cycles increased toxicity; continuation of maintenance paclitaxel in GOG-175 demonstrated no improvement in recurrence-free interval or OS and resulted in increased toxicity; a subset analysis of GOG-157 in patients with high-grade serous tumors demonstrated a decreased risk of recurrence (60%) vs 83% in patients undergoing 3 cycles; considerations for this high-risk, high-grade histology can include 6-cycle treatment in the early-stage setting

Chemotherapy in lower-stage disease: observation is acceptable in stage IA and IB disease with grade 1 histology; in grade 2 disease, stage IA and IB, can consider observation vs administration of 3-6 cycles of carboplatin/paclitaxel; in stage IC grade 3 disease where the relapse risk approaches 20%, consideration should be given to treatment with carboplatin/paclitaxel

Cytotoxic chemotherapy for advanced ovarian cancer:

Platinum/taxane backbone: GOG-111 and OV10 demonstrated improvement in both PFS and OS with combination platinum/taxane therapy; GOG-132 also showed benefit; in GOG-158 and the AGO (Arbeitsgemeinschaft Gynekologische Onkologie) studies, carboplatin was as effective as cisplatin in the treatment of advanced ovarian cancer and was more tolerable with less toxicity; neuropathy is known adverse effect of taxane treatment; the SCOTROC trial substituted docetaxel in place of paclitaxel, in combination with a platinum agent, with no difference in PFS or OS; neuropathy was better in the subgroup receiving docetaxel, but myelosuppression was worse; consider in patients with neuropathy after paclitaxel administration or in patients at risk for worsening neuropathy

Alternate treatment schedules: dose-dense paclitaxel regimen on days 1, 8, and 15 of therapy was initially examined in the Japanese GOG studies; improved PFS (28 months vs 17 months) and OS (100.5 months vs 62 months) receiving standard dosing of platinum and taxane; in a confirmatory study, GOG-162, approximately 80% received bevacizumab, with no difference in PFS or OS in bevacizumab groups; a subgroup analysis of patients not receiving bevacizumab demonstrated a significant improvement in PFS

Alternate administration of chemotherapy: in GOG-172, stage III patients with residual disease <1 cm were randomized to receive paclitaxel/cisplatin intravenous vs an intraperitoneal (IP) regimen of paclitaxel/cisplatin on days 1 and 2 and paclitaxel on day 8; initially demonstrated improvement in PFS and OS, but only ~42% received all 6 cycles; GOG-252 examined IV therapy with dose-dense paclitaxel, standard IP therapy with dose-dense paclitaxel, and the standard IP regimen; patients could receive bevacizumab in the up-front setting; compared with the carboplatin reference arm, PFS was not significantly increased with either IP regimen when combined with bevacizumab; in GOG-252 (completely resected optimal patients) and GOG-218 (newly diagnosed, incompletely resected stage III or IV disease), patients received carboplatin/paclitaxel alone or carboplatin/paclitaxel plus bevacizumab in cycles 2-6 vs carboplatin/paclitaxel plus bevacizumab in cycles 2-22, with no differences between patients receiving bevacizumab vs chemotherapy alone; subset analyses suggest a survival advantage in patients with stage IV disease receiving bevacizumab following front-line chemotherapy

Maintenance therapy: though older studies found no advantage to maintenance therapy, new studies of poly-ADP ribose polymerase (PARP) inhibitors have had positive outcomes; PARP inhibitors inhibit the repair of DNA by PARP, which acts through base excision repair and the non-homologous end joining pathway; PARP inhibition in cells with homologous recombination deficiency is postulated to cause accumulation of unrepaired DNA double-strand

breaks, which ultimately leads to cell death; PARP inhibitors are selectively lethal in cells with homologous recombination deficiency; shown in early studies that PARP inhibitors are effective in platinum-sensitive disease and in patients harboring germ-line BRCA mutations; subsequent studies have examined effectiveness of PARP inhibitors in patients with somatic tumor BRCA mutants as well as patients with homologous recombination deficiency and loss of heterozygosity; though response is not as great in those with BRCA germline mutations, there is a decreased risk of recurrence in patients with somatic mutations and loss of heterozygosity within the tumor

Olaparib: most recently, olaparib was studied as maintenance in the up-front setting in patients who had received standard-of-care cytotoxic combination therapy; patients with a mutation in BRCA1, -2, or both with a complete or partial clinical response after platinum-based treatment were randomly assigned to receive olaparib; after a 41-month follow-up, the risk of disease progression or death was 70% lower with olaparib vs placebo; led to FDA approval in up-front setting maintenance treatment for use of olaparib in patients with a BRCA mutation who have had complete or partial response with a platinum-containing regimen; additionally, FDA approval has been granted in the other PARP inhibitors, rucaparib and niraparib, in the maintenance setting and in recurrent disease after other therapies; future studies are ongoing to determine the role of up-front maintenance therapy with the remaining PARP inhibitors; additional studies are ongoing to examine the role of checkpoint inhibitors CTLA4, PD1, PDL1 in treatment of ovarian cancer

Recurrence: most patients will respond to platinum therapy, but ~80% will experience recurrence within 5 years, with the greatest proportion of recurrences occurring in the first 18-24 months; at the time of recurrence, molecular testing of the tumor can be used to inform pathway-directed treatment; in the recurrent setting, important to establish platinum sensitivity; patients who recur or progress during treatment with a platinum agent are known as "platinum refractory;" patients who experience a recurrence within the first 6 months after completing a platinum-containing regimen are "platinum resistant;" some discussion that patients who have recurrence between 6 and 12 months following platinum-containing treatment are "partially platinum resistant;" however, patients who have a recurrence after 6 months following completion of a platinum-containing regimen are officially considered "platinum sensitive"

Secondary cytoreduction in patients with recurrence: DESKTOP trials were established to create a prognostic score to determine optimal secondary cytoreduction; greatest prognostic factor was disease burden at time of surgery; in DESKTOP I, an AGO score was developed to determine optimal resection; score combined 3 factors: 1 — an ECOG score less than or equal to 1; 2 — whether complete debulking was achieved at the patient's initial ovarian cancer resection; 3 — presence of <500 cc of ascites at the time of surgery; patients with carcinomatosis had a median survival of 19.9 months vs 45.3 months in patients without disseminated disease; DESKTOP II was a prospective test of the AGO score; in patients who exhibited all 3 criteria, 76% underwent an optimal secondary debulking surgery

Recurrence in platinum-sensitive patients: consider retreatment with a platinum-containing regimen with a taxane; however, there are alternate treatment regimens that can be used for patients who experienced taxane-related neuropathy; in the CALYPSO trial, no survival difference was observed between patients who received carboplatin plus pegylated liposomal doxorubicin and those who received carboplatin and paclitaxel; in the OCEANS trial, patients with platinum-sensitive recurrent disease exhibited improved PFS with gemcitabine/carboplatin plus bevacizumab followed by bevacizumab until progression vs gemcitabine and carboplatin plus placebo

Recurrent disease in platinum-resistant patients: platinum-resistant patients have worse clinical outcomes and OS; addition of bevacizumab to standard single-agent therapy demonstrated improved PFS as shown in the AURELIA study; this study examined the addition of bevacizumab to paclitaxel, liposomal doxorubicin, or topotecan; outcomes vary based on stage; stages I and II offer 5-year survival rates of 60%-80%; 5-year overall survival in advanced-stage disease is ~20%-45%; prognostic variables in stage III and IV disease include volume of residual disease after surgery, histology and grade of the advanced disease, and genomic prognostic factors; patients with BRCA1 and -2 mutations have an increased response rate to platinum-based therapies and improved PFS; additional prognostic factors include patient performance status and presence/type of comorbidities

Survivorship: 3 main issues (not inclusive)

1. Issues associated with treatment: patients who are premenopausal and undergo ovarian cancer therapy where an oophorectomy is performed often undergo surgical menopause; may report vaginal dryness and hot flashes; an RCT examining the treatment of patients with hormone replacement therapy in ovarian cancer survivors found no adverse events; OS was improved in patients on hormone replacement therapy; should be considered in appropriate patients; patients may experience ongoing neuropathy
2. Concerns for recurrence: patients may experience anxiety, depression, and require appropriate therapy
3. Second primary cancers: consider in patients who have a genetic predisposition to ovarian cancer, as they may also harbor mutations that increase the risk of cancer of other organs that may not be gynecologic; focus on patients who receive agents with a high risk of secondary primary tumors, eg, platinum-containing agents and PARP inhibitors, which have displayed an increased risk of myelodysplastic syndrome of 2%

Follow-up: follow NCCN guidelines and include more frequent follow-up within the first 2 years, approximately every 3 months, followed by approximately every 4 to 6 months for the following 3 years, for a total of 5 years of intensive follow-up; at that time, attention is drawn to patient clinical symptoms, examination findings, and CA-125 levels to monitor for recurrence; imaging should

only be performed as clinically indicated, if the patient experiences new symptoms or have worrisome findings for recurrence

Suggested Reading

US Preventive Services Task Force et al: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force recommendation statement. *JAMA.* 2019 Aug;322(7):652-65; **Cong J et al:** Therapeutic effect of bevacizumab combined with paclitaxel and carboplatin on recurrent ovarian cancer. *J BUON.* 2019 May-Jun;24(3):1003-08; **van de Laar R et al:** External validation of two prediction models of complete secondary cytoreductive surgery in patients with recurrent epithelial ovarian cancer. *Gynecol Oncol.* 2015 May;137(2):210-15.

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Cervical Cancer

Mark Einstein, MD, *Professor and Chair, Department of Obstetrics, Gynecology, and Women's Health, and Assistant Dean, Clinical Research Unit, Rutgers New Jersey Medical School, Newark, NJ*

Cervical cancer: number one cancer killer of women prior to effective screening with Pap testing, cytology, and human papillomavirus (HPV) testing; no longer in top 10 list of US cancers; affects young women in prime of reproductive life; bimodal peak of cervical cancer in US; young peak related to high-risk HPV types; older peak related to immune senescence

Prevalence: still number two cancer killer of women globally; ≈500,000 women per year diagnosed with cervical cancer; lack of centralized screening programs for cervical cancer in population-dense areas; cervical cancer common without screening or prevention

HPV: ≈13 oncogenic types; HPV 16 and 18 most common globally; HPV 16 implicated in about half of all cervical cancers; HPV 18 accounts for another 20%; most common sexually transmitted infection; most patients with infection do not develop clinical disease; ≈80% of population exposed to HPV and have had active HPV infection by age 50; most infections resolve or become clinically undetectable soon after infection; commercially available HPV tests have clinical threshold; positive above threshold; negative below threshold; though test may be negative, it is thought that HPV remains clinically undetectable at low viral levels in reservoirs throughout body; patients who develop active infection later in life likely experiencing reactivation of infection from younger age; peak prevalence of active HPV infection around 25 to 30; peak prevalence of pre-cancerous disease around 25 to 30; point prevalence rate of HPV in general population ≈25%; most infections go nowhere; small percent of women, particularly with persistent HPV infection documented positive more than 1 year apart, develop precancerous cells of cervix and cancer after malignant transformation; out of everyone infected with HPV, <3% have persistent HPV infection; millions globally with active, persistent HPV infection

Progression from HPV infection to cervical cancer: most HPV infections present as abnormal Pap during cervical cancer screening; most equivocal abnormal Paps essentially cytomorphologic manifestation of active HPV infection; does not mean patient has cancer or even pre-cancer; very few represent active HPV infections; very few equivocal Paps become high grade cervical intraepithelial neoplasia (CIN) and then become cancer; development from infection to precancerous cells in cervix usually takes 5 to 7 years; takes another 7 to 10 years after that to become cervical cancer; peaks of infection in young patients; peaks of precancerous cells in late twenties; peaks of cervical cancer in early forties

Etiology: malignant transformation after HPV infection; HPV genome organization well known; region of six early open reading frames; E6 and E7 oncoproteins inactivate tumor suppressor genes p53 and pRB respectively; inactivating tumor suppressor genes turns off checks and balances and allows potential for malignant transformation; additional late region of L1 and L2; L1 encodes for major capsid proteins of HPV; used for prophylactic vaccines

Prophylactic vaccines: comprised of virus-like particles with noninfectious HPV L1 epitopes; protein causes immune system to recognize and produce intense neutralizing anti-HPV antibody response; L1 has high variability; explains many different types of currently available commercial vaccines; each type stimulates different neutralizing antibody response; Federal Advisory Committee on Immunization Practice (ACIP) recommends routine vaccination of patients aged 11 and 12; can be administered as young as 9 years; if person <15 years old has received 2 doses of vaccine, third dose not needed; catch-up population up to age 26; three dose schedule; second dose administered 1 to 2 months after first; third dose administered 6 months after first; do not restart series for a missed dose; vaccine elicits high neutralizing antibody response; no reason not to give next dose in series; patient starting series with quadrivalent vaccine could complete series with 9-valent vaccine; no requirement to test for HPV in advance of giving vaccine; patients with persistent infection or prior loop electrosurgical excisional procedure (LEEP) due to persistent infection less apt to have response to vaccine; patients should continue to have screening as recommended

Prevention: most common cancer screen in US; ≈85% of women receiving cancer screening receive cervical cancer screening; unscreened population still exists in US, and there is still cervical cancer in part because of issues with access and lack of follow up; cytology responsible for improvement; HPV test highly sensitive; all commercially available HPV tests have >99% sensitivity; lower specificity; higher specificity with Pap test; issues with sampling and reading of Pap tests; co-testing is powerful combination; recommended for women between 30 and 65 in US; most recent US Preventive Services Task Force recommendation on cervical cancer screening recommends HPV test as primary screen; start with more sensitive test to find population of women most at risk, then use cytology depending on genotypes and other factors; recommendation is to move directly to colposcopy for women shown to have HPV 16 and 18 regardless of cytology; almost all commercially available genotype

assay HPV tests reveal high risk HPV types including type 16 and 18 or non-16 and 18 types; guide workup in addition to cytology information; ASCCP (American Society for Colposcopy and Cervical Pathology) and other organizations recommend plugging that information into various algorithms to determine how to triage patient; options include colposcopy, treatment, active surveillance, or routine screening; various clinical action thresholds depending on combination of abnormalities from cervical cancer screening; other tests include molecular tests and dual stains pathologists use to differentiate low and high grade disease on histologic specimens; cervical cancer can be eliminated with active approach to prevent cancer

Precancerous cells: treated with LEEP in US; shaving top layer of cells off cervix and endocervical canal; want to eliminate squamocolumnar junction where cervical cancer starts; active surveillance needed following LEEP; patient can return to routine screening if all active surveillance shows negative HPV testing or negative cytology

Invasive cancer cells: must stage cervical cancer; many invasive cervical cancers in US confined to cervix; many identified at time of LEEP

Microinvasive cervical cancers: measure <3 mm in depth; only identified microscopically; usually identified by pathologist after LEEP

Stage I cervical cancer: includes microinvasive cervical cancer and cervical cancer confined to cervix; <2 cm in greatest dimension up to stage IB1; very operable cervical cancers; Federation of International Gynecologic Oncologists (FIGO) released most recent revised staging for cervical cancer in 2018; separate what used to be IB2 category into IB2 and IB3 categories; IB2 category — invasive cancer between 2 and 4 cm in greatest dimension; IB3 — invasive cancer >4 cm; categories correlate well with treatment strategies; IB2 cervical cancers merit radical hysterectomy, because cancer confined to cervix and cervix not bulky; treatment of IB3 cervical cancers should be considered in shared decision-making with patient; many need chemotherapy and radiation

Stage II cervical cancer: invades beyond uterus but does not extend to lower third of vagina or pelvic sidewall; substage A extends up and down; B extends width; IIA extends down to vagina; IIB represents involvement of parametrium — tissue between cervix and sidewall

Stage III cervical cancer: can involve lower third of vagina and/or extend to pelvic wall; pelvic and/or para-aortic lymph node involvement; patients often present with hydronephrosis or nonfunctioning kidney; called locally advanced cervical cancers; not operable due to inability to achieve effective margins; generally bulky tumors; radiation is primary therapy

Stage IV: split into two categories; stage IVA — spread to adjacent organ; examples — extending into mucosa of bladder or rectum; stage IVB — spread distantly to lungs, liver, or outside pelvis

Survival: good when cancer detected early; not as good if cancer detected later; drops considerably for stage III and IV, particularly for IVB; historically, cervical cancer clinically staged without using imaging; FIGO staging of cervical cancer in 2018 changed to allow imaging and additional pathology to help with staging

Presentation: most early microscopic cervical cancers discovered at time of screening; presenting symptoms include bleeding; includes bleeding after sex, abnormal uterine bleeding, or spotting; patients presenting with active bleeding usually have locally advanced cervical cancer; more ominous symptoms include sciatica, nerve pain, or metastatic disease; rare because cervical cancer often detected early; cancer often relatively slow-growing, starting locally at cervix, growing out into adjacent organs, and then metastasizing to body; severe symptoms can represent atypical presentation

Diagnosis: biopsy of cervix and histologic diagnosis of cervical cancer; usually done in outpatient setting

Treatment of early stage disease: surgical; perform larger LEEP or cone biopsy for microscopic disease; coning between 10 to 15 mm of tissue margins of microscopic cancer; parametrial tissue margins for potentially visible disease confined to cervix; perform radical hysterectomy; not simple hysterectomy riding down cervix surgically; must include all tissues in parametrium and uterosacral ligaments down to insertion; additionally includes top third of vagina to obtain adequate vaginal margin, particularly with encroachment of cancer to edge of cervix or upper third of vagina; perform lymph node dissection in addition to radical hysterectomy; remove pelvic nodes and para-aortic nodes; pelvic node removed around external and internal iliac; obtain nodes around obturator space, common iliac nodes, and para-aortic nodes on both sides

High risk features with early stage disease: include nodal status, tumor size, invasion depth into cervix close to stroma or margins; presence of lymphovascular space involvement; lymphovascular space not involved in staging but taken into account when considering adjuvant treatment; adjuvant treatment is primarily radiation

Locally advanced disease: patients often present with barrel-shaped cervixes; almost appears like barrel of tumor in vagina; either fixed or significant parametrial involvement with tethering on one side or another; radiation therapy primary treatment; learned in eighties to add cisplatin to freeze cells in G0 to make more radiosensitive; similar to head and neck cancers; number of phase two studies in 80s led to large randomized, controlled trials using platinum and other platinum containing regimens; included fluorouracil (5FU) or hydroxyurea; GOG 219 among largest studies; comparative effectiveness trial of different regimens; results maintained platinum as accepted standard of care; toxicity of other drugs and resulting treatment delays did not merit continuation of other drugs despite some added survival benefit; platinum has remained accepted radiosensitizing standard of care for locally advanced cervical cancer for >20 years; formerly used in 5-day inpatient 20 mg/m^2 regimen every 3 weeks; now done as weekly outpatient 40 mg/m^2 during time of radiation; goal of achieving six doses of cisplatin during time of external beam radiation therapy and brachytherapy

Radiation: external beam radiation therapy; more apt to use brachytherapy with larger tumor; helps with central control; perform brachytherapy with tandems and colpostats; high-dose source used in many US sites; low- dose radiation sources acceptable for after-loading; intensity modulated radiation therapy (IMRT) often used instead of traditional external beam radiation therapy

Concomitant chemoradiotherapy: used for locally advanced cervical cancer not amenable to surgery, early

cervical cancer with positive nodes, closely involved surgical margins, or locally advanced disease

Size: large in locally advanced cervical cancer; usually >4 cm or may encompass whole pelvis; univariate predictors of disease-free survival when considering additional adjuvant concomitant chemoradiotherapy in surgical patients with >4 cm tumors confined to cervix (stage IB3) include lymphovascular space invasion, nodal status, depth of invasion, outer 2/3 of invasion; at least half of tumors >4 cm receive concomitant chemoradiotherapy anyway; shared decision making; choice of moving directly to concomitant chemoradiotherapy rather than exposing patients to surgery followed by concomitant chemoradiotherapy; depends on factors including patient comorbidities; GOG attempted randomized comparative effectiveness trial evaluating concomitant chemoradiotherapy *vs* radical hysterectomy; study never finished; patients randomized to surgery arm wanted concomitant chemoradiotherapy after learning of surgical complications; dropped out of study to receive desired treatment; resulted in unevenness and selection bias; sometimes radiation boosts required depending on extent of tumor, parametrial involvement, or nodal involvement

Cervical cancer diagnosed at time of pregnancy: incidence ≈one in 2200; incidence worse over time; many patients might see doctor or receive first cervical cancer screen at time of pregnancy diagnosis; clinical conundrum depending on stage of cancer and pregnancy; requires discussion and shared decision making between patient and GYN oncologist

Treatment of metastatic disease or metastasis following primary treatment: poor survival, even with multimodal chemotherapy; dismal response to many standard treatments; another reason to focus on prevention; taxol with platinum-based therapy standard of care for decades for recurrent cervical cancer; number of trials with taxol and cisplatin at varying doses; in GOG 204 taxol and cisplatin control arm had highest survival and least toxicity; other combinations with platinum include FDA approved topotecan and vinorelbine (Navelbine) with cisplatin; oxaliplatin alternative, particularly for patients with neurotoxicity; median survival in recurrent setting with taxol and cisplatin ≈13 months; GOG 218 and 240 included bevacizumab as doublet included with taxol and cisplatin; GOG 240 — two by two factorial design with taxol cisplatin *vs* non-platinum doublet of topotecan and taxol with and without bevacizumab; results led to approval of bevacizumab; addition of bevacizumab extended overall survival by 4 months; from 13 to 17 months; 33% improvement in overall survival; highly statistically significant; led to NCI (National Cancer Institute) practice alert and NCCN (National Comprehensive Cancer Network) two-way recommendation for approval of bevacizumab in use of treating recurrent cervical cancer

Ongoing trials: current GOG trials stem from fact that cervical cancer is virally based; use novel immunotherapies and immune checkpoint inhibitors; relatively early stage clinical trials; apparent efficacy of immunotherapies in recurrent setting; pembrolizumab approved for treatment of cervical cancer in recurrent setting; shown to have effect on tumors expressing PD-L1, tumors with high microsatellite instability, or mismatch repair solid tumors; additional combination trials with immune checkpoint inhibitors with or without other chemotherapeutic agents and other novel immunotherapies underway

Survivorship issues: vast majority of patients with early disease receive surgery or concomitant chemoradiotherapy; ≈85% with stage I disease live disease-free for remainder of life; focus on improving quality of life during and after cancer treatment; side effects of concomitant chemoradiotherapy or surgery can take toll on patients; sexual side effects include vaginal dryness and dyspareunia; address intimacy issues openly with patients; radiation therapy exposes bowel and bladder to radiation; much higher levels of long term dysfunction of bowel and bladder with 2D treatment; planning prior to IMRT and conformational treatment planning; evaluate for chronic diarrhea immediately after treatment; may also be internal fistulas or more severe complications of bowel; bladder frequency, urgency, or bladder pain can happen long term resulting from radiation cystitis; psychosocial problems include mood and stress disorders, body image issues, and fear of recurrence; many experience acute stress disorder in acute or long-term setting; symptoms of post-traumatic stress disorder often found during or after treatment; encourage support groups and interventions with support staff; psychosocial issues can be worse in recurrent setting; prepare for and address head-on with patients to help them get through difficult treatments

Suggested Reading

Gupta S, et al: Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. *J Clin Oncol.* 2018 Jun;36(16):1548-55; **Stevanović S, et al:** Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J Clin Oncol.* 2015 May;33(14):1543-50; **Wuerthner BA, et al:** Cervical cancer: screening, management, and prevention. *Nurse Pract.* 2016 Sep;41(9):18-23.

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Uterine Cancer

Shannon Westin, MD, MPH, *Department of Gynecologic Oncology and Reproductive Medicine, Division of Surgery, MD Anderson Cancer Center, Houston, TX*

No specific drugs: progesterone only FDA-approved agent for uterine cancer; all other agents off-label

Epidemiology: uterine cancer fourth most common cancer among women; poised to overtake colon and rectal cancer; ≈62,000 patients diagnosed per year; ≈10,000 to 11,000 will die; compared to most cancers, incidence rising; rise tightly linked to obesity; more patients overweight, obese, and extremely obese in US and worldwide

Risk factors: incidence highly dependent on age; majority of women diagnosed with endometrial cancer postmenopausal; median age of diagnosis ≈61 years; more premenopausal patients now being seen; ≈5% to 10% of patients now under 40; relative risk of endometrial cancer two to 10 times increased depending on level of obesity; due to exposure to estrogen; prior gynecological use of unopposed estrogen can cause thickened endometrial lining that subsequently becomes atypical and eventually cancerous; obese patients make extra estrogen in fat cells; other risk factors revolve around estrogen; about two to three times increased relative risk in patients with infertility; polycystic ovarian syndrome increases risk; ovarian cancers producing estrogen, such as granulosa cell tumors, can cause uterine abnormalities; tamoxifen used for breast cancer causes three to seven times increased rate of endometrial cancer; Lynch syndrome increases risk

B-14 and P-1 NSABP (National Adjuvant Breast and Bowel Project) trials: demonstrated increased incidence of endometrial cancer in women taking tamoxifen; does not change treatment; no recommendation for screening for uterine cancer in patients taking tamoxifen unless vaginal bleeding or symptoms develop; uterine cancer in this population tends to be early grade, but may be high-risk histology

Lynch syndrome: no longer called hereditary non-polyposis colorectal cancer, because many women develop uterine cancer first; syndrome caused by inherited germline mutation in DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2; recently observed mutations in EPCAM gene also associated with syndrome; patients have higher lifetime risk of colorectal and uterine cancer; sentinel cancer can be colorectal or uterine; also increased risk of ovarian cancer; less commonly renal and brain cancers; screen patient with diagnosis of colon cancer for uterine cancer; screen for colorectal cancer with uterine cancer diagnosis when suspicious of Lynch; patients with Lynch syndrome recommended to receive yearly transvaginal ultrasound and endometrial sampling biopsy beginning age ≈30; consider risk-reducing surgery; option of hysterectomy once patient has completed childbearing; reduces risk of endometrial cancer to zero

Screening: no recommendations for routine screening for endometrial cancer; screening based on presence of symptoms; biopsy when patient presents with bleeding

Diagnosis: biopsy standard for diagnosis; endometrial biopsy with dilation and curettage; endometrial hyperplasia — overgrowth of inside of uterine lining; precursor to endometrial cancer; evaluate atypical cells to understand risk of cancer; chance of cancer ≈1% if simple with no atypia; ≈3% if more complex but still without atypia; ≈8% for simple hyperplasia with atypia; 30% for complex, atypical hyperplasia — this stage often treated as cancer; almost 50% of these patients with preoperative diagnosis of hyperplasia have cancer at time of final diagnosis

Pathology: endometrioid most common histology; are other rare, more aggressive types; papillary serous uterine cancer more aggressive type; ≈7% to 10% of all endometrial cancers; similar to ovarian cancer; spreads quickly; often diagnosed at high stage; other rare histologies include mucinous, clear cell, secretory, and squamous; often treated similarly to typical endometrioid cancer; squamous differentiation in tumors not as bad as pure squamous; follow patients closely

Staging: based on extension from uterus; stage I — primarily confined to uterine corpus; IA — less than one-half of myometrial invasion; includes patients without any myometrial invasion; IB — invasion of more than one-half; stage II — involves cervical stroma; does not include cervical glands; is stage IA, not stage II, if patient has involvement of cervical glands without stromal involvement; stage III — local-regional spread; IIIA — uterine serosa or adnexal involvement; IIIB — vaginal or parametrial involvement; IIIC — lymph node involvement; IIIC-1 — involving pelvic lymph nodes; IIIC-2 — involves periaortic nodes; stage IV — distant bowel, bladder mucosa metastases; stages correlates well with survival; 70% of patients diagnosed at stage I; have 91% survival; majority diagnosed at early stage due to bleeding and symptoms; stage II ≈10% of cases; survival ≈85%; 50% survival rate when cancer spreads into lymph nodes; stage IV has dismal survival; ≈20% of patients surviving at 5 years

Management: surgery mainstay of treatment; treatment based on local-regional or disseminated disease

Disseminated disease: stage IVB or recurrent patients; treated with chemotherapy

Local-regional disease: broken down by risk; low risk — early stage grade 1 and 2 endometrioid-type tumors;

intermediate risk — stage II endometrioid tumors and stage I high-risk histologies such as serous and clear cell; high risk — stage III, stage IVA, and non-endometrioid tumors

Early stage disease: majority of patients healthy enough to tolerate surgery due to minimally invasive techniques; proportion of patients with multiple medical comorbidities unable to tolerate surgery exists

Radiotherapy for patients unable to tolerate surgery: previously primary radiotherapy only option; radiosensitive disease; control rates ≈90% at 5 yr; radiation has side effects; push to use hormonal therapy

Hormonal therapy: endometrial cancer has estrogen and progesterone receptor expression; progesterone only FDA-approved treatment for uterine cancer; initially used in recurrent setting; progestins now option in young patients with well-differentiated cancer or with poor medical history in early stage setting; include oral medroxyprogesterone and megestrol acetate; intrauterine device (IUD) used for contraception also evaluated

Surgery: hysterectomy generally performed; ovaries and fallopian tubes may be removed depending on age of patient, depth of invasion, and involvement; lymph nodes typically assessed; benefit less clear; some data show lymphadenectomy does not impact survival, but does provide good prognostic information and potentially aids in deciding on therapies; majority of surgeons assess lymph nodes in some way

Treatment: choice mainly based on assessed risk of recurrence

Low-risk endometrial cancer: early grade, 1 or 2, endometrioid-type tumors with minimal myometrial invasion; stage IA; prognosis exceptional with or without treatment

Intermediate high-risk: uncertain-risk stage I and II; not stage III or IV; evaluated in PORTEC study; all patients received surgery; included any stage IB, grade 1, 2, or 3 patients; randomized to adjuvant pelvic radiotherapy *vs* observation; found using radiotherapy reduced recurrence risk; did not impact overall survival; difficult to treat when patients recur; GOG-99 evaluated stage IB to IIB endometrial cancer with full surgical staging; patients received radiotherapy *vs* observation; confirmed reduction in recurrence but no difference in overall survival; similar to PORTEC; also used data to define more high-risk group; found age, grade, and presence of lymphovascular space invasion (LVSI) mattered; created risk score based on patient age >70, grade 2 to 3 tumor, lymphovascular space invasion, or deep invasion; patients >70 only needed one factor; needed two factors if >50 but <70; required all three factors if <50; found reduction in rate of recurrence in high-risk group from ≈30% to 13% with radiotherapy; radiotherapy considered worth doing; study followed with PORTEC-2; same group; high-intermediate risk defined as age >60, deep invasion with grade 1, 2, or not so deep invasion grade 3; attempted cuff brachytherapy rather than pelvic radiotherapy; followed 400 patients for many months; saw no difference in recurrence or survival; patients that only had cuff had better quality of life; cuff brachytherapy current standard of care

Deep invasion, high-grade tumors: patients should still be considered for radiotherapy; two studies evaluated chemotherapy; neither showed benefit to chemotherapy

Advanced and recurrent disease: treatment options include surgery, radiation, chemotherapy, hormonal therapy, and novel therapies

Surgery: push for surgery in stage III with involvement of lymph nodes; belief removing tumor increases benefit; less clear for stage IV patients; bulky abdominal disease; debulking surgery does not make sense with disease in lungs or mediastinum; some data indicate better outcomes in population that can be resected; all those data retrospective; not much prospective data evaluating surgery in advanced stage disease

Radiotherapy: retrospective data evaluating conglomerations of multiple prospective trials initially indicated radiation combined with chemotherapy had better outcomes, improved progression-free survival, and improved overall in patients with stage II and III disease; two recent randomized, controlled trials show this not the case

GOG-258*:* first trial; population of stage III or IV endometrioid-type endometrial cancer and stage I and II clear cell or serous histology; randomized to radiation with chemotherapy *vs* chemotherapy alone; chemotherapy alone considered standard of care based on historical data; high proportion of patients with stage IIIC lymph node-involved disease overall; some stage IV, IIIA, and IIIB; majority of patients endometrioid type; ≈20% serous type in each arm; majority of patients did not have residual disease when starting radiotherapy or chemotherapy; found recurrence-free survival no different between group receiving chemotherapy alone *vs* group receiving chemotherapy with radiotherapy; progression-free survival and overall survival equivalent; recommended chemotherapy as standard of care in advanced stage disease; radiotherapy unnecessary

PORTEC-3*:* used radiotherapy alone as standard of care; compared with chemo-radiotherapy; radiotherapy with cisplatin followed by four cycles of chemotherapy with paclitaxel and carboplatin; included stage II/III disease; also included stage I to stage III serous and clear cell cancers and stage I, grade 3 with deep invasion; expanded definition of high risk in this population; no patients allowed to have residual metastatic tumors; did not include stage IV disease; treated ≈660 patients; majority endometrioid-type; ≈30% serous and clear cell in each arm; majority stage III; moderate amount of stage I and stage II; majority of patients completed chemotherapy in arm with chemotherapy and radiotherapy; found 5-yr failure-free survival better in group receiving radiation and chemotherapy; did not see difference in overall survival; data still maturing; lymph node involvement population with stage III disease received biggest benefit of chemo-radiotherapy; chemo-radiotherapy considered to reduce recurrence risk and improve failure-free survival; no overall survival benefit in whole group; overall survival benefit in group with stage III; perhaps studies included too many patients and should have focused on stage IIIC disease; chemotherapy and radiotherapy both good options; chemotherapy remains standard of care

Stage IV and Recurrent Disease

Isolated pelvic or vaginal recurrence: can give pelvic radiotherapy if patient has never had pelvic radiotherapy;

≈80% to 90% salvage/cure rate; surgery, chemotherapy, and targeted therapy used for those previously treated with radiotherapy

Treatment options: only progesterone FDA approved in advanced and recurrent disease; other potential regimens are compendium listed

Hormonal therapy: only FDA-approved treatment; number of different options; different trials performed; Megace and tamoxifen have response rates of ≈15% to 20%; study alternating Megace with tamoxifen showed response rates approaching 33% with 3 weeks Megace alternating with 3 weeks tamoxifen; reasonable option for patient with endometrioid-type tumor who does not want chemotherapy; can be used before or after chemotherapy; still has activity in proportion of patients; patients not selected based on estrogen or progesterone receptor expression

Chemotherapy: response rates ≈50% with first-line chemotherapy; progression-free survival from 8 to 14 months; overall survival ≈3 yr; response rates ≈15% with second-line agents; progression-free survival ≈3 months; overall survival ≈6 to 12 months; targeted therapies and novel drug combinations under investigation

Paclitaxel and carboplatin: standard of care; previous trials combined agents known to be effective in uterine cancer, including Adriamycin, cisplatin, paclitaxel, carboplatin; randomized trials culminated in GOG-209; trial studied stage III, IV, and recurrent endometrial cancer; patients could have no prior chemotherapy; required to have measurable disease; primary study of equivalence; evaluated for equivalent overall survival; non-inferiority-type trial; paclitaxel and carboplatin compared to previous current standard of paclitaxel, cisplatin and doxorubicin (TAP); enrolled ≈1300 patients; found paclitaxel and carboplatin not inferior to Adriamycin, cisplatin, and paclitaxel; equivalent progression-free and overall survival; paclitaxel/carboplatin became standard of care; better in side effects; equivalent survival and better tolerated

Trastuzumab: uterine serous tumors often express HER2; randomized trial comparing paclitaxel/carboplatin backbone with or without trastuzumab; patients with stage IV or recurrent disease that had never had chemotherapy; population receiving combination with trastuzumab had improved progression-free survival; reduction in risk of progression of ≈55%; hazard ratio of 0.44; absolute difference of ≈5 months; biggest impact with addition of trastuzumab in population with up-front advanced stage III/IV disease *vs* recurrent; some benefit in recurrent patients never treated with chemotherapy, but not quite as profound as population with advanced disease

Pembrolizumab: FDA-approved in microsatellite instability high (MSI-high) tumors; Lynch syndrome associated with microsatellite instability; even outside of Lynch syndrome, ≈20% of uterine cancers overall are MSI-high tumors; can be considered for pembrolizumab therapy; early studies of pembrolizumab included cohorts of mismatch repair deficient so-called non-colorectal cancer; endometrial cancers bulk of those patients; good responses observed in that population; always check for Lynch syndrome in these patients; always check for MSI; clear possibility for treatment outside of chemotherapy

Other options: outcomes after paclitaxel and carboplatin limited if patient does not have MSI; 5% to 10% responses; NCCN (National Comprehensive Cancer Network) guidelines suggest different potential chemotherapies; chemotherapies assessed in endometrial cancers but not quite as active as hoped include cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, albumin-bound paclitaxel, topotecan, docetaxel; any can be considered in recurrent setting; higher levels of activity with some targeted therapies; much activity in PI-3 kinase AKT pathway in these tumors; Ras mutations observed; mTOR (mammalian target of rapamycin) inhibitors/rapalogs evaluated

Bevacizumab: phase two study evaluated use in patients with recurrent endometrial cancer with one to two prior therapies; received bevacizumab 15 mg/kg every 3 weeks; response rate of ≈15%; not much better than chemotherapy but well tolerated; proportion of patients that survived progression-free at 6 months approached 40%; average progression-free survival in this second-line setting ≈3 months; doubling in progression-free survival with bevacizumab; no markers to help predict who responds; option for patients

mTOR inhibitors: IV temsirolimus demonstrated response rates approaching 24% in an all-comer population; compendium listed; drug combination combining mTOR inhibitor everolimus with letrozole; letrozole has response rates of ≈3% or 4% in endometrial cancer; everolimus also has dismal response rates; combination in patients with endometrioid histology yielded response rates of ≈30%; additional 30% of patients had benefit with prolonged stable disease for more than 6 months; combination initially done in single-arm phase 2 trial; randomized trial compared it to hormones; demonstrated better response rates than hormones and longer progression-free survival; studies now pitting combination against chemotherapy in up-front setting; something to offer patients

Uterine sarcomas: rare; similarities to staging of abdominal and pelvic sarcomas; include leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma

Carcinosarcoma: also called malignant mixed Mullerian tumor (MMMT); often considered epithelial tumor rather than sarcoma; included with non-endometrioid tumors arising in endometrium; almost always in postmenopausal women; highly linked to prior pelvic radiotherapy; suspect in patient with uterine bleeding and history of prior radiation

Staging: similar to epithelial tumors; not staged like sarcomas; stage I — uterine corpus; IA — less than half myometrial invasion; IB — more than half invasion; stage II — cervical stroma, not cervical glands; stage III — uterine serosa, adnexa, vagina, nodes; stage IV — bladder, bowel mucosa, or distant metastases

Treatment: similar to treatment of epithelial tumors; ifosfamide has activity in carcinosarcoma; ifosfamide and paclitaxel previous standard of care; combination chemotherapy previously demonstrated improved progression-free survival; recent randomized,

controlled trial demonstrated no difference between paclitaxel and carboplatin and ifosfamide and paclitaxel; paclitaxel and carboplatin now treatment of choice; chemotherapy generally preferred to radiotherapy; radiotherapy can be utilized to prevent pelvic recurrence but has no impact on progression-free or overall survival; use radiation for treatment of symptoms, pain or bleeding; carcinoma part often tumor type when carcinosarcoma patients recur; reason for treating like epithelial endometrial tumor *vs* true sarcoma

Leiomyosarcoma: next most common sarcoma; ≈2% of cases; more common in premenopausal patients; staging more like traditional sarcoma staging; stage I — limited to uterus; IA — <5cm tumor; IB — >5cm tumor; stage II — extended into pelvis; IIA — adnexal involvement; IIB — into extrauterine pelvic tissues; stage III — in abdomen; IIIA — one site of disease; IIIB — more than one site of disease; IIIC — lymph node involvement; stage IV, IVA — bowel and bladder; IVB — distant metastases

Treatment: surgical resection, especially of early stage; mixed data on adjuvant therapy requirement; generally given for tumors IB or greater; options include docetaxel and gemcitabine *vs* ifosfamide/doxorubicin; beyond first line, treat like any sarcoma; gemcitabine/docetaxel or doxorubicin/ifosfamide or doxorubicin alone are other options; cisplatin shows some activity; trabectedin another option; radiation not often utilized; meant to prevent pelvic recurrence but does not impact progression-free and overall survival; patients with bulky disease receive chemotherapy; cancers aggressive; >50% chance of recurrence; majority of patients treated with systemic therapy after surgery

Endometrial stromal sarcoma: rare sarcoma; sarcoma muscle tumor starting in endometrial stromal; ≈ <1% of all cases; hormonally sensitive; megestrol acetate given in advanced stage; early stage treated completely with surgery; staged like any sarcoma — confined to uterine corpus, extending into pelvis, number of sites in abdomen, and distant metastases

Adenosarcoma: rare sarcoma with benign component; can often resect tumor without additional therapy; adenosarcoma with sarcomatous overgrowth poor prognostic sign; treated with adjuvant radiotherapy or chemotherapy to reduce high risk of recurrence

Suggested Reading

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Gestational Trophoblastic Disease and Cancers of the Vulva and Vagina

Brad Monk, MD, *Professor of Gynecologic Oncology, University of Arizona College of Medicine—Phoenix, and Director and Professor of Gynecologic Oncology, Creighton University School of Medicine at St. Joseph's Hospital Medical Center, Phoenix, AZ*

Gestational trophoblastic disease (GTD): includes group of benign and malignant tumors developing from placental tissue in uterus; unique pathogenesis; maternal tumors arise from gestational tissue with locally invasive or metastatic potential; 80% benign; hydatidiform mole most common form; also known as molar pregnancy; considered benign pre-malignant disease; malignant forms of GTD collectively referred to as gestational trophoblastic neoplasia (GTN); hydatidiform mole ≈80% of GTD; invasive mole ≈15%; choriocarcinoma and other rare types ≈5%; high cure rates, approaching 100%; among first solid tumors cured with chemotherapy

Prevalence: rare entity but common enough to be seen by most medical oncologists; incidence varies widely by region; higher incidence rates in Asia and Latin America compared with Europe and North America; differences believed due in part to varying diagnostic criteria and reporting practices; also have basis in diet and nutrition; US incidence of ≈one out of every 1000 pregnancies

Types: two types of hydatidiform moles — complete and partial; 80% complete; lack fetal parts; have higher malignant potential; result from abnormal fertilization of ovum lacking nuclear DNA; have two identical paternal chromosomes; two sperm complements from duplication of single sperm haploid genome; partial moles result from fertilization of ovum with nucleus with either single sperm with subsequent paternal duplication or ovum nucleus and two sperms; generally triploid and can contain fetal parts; post-molar GTN includes invasive mole choriocarcinoma; develops in ≈15 to 20% of complete moles; less common in partial moles which have lower malignant potential; all patients have immunohistochemistry HCG positivity and microscopic trophoblastic disease; choriocarcinoma has more cytologic atypia with absence of chorionic villi and more hemorrhage and necrosis; rare variant intermediate trophoblastic tumors include placental site trophoblastic tumors and epithelioid trophoblastic tumors; simulate cancer and have unique morphologic and histochemical features

Hydatidiform moles: most common presentation of GTD; mostly benign; commonly present with vaginal bleeding at around 2 to 4 months of gestation; most detected by widespread ultrasound screening and accurate HCG testing before signs such as uterine enlargement, preeclampsia, hyperemesis, or benign cysts develop; theca lutein cysts stimulated in ovaries by HCG; partial moles tend to grow more slowly; may present later than first or second trimester; patients often have symptoms of incomplete or missed abortion

Diagnosis: based on evaluation of dilation and curettage (D&C) specimen; patients often present after pregnancy ultrasound shows no fetus in uterus; HCG generally very high; careful uterine evacuation with suction D&C as risk of uterine perforation high; pathologist diagnoses molar pregnancy from hydropic swollen chorionic villi; partial mole has fetal parts

Evaluation: NCCN (National Comprehensive Cancer Network) guidelines; history and physical, ultrasound, and HCG (human chorionic gonadotropin); CBC (complete blood count), CMP (comprehensive metabolic panel), and thyroid function tests; CMP shows liver and renal function; perform type and screen; recommend RhoGAM immunoglobulin at time of evacuation with maternal Rh negative blood type to prevent Rh sensitization; chest x-ray only imaging recommended at time of initial diagnosis; generally handled by OB/GYN doctor; monitor thyroid even if abnormal if patient asymptomatic; HCG, LH, and TSH share common protein structure; increased HCG causes decreased thyroid

Prophylactic chemotherapy: controversial at time of uterine evacuation; can reduce recurrence from 20% to 3% to 8%; however, 80% of patients will not need chemotherapy, and earlier treatment does not result in more cure; recent Cochrane database review of three randomized trials did not conclude sufficient evidence exists for standard administration of prophylactic chemotherapy to prevent post-molar GTN; review stated use does reduce risk of recurrence; best to use in highest risk patients where risk of persistent disease much higher than 20%; risk factors for recurrence — patient age >40, HCG level >100,000, large uterus, theca lutein cysts >6cm

Monitoring: follows uterine evacuation when chemotherapy not administered; monitor HCG levels until return to normal; obtain two or three more weekly levels; then monthly for 3 to 6 months; perform with quantitative assay capable of detecting all forms of HCG; include beta HCG, core HCG, nick-free beta, beta core, and even hyperglycosylated forms; post-molar trophoblastic neoplasia ≈20%; only 1% to 5% of partial moles; initiate workup and staging evaluation if HCG levels plateau or increase ≥10% over 3 weeks or HCG does not normalize within 6 months

Workup: repeat history, physical exam, ultrasound, CBC, CMP, and thyroid; perform brain MRI and CT of chest, abdomen, and pelvis with contrast; MRI for contrast allergy; controversy if repeat D&C needed after molar pregnancy develops persistent lesion; there is risk of

uterine perforation; second D&C more likely to work if HCG levels low; performing repeat D&C if HCG levels plateau can reduce need for chemotherapy by two-thirds; hysterectomy likely excessive

Staging: International Federation of Gynecology and Obstetrics (FIGO) staging system; harmonization with World Health Organization (WHO) staging system; risk factors define two groups — low or high risk GTN; scoring system; zero to four points for each factor; summed score of six or less low risk; treated with single agent chemotherapy; seven or higher treated with multi-agent chemotherapy; factors include age, antecedent pregnancy, interval from index pregnancy, pretreatment HCG, largest tumor, site of metastasis, number of metastases, and previous failed chemotherapy; some factors more worrisome than others; one point for age >40; antecedent pregnancy more serious, with term pregnancy resulting in two points; one point for miscarriage; zero points for molar pregnancy; HCG levels important; <1000 low risk; one point for 1000 to 10,000; two points for 10,000 to 100,000; four points if >100,000; tumors with more time since antecedent pregnancy higher risk; zero points for <4 months; one point for 4 to 6 months; two points for 7 to 12 months; four points for >12 months; brain and liver more serious for site of metastasis; no points for common lung metastases; one point for one to four metastatic lesions; two points for five to eight; four points for more than eight; two points for one chemotherapy agent; two points for prior failed chemotherapy; four points for two or more agents used; patient rescored after every cycle of chemotherapy

Oncologic management of GTD: almost half of gynecologic oncologists do not give systemic therapy; rely on medical oncology colleagues to administer chemotherapy; formerly without reliable evidence-based source of treatment recommendations; National Comprehensive Cancer Network (NCCN) did not have evidence-based GTD guidelines until 2019; second version of guidelines updated May 6, 2019

Management of low risk disease: administer single agent chemotherapy with either methotrexate or dactinomycin; weekly intramuscular methotrexate not effective very often; patients given multi-dose methotrexate or dactinomycin every 2 weeks; level one evidence by NCCN; GOG (Gynecologic Oncology Group) trial attempting to compare agents failed due to biases; methotrexate more commonly used, because dactinomycin causes alopecia and blistering; dactinomycin administered by IV; methotrexate given daily for 5 days at 0.4 mg per kg; can be IV or IM; only agent given IV; max dose 25 mg per day; most receive 25 mg for 5 days every 14 days; can interdigitate leucovorin; leucovorin now an 8-day regimen; complicated because cancer center not open 7 days per week; 1 mg per kg IM methotrexate on days one, three, five, and seven; 15 mg of oral leucovorin 30 hours later on in-between days — days two, four, six, and eight; every 14 days; home health can give Sunday or weekend methotrexate dose; dactinomycin given 10 to 12 mcg per kg IV daily times five every 2 weeks; more traditional dose bolus of 1.25 mg/m^2; maximum 2 mg every 14 days; evidence-based from NCCN guidelines; high cure rates ≈75%; patients treated until complete response plus two or three additional cycles; three additional cycles after negative HCG level; re-stage if single agent methotrexate fails; generally methotrexate will have had at least some efficacy; change patient to dactinomycin; together with methotrexate, cure rate improves to 90%; if treatment fails, patient now considered high risk and requires multi-agent chemotherapy

Compliance: noncompliant patients have trouble; remember treatment process requires much work from patient; begins with D&C revealing molar pregnancy; monitor for weekly HCG levels if deciding against chemotherapy; perform brain MRI, CT scan of chest, abdomen, and pelvis if weekly HCG levels rise; administer day one, three, five, and seven methotrexate with leucovorin between if patient low risk; administer dactinomycin bolus every 2 weeks if patient does not respond; move to second-line chemotherapy if HCG persistently elevated, plateauing, or increasing; if dactinomycin fails, patient will need EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, and oncovin [vincristine]) therapy, which lecturer describes as "rough"

Management of high risk disease: high risk patients relatively uncommon; patients with prognostic score of seven or higher; only ≈6% of patients with GTN; adjuvant surgery and radiation can be considered; cure rates still 90%, assuming patient compliance; factors associated with worse outcomes include liver and brain metastases; EMA/CO primary therapy; EMA — etoposide, methotrexate, and dactinomycin; given on day one and two; CO — cyclophosphamide and oncovin/vincristine given on day 8; EMA/CO used for low-risk patients failing treatment or high-risk patients; chemotherapeutic regimen given every 2 weeks; probably given at least once per year in large cancer centers; NCCN guideline establishes doses; etoposide — 100 mg/m2 IV days one and two; dactinomycin — 0.5 mg push days one and two; methotrexate — 300 mg over 12 hours; generally inpatient regimen but not necessarily; four 15 mg doses of leucovorin given every 12 hours starting 24 hours after methotrexate; 600 mg/m^2 cyclophosphamide and 1 mg/m^2 or 2 mg maximum of oncovin on day eight; day eight can be done as outpatient; can use growth factors to remain at dose intensification and prevent febrile neutropenia and delays; no randomized trials; treatment widely accepted and effective

Ultra-high-risk: patients with prognostic score >12; might bleed and develop tumor lysis syndrome and multiorgan failure with EMA/CO; some early deaths within first 1-2 cycles of treatment; give low-dose induction to improve outcomes; generally etoposide and cisplatin; etoposide 100 mg and cisplatin 20 mg days one and two given every week to decrease HCG to more comfortable level before administering five drugs at once

Brain metastases: patients may require emergency intervention to manage intracranial bleeding or elevated intracranial pressure; rates of CNS metastases low; high in choriocarcinoma; diagnosis based on histology, which is not always available; sometimes neurosurgeon resects unstable patient with intercranial lesion and discovers cerebral metastasis from choriocarcinoma; might have forgotten pregnancy test; three options for brain metastases of high-risk trophoblastic disease; radiation, high-dose methotrexate 1 gm/m^2, which crosses blood brain-barrier, or intrathecal methotrexate, which encourages sufficient

blood-brain barrier penetration; high-dose methotrexate preferred to avoid needles in CNS; radiation probably least favorable option

Salvage chemotherapy: can still work after EMA/CO; sometimes use EMA/EP; replaces cyclophosphamide and oncovin with etoposide and platinum; cisplatin very active in this setting; high salvage rates of 75% to 80%; important to use granulocyte colony-stimulating factor (GCSF) support to prevent neutropenic complications and treatment delays; trophoblastic lesions have high neoantigen load due to genetic makeup and strong expression of PD-L1; checkpoint inhibitors under investigation; anecdotal evidence of salvage rates in highly resistant patients; shown to be effective in placental site trophoblastic and epithelioid tumors; reserve checkpoint inhibitors (pembrolizumab, nevolumab) for particularly resistant tumors; NCI (National Cancer Institute) cooperative group study prospectively evaluating efficacy; other active agents in trophoblastic neoplasia include gemcitabine, capecitabine, and fluorouracil (5-FU); limited data; gemcitabine goes well with cisplatin; favor 5FU in Asia primarily in combination with dactinomycin; no experience with that regimen in US

Intermediate trophoblastic tumors: rare; differentiated from other types by histology from D&C specimen; unique immunohistochemical characteristics; HCG staining only focal; also have diffuse cytokeratins such as Mel-CAM and human placental lactogen; two types — placental site trophoblastic and epithelioid trophoblastic tumors; epithelioid tumors sometimes misdiagnosed as carcinomas; consider expert pathology consult with HCG-positive suspected carcinoma; placental site trophoblastic tumors cytogenetically often diploid or aneuploid; only small cohorts inform treatment due to rarity; FIGO prognostic scoring system does not correlate well with either intermediate trophoblastic tumor; account for only quarter of 1% of GTN; surgery probably best approach; hysterectomy recommended, because cancers rarely metastasize; hysterectomy could be transformational; cancers relatively chemotherapy resistant; employ metastatectomy for isolated, distant metastases, especially in lung; while ineffective, chemotherapy can be given for metastatic disease; EMA/EP preferred chemotherapeutic approach for placental site trophoblastic or epithelioid tumors; 100% survival for non-metastatic disease with hysterectomy; 50% to 60% survival for metastatic disease; can use checkpoint inhibitors

Patients with low, persistently elevated HCG levels: non-malignant syndrome to be aware of; example — HCG in range of 50; discovered when patients present for elective surgery; quantitative levels of 50 to 100; sometimes GTN suspected; evaluation shows no history of molar pregnancy; brain MRI and CT scan of chest, abdomen, and pelvis shows nothing; can be falsely positive HCG level; heterophile antibodies can mimic HCG; can send blood for those heterophile antibodies; approach not commercially available; send urine HCG; urine negative; falsely positive blood HCG; use urine to differentiate between real elevation in tumor marker HCG *vs* false positive heterophile antibodies

Review

Gestational trophoblastic disease (GTD): consists of molar pregnancy and gestational trophoblastic neoplasia (GTN); molar pregnancy mostly benign; neoplasia generally metastatic and requires chemotherapy

Molar pregnancies: ≈1 in 1000 patients; patient presents with bleeding; ultrasound does not show baby in uterus; OB/GYN doctor evacuates uterus with suction D&C; performs chest x-ray and blood tests including CBC and thyroid; monitor post-evacuation patients with weekly HCG levels; ≈20% of complete moles develop persistent disease; sometimes called invasive moles if choriocarcinoma status unknown; partial moles account for only 1% to 5%; more common complete moles have higher malignant potential; patient developing plateauing or increasing HCG during weekly HCG levels necessitates workup

Workup: includes brain MRI, CT scan of chest, abdomen, and pelvis; another CBC, CMP and thyroid; stage patient based on FIGO or WHO staging system; takes into account prognostic factors; help predict correct course of chemotherapy; each prognostic factor scored zero, one, two, or four; highest risk patients have had term pregnancy, longer time since antecedent pregnancy of over 1 year, HCG levels >100,000, organ metastases, particularly brain and liver or intestine, spleen, and kidney; lung metastases do not increase risk; multiple metastatic sites greater than eight, and prior chemotherapy treatment

Treatment of low risk disease: score of six or less low risk; treated with hysterectomy if finished childbearing or single agent chemotherapy; chemotherapy more common; methotrexate or dactinomycin; methotrexate most common; 1 mg per kg of methotrexate on days one, three, five, and seven; interdigitated with leucovorin 30 hours later, 15 mg orally on days two, four, six and eight; cure rates as high as 75%; patients who do not have complete response with single agent methotrexate should be transitioned to dactinomycin; daily times five regimen of dactinomycin or (preferred) bolus 1.25 mg per meter squared given every 14 days; maximum of 2 mg; another 75% of patients not treated with methotrexate cured with dactinomycin; only ≈5 to 10% of patients require EMA/CO multi-agent chemotherapy; hysterectomy also an option; patients treated until complete response plus two or three additional cycles; three additional cycles after negative HCG level

Treatment of high risk disease: patients with prognostic score greater than seven should be treated with EMA/CO; five drug regimen of etoposide, dactinomycin, methotrexate, cyclophosphamide and vincristine every 14 days; receive three agents on day one; receive two agents on day eight; etoposide 100 mg on day one and two; dactinomycin 0.5 mg on day one and two; methotrexate 300 mg over 12 hours; four doses of leucovorin every 12 hours starting 24 hours after methotrexate; all evidence-based on NCCN guidelines; EMA/EP given to patients failing EMA/CO; another dose of platinum and etoposide on day eight; checkpoint inhibitors emerging, active, and well-tolerated regimen; trophoblastic tumors have high PD-L1 expression and mutational load; unique and high risk settings include ultra-high-risk disease (score >12) and brain metastases; patients started on weekly etoposide and platinum; etoposide 100 mg on day one and two;

20 mg of platinum on day one and two; patient at risk for tumor lysis syndrome and death; treated with two or three doses until stable; then convert to EMA/CO or even EMA/EP; can give intrathecal methotrexate or brain radiation for brain metastases or, alternatively, higher dose of IV methotrexate, which drives agent across blood-brain barrier; cure rates can still be high even in setting of brain metastases

Intermediate malignant potential: rarer histologies; placental site trophoblastic tumors and epithelioid tumors; expert pathology review important; tumors frequently in uterus where hysterectomy good option; metastatectomy also an option; tumors relatively chemotherapy resistant; associated with low levels of HCG and unique immunohistochemical profile with only focal IHC expression; also have diffuse cytokeratins such as Mel-CAM and human placental lactogen; epithelioid tumors can be misdiagnosed as carcinomas; pregnancy test important; urine HCG levels common; discrimination from urine test ≈30; can be assured that patient has relatively low HCG level with negative urine

Suggested Reading

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Thyroid Cancer (Follicular, Papillary and Medullary)

Emad Kandil, MD, MBA, *Professor and Elias Hanna Chair in Surgery, Chief, General, Endocrine and Oncological Surgery Division, Department of Surgery, Tulane University School of Medicine, New Orleans, LA*

Epidemiology: dramatic increase in incidence of thyroid cancer over last three decades; predominantly due to increased surveillance and detection of small micropapillary thyroid cancers; also called papillary microcarcinoma; mortality rates have not changed; largest increase observed in South Korea; most commonly diagnosed cancer among women in South Korea; early detection of small, asymptomatic, nonlethal cancer using ultrasounds, CT, and other modalities

Types: papillary thyroid cancer ≈85% of cases; follicular thyroid cancer ≈12%; both considered differentiated cancers; anaplastic thyroid cancer undifferentiated; rare; maximum of 2% of thyroid cancers; other malignant diseases of thyroid include medullary thyroid cancer; sporadic in 80% of cases; can be related to multiple endocrine neoplasia (MEN)2 or familial medullary thyroid cancer; other types include primary thyroid lymphoma; cancers metastasizing to thyroid rare but include breast, colon, renal, and melanoma

Guidelines: National Comprehensive Cancer Network (NCCN) and American Thyroid Association (ATA); guidelines issued in 2006, 2012, 2015

Workup: ATA guidelines recommend every patient undergo preoperative comprehensive neck ultrasound to evaluate central and lateral lymph nodes; assists in planning for surgical procedures; example — patient might need additional lymph node dissection; old guidelines recommended comprehensive neck ultrasound for every cancer patient; new guidelines recommend comprehensive neck ultrasound for every patient with thyroid nodule to avoid doing excess biopsies for small micropapillary carcinomas; avoid biopsies for anything <1 cm; comprehensive neck ultrasound still required, as sometimes small papillary microcarcinoma can lead to metastasis to central lateral neck

Imaging: order CT only for patients with local advanced disease or when retropharyngeal extension suspected; try to avoid ordering CT scans; CT with IV contrast precludes radioiodine therapy for 3 months

Surgical considerations: surgery primary modality of treatment for thyroid cancer; followed by radioiodine treatment if indicated; not every patient needs radio-iodine; not every patient needs total thyroidectomy; surgery for thyroid cancer or any thyroid surgery should be performed by high-volume experienced thyroid surgeon to minimize associated risk of complications; complications rare but can be devastating; include injury to recurrent laryngeal nerve with temporary or permanent hoarseness of voice; bilateral nerve injury can require tracheostomy; injury to parathyroid glands causes temporary or permanent hypoparathyroidism and hypocalcemia; permanent hypoparathyroidism associated with increased risk of overall mortality; most thyroid surgery performed in US performed by occasional thyroid surgeons — surgeons who perform less than five thyroid surgeries per year; account for perhaps >95% of surgeries; numerous studies show surgical complications significantly lower when surgery performed by surgeons performing at least 25 to 100 cases per year; risk of complication <1%; surgeons now offer remote access surgery avoiding visible neck scars; hide incisions in different parts of body; transaxillary surgery under arm, retroauricular behind ear, or transoral behind lip

Papillary thyroid cancer:

- **Cancer <1 cm without extrathyroidal extension and metastatic lymphadenopathy:** thyroid lobectomy sufficient; recent data that total thyroidectomy can help resolve compressive symptoms related to thyroiditis in patients with disease in contralateral lobe in Hashimoto thyroiditis, another cancer on contralateral lobe, or patient already on thyroid hormone replacement; Hashimoto thyroiditis caused by antibodies attacking thyroid; affects entire body; removal of thyroid decreases antibodies and patients become more energetic; complete thyroidectomy option if patients have history of neck radiation, strong family history of thyroid cancer, or imaging abnormality in contralateral side; family history important; example — patient with sister with thyroid cancer has nine-fold risk of cancer compared to general population
- **Cancer up to 4 cm:** T1 and T2; T1 — up to 2 cm; T2 — up to 4 cm; ATA guidelines state thyroid lobectomy option if no extrathyroidal extension or metastatic lymphadenopathy or lymphovascular extension; total thyroidectomy another option; consider for patient with thyroiditis, multiple contralateral nodules, existing thyroid medication, or lack of willingness to follow up
- **Cancers >4 cm or with extrathyroidal extension or evidence of cervical lymphadenopathy or metastasis:** perform total thyroidectomy; can suspect extrathyroidal extension with preoperative ultrasound; some studies show CT more sensitive in detecting extrathyroidal extension; make preoperative decision according to results; total thyroidectomy also considered with history of childhood head and neck radiation, due to high risk of recurrence

Multifocal papillary microcarcinomas: total thyroidectomy best approach with more than five foci

Surveillance: thyroid cancer one of most expensive cancers to treat in US; one of most common cancers causing bankruptcy in cancer patients; patients live long; extensive and expensive surveillance; 5- and 10-year survival rates approach 100% with low-risk differentiated thyroid cancer; workup can lead to cascade of testing not associated with longer survival; may cause harm with treatment approaches like radioiodine therapy; use caution when offering active surveillance for patients with thyroid cancer; ideally done through clinical trials; active surveillance programs exist for small thyroid cancers, but not standard of care

Recurrence: 95% of recurrence happens in first 5 years; most happen in first 2 years; ATA specifies risk stratification for disease recurrence; patients do not need radioiodine therapy if risk of recurrence low; need significantly higher doses of radioiodine therapy >100 millicuries and extensive TSH suppression if risk of recurrence high; patients do not require high dose of radioiodine with intermediate risk; can offer small dose up to 30 millicuries of radioiodine; can do TSH suppression; should not be extensive

Low risk: well differentiated intrathyroidal cancer; cancer <4 cm without BRAF (human gene encoding B-raf protein) mutation or small unifocal micropapillary carcinoma with BRAF mutation both have 1% to 2% risk of recurrence; evaluate size of metastasis and number of lymph nodes with micrometastasis in central nodes; low recurrence risk if less than five nodes and metastasis <2 mm; patients do not need radioiodine or extensive TSH suppression

High risk: recurrence up to 40% for patients with gross extrathyroidal extension, incomplete tumor resection, distal metastasis, metastasis to cervical lymph nodes >3 cm, or large tumors with BRAF mutations with extrathyroidal extension; >40% for patients with tumors ≥ 1 cm and BRAF mutations and TERT (telomerase reverse transcriptase) mutations; treated with higher dose of radioiodine and significant THS suppression

Intermediate risk: risk of recurrence up to 10%; patients with some vascular invasion, some lymph node metastasis, or intrathyroidal cancer <4 cm but some BRAF mutation; or patients with more than five lymph nodes but metastasis 2 to 3 mm; can offer small dose of radioiodine therapy ≈30 millicuries; no need for extensive TSH suppression

Radioiodine therapy: previously frequently used; multiple recent reports show patients receiving radioiodine can present with secondary malignancy; up to 1% to 2% present with cancers like hematological malignancies or salivary gland cancers

Treatment of metastatic disease: radioiodine therapy can be curative with distant metastatic disease in some patients but not in majority; TSH suppression slows pace of disease; external radiation useful in some; historically TSH suppression and external beam radiation used in patients with metastatic, well-differentiated thyroid cancer progressing despite radioiodine; now targeted chemotherapy offered for progressive and symptomatic disease; limited role for cytotoxic agents due to availability of multi-targeted kinase inhibitors that can stabilize progressive metastatic thyroid cancer; most available treatments tumoristatic rather than tumoricidal; no published studies demonstrating agents improve overall survival; for asymptomatic patients with metastatic tumors <1-2 cm with growth rate <20%/year; ATA recommends treatment with TSH suppression alone, to as low a level as patient can tolerate without tachycardia and hypertension; these patients should have surveillance every 6 months

Targeted therapy in more aggressive disease: in patients with metastatic, unresponsive, well-differentiated thyroid cancer with tumors up to 2 cm growing at least 20% per year or for patients with significant symptoms, should consider use of oral multikinase inhibitors (rather than cytotoxic agents) targeting angiogenesis; targeted therapies have significant toxicities; only offer to patients at significant risk of morbidity or mortality; check baseline ECOG (Eastern Cooperative Oncology Group) performance status; should be two or better according to ATA guidelines; sorafenib and lenvatinib approved by FDA for use in selected patients with refractory metastatic differentiated thyroid cancer; many other drugs remain investigational; lenvatinib preferred by majority of oncologists; sorafenib next preferred option; head-to-head comparisons among various kinase inhibitors have not been performed; lenvatinib favored because of efficacy compared to sorafenib side effects; FDA also approved selective BRAF inhibitor dabrafenib in addition to MEK inhibitor in patients with mutant BRAF tumors; consider genetic testing for BRAF mutations before offering cytotoxic chemotherapy; doxorubicin only cytotoxic agent approved by FDA for patients with aggressive metastatic disease and patients who cannot tolerate multi-targeted kinase therapy; clinical trials of immune checkpoint inhibitors in combination with targeted agents underway

Summary: most papillary thyroid cancers present with early stage disease without any metastasis; thyroid lobectomy sufficient in cancers up to 4 cm with no extrathyroidal extension, metastatic lymphadenopathy, or lymphovascular invasion; radioiodine therapy should not be offered for patients with low risk for recurrence, tumors up to 4 cm, and tumors without BRAF mutations; with some small tumors can consider active surveillance; new surgical techniques can avoid neck scars

Medullary thyroid cancer: more aggressive disease; neuroendocrine tumor of thyroid parafollicular or C cells; accounts for ≈2% of thyroid cancers in US; production of calcitonin is characteristic; C cells originate from embryonic neural crest; cancers often have clinical and histological features of other neuroendocrine tumors such as carcinoid or islet cell tumor; up to 80% of cases sporadic; 20% to 30% of cases familial; can be part of MEN2 syndrome; ≈50% of sporadic medullary thyroid cancer can present with somatic mutation of RET protooncogene

Sporadic medullary thyroid cancer: most common; account for ≈75 to 80% of all cases; typically presents in fourth to sixth decade; up to 95% of patients present with solitary thyroid nodule; aggressive disease; two-third of patients have clinically detectable cervical lymph nodes; up to 15% [50%? I can't tell. –Editor] have symptoms of upper airway/digestive tract compression or invasion, such as difficulty swallowing, difficulty breathing, or hoarseness of voice; up to 10% of patients present with distal metastatic disease

Calcitonin screening: controversial to check calcitonin levels in patients with thyroid nodules; not standard of care in US because of cost; standard of care in Europe; ATA does not recommend for or against routine use of calcitonin screening for medullary thyroid cancer in patient with thyroid nodules

Symptoms: tumor can secrete calcitonin or other substances causing diarrhea or facial flushing with advanced disease; corticotropin (ACTH) secretion if present causes ectopic Cushing's syndrome; test for calcitonin, CEA (carcinoembryonic antigen), and ACTH levels; basal serum calcitonin concentration usually correlates to tumor volume; calcitonin and CEA levels two markers for disease; expression of CEA on medullary thyroid cancer cells led to use of anti-C antibodies for immunotherapy; thyroid function tests usually normal in medullary thyroid cancer, similar to patients with papillary thyroid cancer

Imaging: ultrasound does not distinguish medullary thyroid cancer from other thyroid cancers; requires biopsy; suspicious features for papillary as well as medullary thyroid cancer on ultrasound include hypoechoic tissue, irregular borders, taller than wide shape, and microcalcifications

Inherited medullary thyroid cancer: MEN2-2A or 2B; both transmitted as autosomal dominant; syndromes result from different mutations in RET protooncogene; typically bilateral and multicentric disease with multiple lesions in thyroid; familial medullary thyroid cancer or familial isolated medullary thyroid cancer another inherited disease; all three subtypes involve high risk of development of medullary thyroid cancer; MEN2A and 2B also have increased risk for pheochromocytoma; 2A has increased risk of parathyroidoma or parathyroid hyperplasia; additional features of 2B include mucosal neuromas of lips and tongue, enlarged lips, ganglioneuromatosis of GI tract, and marfanoid habitus; medullary thyroid cancer occurring in early childhood in 2B carries worst prognosis; 2A occurs in early adulthood; familial medullary thyroid cancer occurs in middle age

Diagnosis: fine needle aspiration biopsy of thyroid nodule; sensitivity ≈50%; up to 80% in some series; increased sensitivity with additional immunohistochemical staining for calcitonin; requires clinical suspicion; symptoms such as diarrhea and flushing in addition to thyroid mass; serum calcitonin or calcitonin washout, which is also used to test for parathyroid cancer; often diagnosed after thyroid lobectomy; patient presents with thyroid mass, biopsy indeterminate, suspicious, or nondiagnostic; after counseling patient proceeds with diagnostic thyroid lobectomy; if pathology indicates medullary thyroid cancer, calcitonin level guides plan; lobectomy sufficient in small cancers with non-elevated calcitonin; be cautious about decision to proceed if calcitonin elevated, indicating more aggressive disease; pentagastrin testing in Europe — stimulation test checking serum basal and stimulated calcitonin levels for evaluation of thyroid nodule for early diagnosis of medullary thyroid cancer

Evaluation: NCCN guidelines recommend obtaining calcitonin levels in initial management of medullary thyroid cancer diagnosed by fine needle aspiration biopsy; obtain CEA level; rule out pheochromocytoma with serum epinephrine, norepinephrine, or 24-hour urine collection for metanephrines; must treat pheochromocytoma first to prevent surgical complications such as stroke and death; obtain calcium level to evaluate for hypoparathyroidism; consider genetic counseling; check for RET protooncogene mutation in exomes 10, 11, and 13 to 16; comprehensive neck ultrasound from ear to ear at central and lateral compartment (should be done for any thyroid cancer); evaluate for vocal cord mobility; sometimes patient will not have hoarseness but have compensation from contralateral cord; status of vocal cords helps decide extent of surgery; consider CT of chest and abdomen, specifically if calcitonin level high; liver MRI or three-phase CT of liver if calcitonin >400 pg per mL; MRI more sensitive

Assessment after thyroid lobectomy: staging done with ultrasound; baseline serum calcitonin and CEA can be compared with postoperative values; need metastatic workup; postoperative results might provide prognostic factors and indicate biochemical cure; calcitonin may never return to normal; preoperative calcitonin concentration can correlate with tumor size in both sporadic and familial cases and can correlate with extent of metastatic disease; most patients with low preoperative calcitonin up to 50 pg per mL should have normal concentration of calcitonin after appropriate surgical resection; less than half of patients with preoperative serum calcitonin >50 will eventually have normal levels after surgery; up to 60% of patients without lymph node metastasis will have normal levels; only 10% of patients with metastatic lymphadenopathy expected to have normal postoperative calcitonin level; assess for doubling time for both calcitonin and CEA level; sensitive marker for quantifying tumor aggressiveness and disease progression; 8% 10-yr survival for patients with doubling time under 6 months in one study; 37% for patients with doubling time between 6 month and 2 years; survival rate 100% in patients with doubling time >2 years; extensive workup to rule out distant metastasis with local lymph node mass on ultrasound or basal calcitonin level >500 pg per mL; three-phase contrast-enhanced liver CT or liver MRI to rule out distant metastasis to liver, most common site for metastasis; not recommended to do FDG (18-fludeoxyglucose) PET (positron emission tomography) scan for routine initial screening with metastatic disease; sensitivity of PET scan detecting metastatic disease variable; improves with high calcitonin levels

Genetic screening: recommended with sporadic medullary thyroid cancer; RET testing should be considered in all patients with newly diagnosed medullary thyroid cancer; physicians can directly order genetic testing from reference laboratories, but recommended to consult with genetic counselor familiar with ethical issues and legal informed consent requirements, which can vary significantly from one state to another; family members should be offered genetic counseling and screening when index patient positive for germline mutation; 75% of familial medullary thyroid cancer have no prior family history; test for coexisting tumors, pheochromocytoma and hyperparathyroidism most important; biochemical testing for coexisting tumors not required in patients with negative RET protooncogene testing and no family history of MEN2 syndrome; easier to check for pheochromocytoma with serum levels of epinephrine, norepinephrine, and 24-hour urine collection, calcium and PTH levels, compared to waiting for genetic testing; check serum calcium to rule out primary hyperparathyroidism that would require concomitant surgery

Staging: stage I — tumors <2 cm without evidence of any disease outside thyroid; stage II — >2 cm confined to thyroid without any lymph node metastasis; possible gross extrathyroidal extension invading only strap muscles; stage III — tumors of any size with metastatic lymph nodes to central or lateral neck; stage IV — distant metastasis

Surgical management: guidelines recommend surgical resection for persistent or recurrent medullary thyroid cancer; surgery first modality to treat patients with recurrent disease; consider compartmental dissection with biopsy-proven diagnosis; comprehensive lymph node dissection; treat more aggressively than papillary thyroid cancer, where surgeon shaves cancer off nerve or trachea and patients can be treated well with radioiodine postoperatively; involved nerve in medullary thyroid cancer must be resected; tracheal resection if needed

Radioiodine therapy: no role in medullary thyroid cancer

Chemotherapy: tyrosine kinase inhibitors (TKIs) cabozantinib and vandetanib most commonly used, available in US for treatment of symptomatic and progressive medullary thyroid cancer with unresectable local or metastatic disease; significant prolongation of progression-free survival in randomized, phase three trials; complete response rare; can provide long-term disease stabilization; limited data on ability to improve survival; mostly considered in patients with progressive advanced medullary thyroid cancer; otherwise recommended to participate in clinical trials with targeted therapies; can use sorafenib and lenvatinib; doxorubicin also FDA approved for all histologies of metastatic thyroid cancer; <30% of patient will have objective response; none will have complete response; investigation of immunotherapy

Summary: observation most appropriate treatment for patients with asymptomatic metastatic tumors <2 cm and growth in diameter <20% per yr; follow up on metastatic disease; known sites of metastatic disease should be imaged by CT or MRI; overall goal of extending duration of life without harming quality of life; extensive and meticulous surgical resection primary goal of treatment of medullary thyroid cancer; limited role for external beam radiotherapy; no role for radioiodine therapy; only consider chemotherapy in patient with metastatic tumors at least 1 to 2 cm in diameter growing at least 20% per yr or for symptomatic patients; consider for clinical trials if unable to treat with surgical intervention; treat bone metastasis with external beam radiation; consider tyrosine kinase inhibitors rather than traditional cytotoxic chemotherapy for patients not in clinical trials

Anaplastic thyroid cancer: aggressive cancer; undifferentiated tumors of thyroid follicular epithelium; 100% disease-specific mortality; because of rapid disease progression, consider plans for comfort care measures as integral part of initial management; rare disease; age-adjusted annual incidence one to two per million persons; mean age at diagnosis 65 years; 20% of patients have history of well-differentiated thyroid cancer; up to 30% present with coexisting differentiated cancer; mutations in BRAF and RAS observed in well-differentiated thyroid malignancies and anaplastic thyroid cancer; presumed to be early events in progression from well-differentiated to anaplastic thyroid cancer; 90% rules of anaplastic thyroid cancer — patients present with thyroid mass in 90% of cases; up to 90% present with regional or distant disease; 90% of metastasis in lungs; only up to 10% have bone metastasis; relative favorable prognostic factors include unilateral tumors and those <5 cm, no extrathyroidal invasion or cervical lymph node involvement

Workup: patients usually present with goiter; typically hard; may be tender; may not move with swallowing; most patients have normal thyroid function tests; serum thyroglobulin concentration may be high; thyroglobulin can be high because of multiple exams; ATA does not recommend routine thyroglobulin level, though some believe it aids disease understanding; no data supporting that; significant symptoms of dysphagia, hoarseness; ultrasound nonspecific; may diagnose by cytology, but pathologist will likely prefer fine needle aspiration biopsy, larger needle biopsy, true cut needle biopsy, or in some cases surgical incisional biopsy in order to obtain sufficient tissue; cytology includes spindle cells, pleomorphic giant cells, and squamoid cells; many anaplastic thyroid cancers have mixed morphology; cytopathologist looks for numerous mitotic figures, atypical mitosis; typically extensive necrosis due to tumor outgrowing blood supply; anaplastic thyroid cancer less likely to stain positive for TTF1 (thyroid transcription factor 1) or PAX8 (paired box gene 8) and thyroglobulin; immunohistochemical staining not always helpful

Imaging: ATA guidelines recommend PET scans and MRI of brain; perform cross-sectional imaging from head to toe if PET scan not available; includes scanning brain, head, neck, chest, abdomen, and pelvis with CT and MRI for initial staging

Genetic testing: routinely evaluate for BRAF mutations; BRAF inhibitors approved for treatment of this disease in combination with MEK (mitogen-activated protein kinase) inhibitors

Staging: all anaplastic thyroid cancers considered stage IV cancers; IVA — intrathyroidal anaplastic cancers; IVB — extrathyroidal extension or cervical lymph node metastasis; IVC — distant metastasis

Management: most cases unresectable; can biopsy distant metastasis in patient with surgically resectable disease; surgical resection followed by combined radiotherapy and chemotherapy; consider combined chemoradiation for local control of disease if patient presents with locally advanced and inoperable disease and desires active therapy rather than palliative care; surgical resection afterwards in some cases; send patient with referral for testosterone prescription [presumably for men? — editor] after surgery; enroll patients with good performance status in clinical trials with targeted therapy; patients with surgery for resectable disease can have prolonged survival >2 years; usually with adjunct chemoradiation; treatment should be directed toward securing airway in patients with metastatic disease

Palliation of symptoms: priority in patients with advanced disease; treatment should be directed towards securing airway and ensuring access for nutritional support; unable to perform tracheostomy when disease extends below clavicle; palliative radiotherapy may be beneficial to improve pain with bone metastasis

Chemotherapy: options include doxorubicin and cisplatin; lack of effective standard of care; try to enroll patients in clinical trials; lenvatinib reported to have some reasonable results; most important is to do genetic mutation testing; can offer dabrafenib or MEK inhibitor trametinib if BRAF-mutation positive; trametinib approved for locally

advanced unresectable metastatic anaplastic disease with BRAF mutations; radioactive iodine has no role in primary treatment of anaplastic thyroid cancer

Medical management: thyroid hormone replacement for patients after total thyroidectomy; monitor TSH levels, try to keep patients in euthyroid status; no role for extensive TSH suppression unless testing shows coexisting differentiated thyroid cancer, which occurs in 30% of cases

Suggested Reading

Cabanillas ME, et al: Thyroid cancer. *Lancet,* 2016 Dec 3;388(10061): 2783-95; **Li Q, et al:** Imaging and screening of thyroid cancer. *Radiol Clin North Am.* 2017 Nov;55(6):1261-71; **Raue F, et al:** Thyroid cancer: risk-stratified management and individualized therapy. *Clin Cancer Res.* 2016 Oct 15;22(20):5012-21.

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Head and Neck Cancer

Nikhil Joshi, MD, *Department of Radiation Oncology, Cleveland Clinic , Cleveland, OH*

Evaluation: symptoms of head and neck pathology include painless neck mass, odynophagia, dysphasia, change in voice or hoarseness, hemoptysis, trismus, ear pain, loose teeth, ill-fitting dentures, non-healing oral ulcers, and nasal bleeding; refer any adult patient with symptoms persisting for more than 2 weeks to otolaryngologist; history should include extent of tobacco exposure, alcohol exposure, and other risk factors like oral lichen planus and chronic dental irritation

Physical examination: comprehensive; begin with inspection of various head and neck structures; palpation of neck including thyroid gland and oral cavity, especially if abnormality found; examine cranial nerves; evaluate for possible skin cancers

Workup: in-office flexible endoscopy part of complete head and neck examination; biopsy from primary site of disease or involved lymph node; may be obtained during direct laryngoscopy or examination under anesthesia; cross sectional imaging including CT, MRI with contrast, and PET/CT aids in staging of cancer; specialized testing includes p16 immunohistochemistry for oropharyngeal tumors, Epstein-Barr virus (EBV) encoded RNA (EBER), and plasma EBV DNA and copy number for nasopharyngeal carcinomas; basic lab work includes baseline thyroid function test; pregnancy testing in females of childbearing age; comprehensive dental examination and evaluation; perform needed extraction at least 2 weeks prior to radiation; baseline speech, swallow, and audiometry evaluation indicated depending on primary site involved and treatment anticipated; cigarette smoking cessation important

Staging: use eighth edition of American Joint Committee on Cancer (AJCC) staging manual for staging all cases; several changes from seventh edition; useful to know both; oral cavity cancer staging now reflects depth of invasion as important factor for staging; deeper tumors now upstaged; p16-positive and p16-negative oropharyngeal cancers have separate staging system for T and N stage, including in postoperative setting; nodal staging for p16-positive oropharyngeal cancers now more akin to nasopharyngeal nodal staging; stage grouping different from other head and neck subsites; staging for nasopharyngeal cancer revised to more accurately reflect anatomic involvement of primary; nodal staging for nasopharyngeal cancer revised to reflect involvement above and below cricoid cartilage; stage IVC eliminated; non-oropharyngeal or nasopharyngeal cancer nodal staging revised to reflect importance of extranodal extension; clinical and pathological nodal staging different on basis of node size and presence of extranodal extension

Early disease: usually includes stages I and II and selected stage III patients; optimally managed with single modality treatment; includes surgery or radiation; goal is achieving high rates of local regional control and cure while limiting morbidity of treatment and preserving functional outcomes; organ preservation central to management of early stage cancers

Local regionally advanced disease: include stages III, IVA, and IVB; two or more treatment modalities often combined to achieve optimal disease control; primary modality of treatment depends on site of disease; trimodal treatment necessary on occasion

Oral cavity cancers: oral cavity includes lip, anterior two thirds of tongue, floor of mouth, buccal mucosa, gingiva, hard palate, and retromolar trigone

Early oral cavity cancers: usually treated with surgery alone; includes wide local excision of primary with surgical management of neck; lymph node dissection considered standard except for very small and superficial primaries of limited thickness; resected small primaries of oral cavity with wide margin without adverse pathologic features and negative lymph nodes may be followed without adjuvant management with generally good local-regional control and outcomes

Local-regionally advanced oral cancers: include T2 oral tongue cancers with >4 to 5 mm depth of invasion; usually treated with surgery, including neck dissection; extent of primary site surgery depends on size and extent of primary; example — an oral tongue resection might range from wide local excision with margin around primary to near total or total removal of tongue (glossectomy); extent of neck dissection varies by extent of disease and structures involved; important phase III trial (D'Cruz et al.) of elective nodal dissection *vs* therapeutic nodal dissection at relapse for early stage lateralized oral squamous cell carcinomas demonstrated survival advantage to elective nodal dissection

Adjuvant therapy: radiation important in adjuvant management of local-regional cancers of oral cavity; demonstrated to improve local-regional control; chemotherapy added for positive margins or extracapsular extension of nodal disease; demonstrated to provide both local-regional control benefit over radiation alone and disease-free survival benefit; combined analysis of RTOG 9501 and EORTC landmark studies demonstrated this advantage; forms basis of concurrent chemotherapy and adjuvant radiation for high-risk head and neck cancers; adjuvant radiation remains standard of care for adjuvant treatment of intermediate risk cancers; several studies ongoing

Intermediate risk factors for oral cavity cancers: close margin; usually defined as <5 mm from tumor edge; lymphovascular space invasion; perineural invasion; T3 or

T4 disease; T2 oral cavity cancers with >5 mm thickness or depth of invasion of primary; node-positive disease without extracapsular extension

Oropharyngeal carcinomas: oropharynx includes various subsites; tongue base, vallecula, tonsils, posterior pharyngeal wall, and soft palate; cancers divided into two large prognostic categories based on etiology — HBV-induced cancers and HBV-unrelated or usually tobacco-induced cancers; AJCC staging manual now recognizes these two as different diseases with separate staging systems

HPV (human papilloma virus): overwhelming majority of oropharyngeal cancers in Western world HPV-positive; might not be so in other parts of world; positive immunohistochemistry for p16 surrogate for presence of HPV as causative factor; HPV DNA can be performed instead of p16 immunohistochemistry; sometimes used to confirm HPV-related cancer in case of doubt when clinical scenario not fitting; extensive RTOG (Radiation Therapy Oncology Group) experience has validated prognostic value of HPV; divided oropharyngeal cancers into low, intermediate, and high risk groups; retrospective analysis of RTOG 0129 study used HPV status, smoking, tea, and end-stage based on AJCC seventh edition staging to establish risk groups; HPV-related oropharyngeal cancers also categorized into low-and high-risk groups by Princess Margaret group, O'Sullivan and colleagues; HPV-related oropharyngeal cancer has much better prognosis compared to HPV-unrelated oropharyngeal cancer; treatment of oropharyngeal cancer does not change with HPV status; likely to change in future with various treatment de-intensification strategies being explored for favorable HPV-related oropharyngeal cancers

Management: early stage oropharyngeal cancers usually managed with single modality treatment — surgery or definitive radiation; categories include T1, T2, N0, N1 tumors per AJCC seventh edition staging system; local regional control and overall survival remain high for these stages when treated with single modality; more locally advanced disease traditionally managed with definitive chemoradiation; surgery reserved for salvage, especially for advanced neck disease; bio-radiation with cetuximab typically used for cisplatin-ineligible patients; trial by Bonner and colleagues demonstrated survival advantage to adding cetuximab to radiation *vs* radiation alone; bio-radiation with cetuximab inferior to chemoradiation with cisplatin in recently reported RTOG 1016 large phase III study by Trotti and colleagues; select subset of patients can be managed with surgery followed by adjuvant treatment

Surgical options: include transoral resection and less commonly open surgery along with appropriate neck dissection; case selection often tailored to achieve optimal outcome and avoid multiple modalities of therapy to minimize morbidity; example — T2N2bM0 tonsil cancer staged by AJCC seventh edition staging primarily amenable to transoral robotic surgery (TORS); may undergo this procedure and neck dissection in absence of clinical extracapsular extension of disease in nodes, thereby avoiding addition of concurrent chemotherapy with adjuvant radiation; radiotherapy and TORS with neck dissection studied recently in phase II study by Palma and colleagues; radiotherapy arm had superior swallowing-related quality of life scores at 1 year after treatment; differences not clinically meaningful; discuss both options with patient in appropriate clinical context

High-risk cancers: high risk HPV-positive oropharyngeal cancers, T4 and N2c to N3 category by seventh edition staging system, associated with high local-regional control rate; distant failure occurs in up to a quarter of cases; group may not benefit from treatment de-escalation — elimination of systemic therapy component; strategies to improve systemic control warranted; high-risk HPV-negative cancers including T3, T4, and N2c to N3 disease categories associated with equally poor distant failure; local-regional control also inferior with ≈40 to 50% failure at 3 years; aggressive therapy warranted for these patients, usually definitive chemoradiation followed by surgical salvage as needed

Laryngeal cancers: can be supraglottic, glottic, or subglottic; mainly comprised of cancers of glottis and supraglottis; less commonly subglottis; distinction important, considering glottis devoid of lymphatics; supraglottis and subglottis rich in lymphatics

Treatment: early T1 glottic cancers can be managed with voice-conserving peroral laryngeal microsurgical procedures; excellent local control; often superior voice quality; definitive radiation alternative for early glottic cancers, especially when lesion more extensive and unsuitable for microsurgical excision; usually happens with deeply invasive tumor; voice quality often superior with radiation; depends on baseline voice quality; early glottic cancers can be treated with definitive radiation with excellent outcomes; T1 cancers of supraglottis can be treated with transoral voice-preserving surgery; open or endoscopic supraglottic laryngectomies often performed; some form of bilateral neck management usually advocated, given high risk of lymph node spread; definitive radiation is alternative management option; usually includes both necks in treatment fields

T2 tumors of glottis and supraglottis: can be managed with either surgery or definitive radiation; various forms of voice-preserving laryngeal procedures utilized depending on tumor extent; options include supraglottic laryngectomy, supracricoid laryngectomy, and vertical partial laryngectomy; bilateral neck dissections also advised for supraglottic disease; primary in both necks can alternatively be treated with definitive radiation; dose usually slightly higher than for T1 tumors; though not part of formal AJCC staging, T2 glottic cancers are divided into T2a and T2b based on mobility of true vocal cord; T2b glottic cancers have restricted mobility and worse outcomes with standard dose radiation alone; believed these cases represent early paraglottic space involvement; may require more intense treatment; hyperfractionation — radiation delivered twice per day — and radiation with chemotherapy strategies often utilized to achieve better local control for T2b glottic cancers

T3N0M0 tumors: management of T3N0M0 laryngeal cancer controversial; voice-preserving surgical approach warranted in certain cases; fixed cord usually contraindication for vertical partial laryngectomy; patient may be observed without any further adjuvant treatment if no adverse postoperative pathologic features identified after surgery; total laryngectomy

usually avoided; remains oncologically acceptable option; definitive chemoradiation remains alternative voice-preserving treatment strategy per landmark RTOG 9111 trial

Management of locally advanced laryngeal cancer: takes into account baseline function of larynx, baseline swallowing function, and disease extent; standard surgical procedure total laryngectomy with bilateral node dissection; may be followed by adjuvant radiation or chemoradiation based on various pathologic risk factors; surgical management approach best used for patients with severely compromised laryngeal or swallowing function; select cases might undergo voice-preserving surgery for primary with neck dissection followed by adjuvant treatment as indicated; larynx-preserving non-operative approaches have emerged as reasonable option; mostly appropriate for those patients without significant preexisting laryngeal or pharyngeal dysfunction

Studies: two landmark studies established larynx-preserving approach to locally advanced laryngeal cancer with adequate baseline laryngopharyngeal function; Larynx study compared induction chemotherapy with cisplatin and 5FU followed by definitive radiation to total laryngectomy followed by radiation for locally advanced laryngeal cancers; 64% rate of larynx preservation; overall survival not compromised; RTOG 9111 study compared induction chemotherapy followed by definitive radiation to definitive concurrent chemoradiation with cisplatin or radiation therapy alone; large volume T4 lesions with destruction of larynx or massive extension of supraglottic cancers to tongue base excluded, as these felt best treated with primary surgical approach; 82% larynx preservation rate at 10 yrs for concurrent chemoradiation arm; has become standard for non-operative management of locally advanced laryngeal cancer in North America; overall survival statistically similar between all three treatment arms; likely reflected success of salvage surgery; concerning trend towards inferior survival noted in concurrent arm; reasons unclear; induction chemotherapy followed by radiation or radiation alone remains acceptable treatment despite reduced likelihood of laryngeal preservation when surgery not an option or patient refuses surgery

Management of hypopharynx cancer: similar to management of laryngeal cancers; large majority of hypopharynx cancers present at advanced stage; hypopharynx has rich lymphatic network; nodal metastasis common at presentation; retropharyngeal nodes may be involved early as well; early stage primary cancers may be addressed with transoral or open voice-conserving procedure with neck dissection as indicated; adjuvant therapy can then be administered as required; total laryngectomy with partial pharyngectomy and bilateral node dissection with reconstruction standard surgical approach for locally advanced hypopharynx cancers; adjuvant treatment based on various adverse features on pathology; often includes adjuvant radiation

Studies: voice-conserving, non-operative treatments studied for hypopharyngeal cancers; similar to trials conducted in laryngeal cancer; EORTC 24891 study compared induction cisplatin-5FU followed by radiation with surgery followed by radiation; 22% larynx preservation at 5 yrs in surviving patients; overall survival similar in both arms; trial established voice-conserving approach to treating locally advanced hypopharyngeal cancers; several recent retrospective institutional series have shown high larynx preservation rates of ≈90% at 3 years; better overall survival of ≈50% at 3 years with modern radiation and chemoradiation techniques; as with laryngeal cancer, patients with significant laryngeal and swallowing dysfunction at baseline best treated with initial surgery followed by adjuvant therapy per pathology; patients with retained laryngeal and swallowing function may be best served by definitive non-operative chemoradiation; patients often medically compromised; general medical fitness for either approach important

Nasopharyngeal cancer: spectrum from more endemic EBV-associated undifferentiated carcinoma, labeled as WHO type III cancer, to keratinizing squamous cell carcinoma (WHO type I cancer); more recently, p16-positive EBV-negative subset identified; nasopharynx rich in lymphatics; nodal metastases commonly found with nasopharyngeal cancer; anatomy of nasopharynx generally precludes primary surgical approach, especially since both necks at risk from disease; radiation along with chemotherapy plays major role in management

Early stage node negative primaries: treated with radiation alone; includes primary and both necks; appropriate elective skull-based coverage necessary as tumors tend to spread along cranial nerves toward brainstem

Locally advanced nasopharyngeal cancers: often treated with definitive radiation and chemotherapy, followed by three cycles of adjuvant chemotherapy; treatment paradigm based on landmark study by Al-Sarraf and colleagues; demonstrated large survival benefit with concurrent and adjuvant chemotherapy *vs* radiation alone in locally advanced nasopharyngeal cancers; ongoing NRG-HN001 randomized trial exploring importance of adjuvant chemotherapy approach based on clinical response and plasma EBV DNA levels; patients with undetectable plasma EBV DNA after concurrent chemoradiation randomized to standard adjuvant cisplatin-5FU *vs* observation; patients with detectable plasma EBV DNA after concurrent chemoradiotherapy then randomized to standard adjuvant cisplatin-5FU *vs* alternative paclitaxel-gemcitabine combination

New adjuvant chemotherapy in nasopharyngeal cancers: gemcitabine and cisplatin for three cycles followed by definitive chemoradiation showed improved recurrence-free survival and overall survival compared with definitive chemoradiation alone in recently reported randomized, phase III trial by Sang and colleagues; trial did not compare experimental arm of neoadjuvant chemotherapy followed by definitive chemoradiation to definitive chemoradiation followed by adjuvant chemotherapy, which is still considered standard

Non-metastatic, locally recurrent nasopharyngeal cancer: treated with surgical and non-surgical approaches; re-radiation usually advocated, especially when patient not surgical candidate

Salivary gland cancers: rare subsite of head and neck cancers; comprise variety of histologies; found in various locations throughout head and neck, including major and minor salivary glands; may be benign or malignant; benign lesions more commonly found in major salivary glands; lesions of minor salivary glands more likely malignant; recent WHO classification can be referred to

for the various histologies; grade important variable and prognostic factor; major salivary gland cancers clinically obvious as to site of origin; minor salivary gland tumors often mistaken for more common mucosal lesions

Management: pre-treatment imaging and tissue diagnosis important; inadvertent excision of lesion can compromise further oncologic surgical cure; fine needle aspiration biopsy usually first diagnostic step; definitive classification of salivary gland cancers can be difficult using limited pathologic approach; definitive surgical management considered standard initial treatment for wide variety of salivary gland cancers seen clinically; in absence of clear diagnosis, major salivary gland lesions often resected with intraoperative frozen section for initial diagnosis; oncologic resection attempted after establishing diagnosis; benign lesions like pleomorphic adenomas also resected with oncologic principles — no tumor spillage during surgery and no capsule violation, as tumors show preponderance for local recurrence; malignant lesions such as those with fast preoperative growth or facial nerve paralysis at presentation resected with wide local margin; negative resection margins often desired; may be difficult to obtain due to proximity to facial nerve; facial nerve usually preserved if functioning before surgery and grossly uninvolved intraoperatively; paralyzed facial nerve usually sacrificed in attempt to obtain negative proximal margin; might require meticulous skull-based dissection; facial nerve should be reconstructed and grafted during primary surgery; other adjunct procedures like temporalis tendon transfer considered for facial reanimation; management of neck controversial; patients with T3-T4 high-grade or node-positive disease status usually managed with ipsilateral neck dissection

Adjuvant management: based mostly on retrospective data; adjuvant radiation plays important role in improving local regional control; general indications for postoperative radiation include T3 or T4 primary lesions, high grade, lymphovascular space invasion by cancer, microscopic and clinical perineural spread, close positive margins, and node-positive or recurrent disease; role of chemotherapy controversial and far less established; RTOG 1008 study — phase three trial exploring role of concurrent cisplatin with radiation for high-risk salivary gland tumors; certain histologic subtypes may express potential hormonal or other therapeutic targets such as HER2 and androgen receptors in salivary duct carcinomas; emerging role for targeted therapies including trastuzumab and androgen deprivation therapy

Unknown primary cancers of head and neck: comprise ≈3% of all head and neck cancers; squamous cell carcinomas thought to originate mostly from mucosal sites; other histologies also seen and may indicate source of primary origin; example — adenocarcinoma noted in lymph node might have arisen from salivary gland cancer or thyroid or parathyroid gland; site of lymph node presentation often linked to potential site of primary; knowledge of anatomy helps in evaluation and management

Examples: level three lymph node with squamous cell carcinoma might arise from larynx, hypopharynx, or upper cervical esophagus primary; level 1A lymph node likely to arise from oral cavity primary; level 1B lymph node might indicate primary in oral cavity, maxillary sinus, or nasal cavity; level two lymphadenopathy might indicate primary in oropharynx; this is most common site of metastases from various head and neck cancers; level five lymph node raises possibility of nasopharyngeal or skin cancer; parotid gland lymph node showing squamous cell carcinoma usually indicates cutaneous primary squamous cell carcinoma; isolated supraclavicular lymph node unlikely to indicate head and neck cancer primary; primary almost always below clavicle, such as pulmonary primary, thoracic esophagus primary, or even breast cancer

Evaluation: follows usual workup of head and neck cancers when head and neck primary noted; core needle biopsy of node preferred, especially to obtain p16 and EBER) evaluation; may point to HPV-related oropharyngeal primary or nasopharyngeal primary, respectively; caution advised; primary drainage pattern of involved lymph node should be taken into account before interpreting immunohistochemistry results; example — isolated level five lymph node might be p16 positive but more likely to indicate cutaneous primary or nasopharyngeal primary rather than oropharynx primary; consider PET/CT before surgical diagnostic procedures performed, since information might aid in finding primary; tonsillectomy, tongue base, and nasopharynx biopsy standard during examination under anesthesia; rare yield for such blind biopsies; transoral lingual tonsillectomy, otherwise known as tongue-based resection, increasingly utilized to detect tongue-based primary; found in high number of cases with level two node presentation

Management: usually follows expected site of primary when no primary found after surgical biopsies; example — level one node subjected to neck dissection assuming oral cavity, maxilla, or nasal cavity as primary site; N1 disease may be resected; in absence of adverse pathologic features, patient may be observed without any further treatment; this is based on data regarding low emergence rates of primary, although literature is inconsistent; radiation considered standard to prophylactically radiate potential primary sites, considering morbidity involved

P16-positive lymph node without apparent primary: signifies oropharyngeal primary in correct context; staged as such in eighth edition of AJCC staging manual; treatment advised accordingly; p16-positive level two lymph node is treated with definitive neck radiation and prophylactic coverage of oropharynx if radiation chosen as treatment option; EBV-positive lymph node points to nasopharyngeal primary; case should be staged as nasopharynx primary per new AJCC eighth edition staging system; treatment follows accordingly; p16-negative level two lymph node treated similarly, but prophylactic coverage often includes nasopharynx and hypopharynx as well, although there is considerable variability among radiation oncologists regarding extent of mucosal coverage and dose of radiation utilized; oral cavity, larynx, and hypopharynx excluded from prophylactic radiation volume, as such an approach considered excessively morbid with low yield; more advanced disease may be treated with surgery followed by radiation with or without chemotherapy based on various pathologic risk factors

Treating N2 or N3 disease non-operatively: concurrent chemotherapy usually added to radiation, although

benefit of this approach less clear; salvage surgery may be needed for more advanced neck disease; patients with distant metastases presenting with neck node and no primary treated with palliation, including radiation and chemotherapy; results of treatment usually follow similarly staged head and neck cancers with known primary site; cure still possible despite not knowing where primary originated in non-metastatic cases with unknown primary

Studies of recurrent or metastatic squamous head and neck carcinoma:

EXTREME study (Vermorken et al.): studied combination of cisplatin or carboplatin and 5FU *vs* added cetuximab; landmark phase III trial exploring role of cetuximab in recurrent or metastatic head and neck squamous cell carcinoma, a patient group with poor prognosis; median survival significantly improved with addition of cetuximab to chemotherapy; study established new standard of care

Keynote-048 study: explored role of immunotherapy for recurrent or metastatic head and neck cancers; locally incurable, recurrent, or metastatic head and neck squamous cell carcinoma with no prior systemic therapy in recurrent metastatic setting randomized to pembrolizumab for 2 yrs or pembrolizumab plus six cycles of chemotherapy with cisplatin-carboplatin-5FU combination or to EXTREME regimen; compared with EXTREME regimen, combination of pembrolizumab and chemotherapy had superior overall survival in PD-L1 CPS (combined positive score) >20 and CPS >1 categories with comparable safety; pembrolizumab alone had superior overall survival in CPS >20 and >1 population with non-inferior overall survival in total population; favorable safety profile; results support role of pembrolizumab and pembrolizumab plus combination chemotherapy with platinum agent and 5FU as new first line standards of care for recurrent and metastatic head and neck squamous cell carcinoma

Suggested Reading

Hamilton D, et al: The changing landscape of oropharyngeal cancer management. *J Laryngol Otol.* 2017 Jan;131(1):3-7; **Obid R, et al:** The treatment of laryngeal cancer. *Oral Maxillofac Surg Clin North Am.* 2019 Feb;31(1):1-11; **Svider PF, et al:** Head and neck cancer. *Otolaryngol Head Neck Surg.* 2017 Jan;156(1):10-3.

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Neuro-oncology

Tracy T. Batchelor, MD, MPH, *Miriam Sydney Joseph Professor of Neurology, Harvard Medical School, and Neurologist-in-Chief and Chair, Department of Neurology, Brigham and Women's Hospital, Boston, MA*

Epidemiology: best source for epidemiological data for primary brain tumors is the Central Brain Tumor Registry of the United States; based on 2018 estimates, approximately 85,000 primary CNS tumors were diagnosed in the US; most common primary brain tumor is meningioma, accounting for ~30%; most common primary malignant brain tumor is glioblastoma, accounting for ~20%; classification of CNS tumors was revised by the World Health Organization in 2016; one of the main changes involved a subtype of glioma (anaplastic oligoastrocytoma), which was discontinued; this was the first time that biomarkers were incorporated into the diagnosis of a primary brain tumor; specifically, the status of chromosomes 1p and 19q must be assessed in order to make a diagnosis of an anaplastic glioma; 1p/19q co-deletion is synonymous with an anaplastic oligodendroglioma; 1p/19q retention or non-co-deletion is synonymous with an anaplastic astrocytoma; anaplastic astrocytoma is further subdivided based on the presence or absence of a mutation in the isocitrate dehydrogenase 1 (IDH1) gene; there are anaplastic astrocytomas with and without ("IDH1-wild type")an IDH1 mutation; IDH1-wild type anaplastic astrocytomas have a more aggressive phenotype, and a prognosis that is similar to glioblastoma

Glioblastoma: most common primary malignant brain tumor; approximately 15,000 new cases diagnosed in the US each year; first or second leading cause of cancer-related death among young adult males in the US; median age at diagnosis is 64 years; median survival is <1 year; 5-year survival is <5%

Glioblastoma classification: 4 cardinal features in the histopathological diagnosis of glioblastoma: 1) pleomorphism in either the cells or the nuclei, 2) mitotic activity, 3) microvascular proliferation, 4) necrosis or a unique pattern of necrosis known as pseudopalisading necrosis; with the presence of all 4 features, the diagnosis is glioblastoma; The Cancer Genome Atlas (TCGA) further subtypes glioblastoma into 4 categories: classical, mesenchymal, neural, or proneural; these have not made it into clinical practice, but are used in experimental studies; there are also primary and secondary glioblastomas; a secondary glioblastoma arises from a prior low-grade glioma; this type of glioblastoma is also characterized by the presence of an IDH1 mutation; an IDH1 mutation discovered in a glioblastoma is diagnostic of secondary glioblastoma; in contrast, a primary glioblastoma arises de novo (ie, not from an underlying low-grade tumor) and there is no IDH1 mutation; ~90% of glioblastomas are primary and ~10% are secondary

Imaging: very important in the diagnosis of brain tumors; glioblastoma has a characteristic imaging appearance; after contrast administration, borders appear indistinct and infiltrative; there is diffuse contrast leakage throughout the tumor, and there are often darker, non-contrasting elements within the tumor; these are likely areas of necrosis within the tumor; 99% of these tumors enhance and 90% of the time appear as a single lesion

Prognostic factors: there are a number of prognostic factors that have been described for glioblastoma; these include age, performance status, status of the MGMT (0-6-methylguanine-DNA methyltransferase) gene, and status of the IDH1 gene; younger age (ie, <55) is associated with a better prognosis; patients with minimal functional deficits or better performance status have an improved prognosis; patients with methylated MGMT or an IDH1 gene mutation have a better prognosis; methylation of the MGMT promoter is observed in ~35-40% of glioblastomas

Treatment: surgery, radiation, and medical therapies; surgery can consist of a biopsy or a resection; radiation is typically fractionated over 30 treatments or 6 weeks and is delivered from an external energy source specifically to the tumor and a 1-2 cm border around the tumor; tumor is often defined by MRI, and specifically the T2 and FLAIR (fluid-attenuated inversion recovery) borders; another, not radiation-based, energy source treatment for is the Novocure TTF device; medical therapies include chemotherapy drugs (eg, temozolomide and lomustine) and the monoclonal antibody bevacizumab

Surgery: rationale is to provide adequate tissue for a pathological diagnosis and for molecular profiling; often, patients will experience improvement in their neurological symptoms and signs if significant debulking of a tumor can be achieved; this will allow clinicians to also reduce the dose or eliminate corticosteroids; it is more controversial whether an aggressive resection improves survival; a study that addressed this issue examined the use of aminolevulinic acid (ALA) as a guide for resection; ALA is a non-fluorescent prodrug that when taken up by dividing glioma cells, is converted into a fluorescent porphyrin; when a specific type of filter is applied to the surgical microscope, the ALA-containing tumor appears pink or purple, allowing surgeons to better remove tumor from the surrounding brain that does not take up ALA; in a randomized, multicenter,

phase III trial, 270 newly diagnosed malignant glioma patients who were resection candidates based on their initial MRI and were suspected of having glioblastoma were enrolled, and it turned out 243 actually had glioblastoma; this study demonstrated that the patients who received ALA had a higher proportion of gross total resections vs subtotal resections, and of the 243 glioblastoma patients, those who had a gross total resection had a significant improvement in overall survival vs those who had a subtotal resection (16.7 vs 11.8 months); based on these data, the Food and Drug Administration approved 5-ALA as an adjunct to glioma surgery in 2017

Radiation: studies that demonstrated the utility of radiation in glioblastoma were done in the 1970s and 1980s when fractionated external beam radiation was compared with best supportive care or chemotherapy alone, with consistent demonstration that the patients who received radiation had improved survival; this became a part of the standard of care in the 1970s and 1980s and has remained to this day

Novo TTF device: an energy source that delivers alternating electrical fields to the scalp and tumor; there is evidence that these alternating electrical fields have an anti-mitotic effect; this was shown to be safe in the EF-14 trial, which was published in *JAMA* (*Journal of the American Medical Association*) in 2015; patients with newly diagnosed glioblastoma all received the standard of care (ie, resection, radiation, temozolomide), but half received the Novo TTF device; patients who received the Novo TTF device achieved a significant improvement in overall survival (19.6 vs 16.6 months); this device was approved by the FDA in 2015; note that this treatment requires that patients shave their heads and wear scalp electrodes attached to the energy source almost continuously

Chemotherapy: temozolomide in the newly diagnosed setting; this oral methylating drug was demonstrated to improve overall survival in a trial published in the *New England Journal of Medicine* (*NEJM*) in 2005, with a follow-up study in *The Lancet Oncology* in 2009; after surgery, patients were randomized to radiation alone, or radiation plus temozolomide for 6 weeks, followed by 6 monthly cycles of temozolomide; the treatment was well tolerated; patients who received the combination had significantly improved median overall survival (14.6 vs 12.1 months); 2-, 3-, 4-, and 5-year follow-up results published in *The Lancet Oncology* in 2009 demonstrated that this survival advantage was maintained at each point in patients who received the combination

MGMT methylation status: a prognostic marker and may also be a predictive marker in patients with glioblastoma; it has changed the landscape in terms of clinical trials in glioblastoma, as there are now trials that are being developed in unmethylated or poor prognosis glioblastoma patients who defer the use of chemotherapy and allow the use of a novel drug; there are trials in the methylated MGMT glioblastoma population that attempt to supplement temozolomide; the CeTeG/RNOA-4 trial, published in *The Lancet* in 2019, randomized 141 newly diagnosed methylated MGMT glioblastoma patients between the ages of 18 and 70 to the standard of care arm (surgery, radiation, temozolomide) vs an experimental arm (surgery, radiation, temozolomide, lomustine) — an intensification of chemotherapy in this methylated MGMT group; analyses demonstrated a trend favoring the combination of lomustine and temozolomide; there was more grade 3/4 hematologic toxicity and a lower rate of treatment completion in the combination arm, indicating that this combination is not as easy to administer; results do not provide conclusive evidence that we should be adding lomustine to temozolomide in newly diagnosed methylated glioblastoma patients, but this should be discussed with patients and colleagues

"Tumor pseudoprogression:" approximately 20% to 40% of patients with glioblastoma will have a worsening of contrast enhancement and swelling in their brain after completion of chemotherapy and radiation; tends to occur in the first 3 months after completion of radiation and slowly resolves over the ensuing 3-12 months with no intervention; this is important to recognize because these individuals generally should continue their temozolomide and should not be switched to alternative drugs; some key points here are that the changes, again, are most common within 3 months of completion of radiation; the changes occur within the original radiation field; in that situation, it would be reasonable to continue temozolomide; however, if such changes are noted at 6 months or longer, or there are any changes that occur outside the radiation field, there should be a high suspicion of actual tumor progression; nevertheless, this so-called tumor pseudoprogression is noted in 20-40% of newly diagnosed glioblastoma patients and should be factored into the interpretation of scans immediately following completion of radiation

Treatment of older glioblastoma patients: patients in their 60s to 80s often will not tolerate radiation and combinations of radiation and temozolomide as well as younger patients; studies have examined less intensive treatments in elderly patients with glioblastoma; the Nordic trial, published in *Lancet Oncology* in 2012, randomized newly diagnosed glioblastoma patients over the age of 60 to three arms: radiation alone at the standard 60 Gy dose over 30 fractions; a modified radiation arm at a lower total dose (34 Gy over 10 fractions); and a non-radiation arm treating patients only with temozolomide for 6 monthly cycles; in the subset analysis of this trial, patients who had methylated MGMT seemed to fare equally well whether or not they received radiation; this has led some investigators and practitioners to advise temozolomide to elderly patients who have methylated MGMT, especially those who might have very large tumors that may not tolerate radiation, but note that this is based on subgroup analysis only and cannot be considered conclusive

Treatment of recurrent glioblastoma: virtually all glioblastoma patients experience recurrent disease; at this time, options include a repeat resection either alone or with implantation of a BCNU (β-chloro-nitrosurea, carmustine) wafer or polymer, which was FDA approved approximately two decades ago for recurrent glioblastoma; treatment could also include radiation or re-irradiation, or the use of chemotherapy; no solid evidence supports re-irradiation in these

patients, and there is no conclusive evidence that radiosurgery is beneficial at the time of recurrent glioblastoma; chemotherapy drugs include lomustine, which, when used alone, will achieve a 20-25% progression-free survival at 6 months, or bevacizumab as monotherapy, which can also be used, can be very effective for symptom control in these patients, and appears to be associated also with improved progression-free survival at 6 months; recurrent glioblastoma is a setting in which many patients will also undergo clinical trials

Bevacizumab: the utility of this drug was first demonstrated in a series of case reports and papers in 2005 to 2007; in one study of 35 recurrent glioblastoma patients, published in the *Journal of Clinical Oncology*, approximately 46% of patients treated had no progression at 6 months and over half had objective radiographic responses to bevacizumab; the BRAIN study included 167 recurrent glioblastoma patients who were randomized to either bevacizumab alone or bevacizumab plus irinotecan, and assessed with central radiographic review; both bevacizumab-containing arms had radiographic responses ranging from 28-38%, and progression-free survival ranged from 43-50%, demonstrating the utility of bevacizumab in recurrent glioblastoma; based on this trial and subsequent follow-up, the FDA granted full approval for bevacizumab as monotherapy for recurrent glioblastoma in 2017; it has been a matter of debate as to the biological effect of bevacizumab in glioblastoma; the drug is a potent anti-permeability drug, which will reduce contrast leakage from tumor vessels; much of the radiographic response observed after use of bevacizumab is likely based on the anti-permeability effects of bevacizumab and some have termed these responses pseudo-responses; nevertheless, many patients will experience stability or improvement in their neurological symptoms and signs; the drug is available for use in recurrent glioblastoma, and many patients do receive it

Anaplastic gliomas: defined by chromosome 1p/19q status and IDH1 status; trials launched prior to reclassification based on biomarkers have influenced the standard of care

Anaplastic oligodendroglioma: defined based on chromosome 1p/19q loss; tumors have a characteristic histopathological appearance, but all patients should have confirmatory 1p/19q testing; it was observed in the 1980s that patients had variable clinical outcomes, and some responded to chemotherapy; this led to randomized trials in the EORTC (European Organization for Research and Treatment of Cancer) and RTOG (Radiation Therapy Oncology Group); in both of these, patients were randomized to receive radiation alone or radiation plus chemotherapy following surgery; in both trials, chemotherapy was PCV (procarbazine, CCNU [lomustine], and vincristine); both trials were published in the *Journal of Clinical Oncology* in 2006 and demonstrated that PCV was associated with improved progression-free survival but not overall survival; subsequent analysis revealed that in patients who had 1p/19q co-deletion (today, what we would call an anaplastic oligodendroglioma), the addition of PCV to radiation doubled survival in both trials, demonstrating the utility of chemotherapy plus radiation for anaplastic oligodendroglioma; we do not know whether temozolomide has a similar effect; temozolomide is less toxic than PCV and easier to use; conversely, in the anaplastic glioma subtype where there is 1p/19q retention or non-co-deletion (today, we would call these anaplastic astrocytoma), the CATNON study randomized patients after surgery to a radiation alone arm vs a radiation and temozolomide approach with three separate chemotherapy arms (radiation plus temozolomide for 6 weeks only, radiation followed by temozolomide, and radiation plus temozolomide for 6 weeks followed by temozolomide); when the initial results of this trial were published in *The Lancet* in 2017, the analysis was restricted to the radiation arm vs all of the other radiation-chemotherapy arms combined; in that analysis, there is a clear advantage of adding chemotherapy to radiation in terms of a significant extension of progression-free and overall survival, although we do not yet know the specific results of these individual chemotherapy schedule arms

Low-grade gliomas in adults: grade II gliomas; these can be astrocytomas or oligodendrogliomas; historically managed with maximal safe resection; a number of randomized trials have asked whether the addition of radiation improves outcomes after surgery in low-grade gliomas; there appears to be some advantage of radiation in delaying time to disease progression, but no significant overall survival advantage; there is a subtype of low-grade glioma that was studied in a randomized trial that asked a chemotherapy question, and these are so-called high-risk, low-grade gliomas; high risk defined as anyone over the age of 40 or anyone who has a subtotal resection or only a biopsy of a low-grade glioma; the standard of care at the time of this study was radiation; in the study design, these high-risk, low-grade glioma patients were randomized to receive radiation alone or radiation followed by 6 cycles of PCV; long-term follow-up results published in *NEJM* in 2016 demonstrated a significant improvement in overall survival in patients who received PCV plus radiation, again demonstrating the benefit of chemotherapy in this glioma subtype; we do not know if temozolomide would have a similar effect

Meningiomas: most common primary brain tumor; occur along the covering of the brain; so-called extra-axial tumors because they grow within the meninges; tumors can grow to a point that they compress the underlying brain or adjacent neurologic structures, such as the cranial nerves, and result in neurologic morbidity; asymptomatic meningiomas that are discovered after an MRI (eg, after a car accident) are generally observed with serial MRI scans over time if they are not significantly compressing or threatening important structures such as the carotid artery or cranial nerves; meningiomas do grow, and eventually, these patients may require operation; symptomatic meningiomas should be resected if this can be safely accomplished; if a gross total or near-total resection is achieved, and if the tumor is non-malignant, which is the case >90% of the time, there is no additional therapy advised, and patients can be followed with serial MRI scans; radiation is generally reserved for malignant meningiomas, atypical meningiomas, or meningiomas that have recurred after surgery and are threatening neurological structures; there is no standard treatment for

atypical meningiomas; some recommend radiation, others recommend observation; clinical trials are ongoing; there are no effective medical therapies for meningiomas

Primary CNS lymphomas: extranodal, non-Hodgkin lymphoma confined to the brain, the eye, the meninges, the spinal cord, or combinations thereof; less common than when an established systemic lymphoma disseminates into the nervous system, most of the time into the meninges, but sometimes also into the brain; these have characteristic features; 90% of non-Hodgkin lymphoma of the brain is diffuse large B-cell lymphoma, which in contrast causes only about 30% of systemic non-Hodgkin lymphoma; of diffuse large B-cell lymphoma of the brain, nearly all are most closely related to the activated B-cell (ABC) subtype of large cell lymphoma; this may account for the inferior prognosis of diffuse large B-cell lymphoma when it occurs in the nervous system; recently, we have learned more about the signal transduction pathways driving primary CNS lymphoma; some are through the B-cell receptor or in genes that converge on the NF-κB (nuclear factor kappa-beta) pathway and result in oncogenic signaling; this offers some opportunities to develop targeted therapies against the B-cell receptor or other signal transduction elements; around 1500 cases each year in the US; incidence increased 3-fold from the 1970s to the 1980s, but some recent data suggests there has been some plateau of incidence; 5- and 10-year survival rates are 33% and 25%; if you look at other forms of extranodal lymphomas — intestine, stomach, bone, etc. — the single subtype with the worst prognosis of all extranodal lymphomas is primary CNS lymphoma; again, that could be due to the fact that it is mainly aggressive large cell lymphoma (the ABC immunophenotype) or it could relate to the fact that perhaps our treatments are not as impactful in the CNS; the median age of diagnosis is 66 and it is slightly more common in men; it tends to be a rapidly progressive tumor with an average symptom duration of under 3 months from the time of first symptom to the time of diagnosis; diagnosis is typically achieved by needle biopsy because CT and MRI have characteristic appearances; in contrast to glioblastoma, this tumor usually has a uniform contrast enhancement throughout; tumor typically located in deep structures adjacent to the ventricles or in the corpus callosum of the brain; recognizing this in the differential diagnosis leads to a biopsy rather than a resection; the International Primary CNS Collaborative Group (IPCG) has established baseline clinical laboratory extent-of-disease evaluations for primary CNS lymphoma, which were published in the *Journal of Clinical Oncology* in 2005; this can be a multi-compartmental disease; the gold standard for imaging the brain is contrast-enhanced MRI; ~10-20% of patients will have concurrent involvement of the cerebral spinal fluid (CSF); in patients where a lumbar puncture can be safely performed, it should be performed, and CSF should be sent for cytology and flow analysis; some patients will have mass effect and will be at risk of herniation; in those cases, a lumbar puncture should not be performed; if considering a lumbar puncture but you are unsure, then a neurosurgical consultation should be obtained; similarly, ~10-20% of patients will have concurrent involvement of the eye (any part of the uveal tract or the retina itself); every patient should have an ophthalmological examination that includes a slit lamp evaluation; to prove that this is a primary CNS lymphoma, need to exclude lymphoma outside of the brain; CT-PET imaging of chest, abdomen, and pelvis, and bone marrow aspirate and biopsy are advised by the IPCG

Treatment: because this is a multi-compartmental disease, responses are assessed based on not only the brain imaging but also the eye examination results, CSF results, and steroid dose; because this is a diffuse disease, only part can be visualized by MRI; treatment of primary CNS lymphoma has evolved over time; when radiation is used, it has to be whole-brain radiation (WBRT); this is typically administered over 2-3 weeks at a dose of 30-36 Gy; adding chemotherapy to WBRT improved survival in primary CNS lymphoma, but surviving patients often were afflicted with cognitive impairments; led to interest in eliminating WBRT and using chemotherapy-alone approaches or reducing the dose of WBRT in an attempt to mitigate the toxicity to the brain and combining that reduced-dose radiation with chemotherapy; more recently, effort on intensifying chemotherapy with high-dose treatment and autologous stem cell transplant, and targeted agents; the IELSG-20 (International Extranodal Lymphoma Study Group-20) study randomized newly diagnosed patients to methotrexate alone or methotrexate plus ARA-C (arabinosylcytosine cytarabine) as induction chemotherapy; all patients then received consolidative WBRT; patients randomized to the combination of methotrexate and ARA-C had a higher complete response rate and improved failure-free and overall survival vs those patients who received methotrexate alone; this study and others show that a subset of patients develops neurological symptoms while in remission, including cognitive difficulties, gait difficulties, urinary incontinence; MRI scans often show a bright signal within the cerebral hemispheres and atrophy of brain; this is the neurotoxicity that often accompanies treatment of primary CNS lymphoma; a task force of neuropsychologists identified age as the most important risk factor; 4 cognitive domains were most sensitive (attention, executive functioning, memory, and psychomotor speed); our neuropsychology task force developed an abbreviated cognitive battery, which we incorporate into clinical trials to measure the impact of neurotoxicity; this neurotoxicity is largely driven, most believe, by WBRT; this has led to an effort to reduce the WBRT dose using combined modality approaches with methotrexate-based chemotherapy followed by WBRT; one approach is to reduce the WBRT from 30 Gy to 23.4 Gy; in study RTOG 1114, patients with newly diagnosed disease were randomized to a chemotherapy-alone approach built around rituximab, methotrexate, procarbazine, and vincristine (RMPV) vs the other arm (RMPV chemotherapy plus low-dose WBRT at 23.4 Gy); this trial has been completed and we are awaiting results; a multicenter, German trial asked whether WBRT could be eliminated; patients were randomized to chemotherapy alone (methotrexate and ifosfamide) vs chemotherapy and WBRT; results

were published in *Lancet Oncology* in 2010; in the intent-to-treat analysis, although there was an improvement in progression-free survival in those patients receiving WBRT, there was no difference in overall survival between groups; this trial was specifically designed as a non-inferiority trial, and they did not achieve a significant non-inferiority result

Rituximab: revolutionized the treatment of non-CNS non-Hodgkin lymphoma; there has been interest in using this drug in primary CNS lymphoma based on early case reports of responses in patients with relapsed primary CNS lymphoma to rituximab alone; a small pilot study by a National Cancer Institute Cooperative Group demonstrated in 12 patients that the majority had some degree of response to rituximab alone; a randomized, multicenter, open-label, phase III trial was conducted and was published in *Lancet Oncology* in 2019; in the study, 200 patients with newly diagnosed primary CNS diffuse large B-cell lymphoma aged 18-70 were randomized to MBVP chemotherapy alone vs MBVP plus rituximab chemotherapy in the induction stage of treatment; all patients received post-induction ARA-C; younger patients also received WBRT; there was no difference in 1-year event-free survival, which was the primary endpoint, for MBVP vs RMBVP; there did not appear to be an advantage of adding rituximab

IELSG 32 trial: a study with intensive, aggressive, high-dose chemotherapy and stem-cell transplant which studied the role of rituximab in induction and of WBRT vs high-dose chemotherapy and stem cell transplant in consolidation; in the first part of this trial, patients with newly diagnosed primary CNS lymphoma were randomized to methotrexate and ARA-C (control) vs methotrexate/ARA-C/rituximab, vs methotrexate/ARA-C/rituximab/thiotepa (4-drug or matrix arm); primary endpoint for this part of the study was overall response rate; patients who had stable disease, partial response, or complete response were then randomized to either WBRT therapy at 36 Gy or high-dose chemotherapy and transplant; the results of Part I were published in *Lancet Hematology* in 2016, demonstrating a clear overall response and complete response advantage to all 4 drugs, the matrix arm; this indirectly supports rituximab as a component of induction; however, remember that there was also thiotepa in the matrix arm, so teasing out what was thiotepa from what was rituximab may not be possible; the matrix arm was associated with higher radiographic response rates; the results of the second randomization, which addressed the consolidation question, WBRT vs high-dose therapy transplant, involved 118 patients; both arms achieved progression-free survival at the 2-year endpoint; there was a suggestion that patients who received the high-dose therapy and stem cell transplant had less cognitive impairment and better quality of life, although this was only noted in the subset of 57 patients who had these serial assessments; these results were published in *The Lancet Hematology* in 2017; another randomized phase II study asking essentially the same consolidation question was conducted by the ANOCEF-GOELAMS (Association des Neuro-Oncologues d'Expression Francaise-Groupe Ouest-Est des Leucémies et Autres Maladies du Sang) group, and published in *Journal of Clinical Oncology* in 2019; this was a randomized, intergroup, phase II study of 140 newly diagnosed, primary, CNS diffuse large B-cell lymphoma patients, randomized to rituximab, methotrexate, BCNU, and VP16, followed by two cycles of ARA-C; then the randomization was to high-dose WBRT and transplant; both arms achieved their primary endpoint in terms of 2-year progression-free survival; cognitive impairments were noted after WBRT, whereas there was cognitive preservation or improvement after high-dose therapy and stem cell transplant; there was 1 toxicity-related death in the WBRT arm and 5 toxicity-related deaths in the high-dose chemotherapy/transplant arm

Novel therapies for primary CNS lymphoma: the B-cell receptor and the BTK (Bruton's tyrosine kinase) signaling axis is felt to be an important, potential oncogenic driver of primary CNS lymphoma; interest in the use of BTK inhibitors in primary CNS lymphoma; some phase I studies of ibrutinib in relapsed primary CNS lymphoma; one study involved 13 patients, one involved 18 patients; these were heavily pretreated populations and some had had transplants before ibrutinib monotherapy; in both studies, there were significant rates of response; 5 of 13 had complete responses in one study, and in the other study, 94% of patients had some tumor regression with ibrutinib alone

Lenalidomide: being studied in primary CNS lymphoma; a phase II study in refractory/relapsed primary CNS lymphoma or primary vitreoretinal lymphoma was published in *Annals of Oncology* in 2019; in this study, lenalidomide was combined with rituximab as an induction therapy, and then those who responded received maintenance therapy with lenalidomide; 36% of patients had an overall response rate at the end of induction (primary study endpoint); lenalidomide is being studied in larger studies in primary CNS lymphoma

Summary: primary CNS lymphoma is an uncommon subtype of non-Hodgkin lymphoma; there is really no role for surgical resection; the role for the surgeon is to make a diagnosis; WBRT alone is palliative and associated with clinical neurotoxicity, especially in patients over the age of 60; methotrexate-based chemotherapies are the standard induction, but the specific regimen is not defined; optimal consolidation after response is not clearly defined; options include high-dose therapy and stem cell transplant, WBRT, or chemotherapy, and there are novel therapies under study, including ibrutinib, lenalidomide, and immunotherapies

Suggested Reading

Carabenciov ID, Buckner JC: Controversies in the therapy of low-grade gliomas. *Curr Treat Options Oncol* 2019 Mar;20(4):25; **Ferreri AJM et al:** Evolving treatments for primary central nervous system lymphoma. *Am Soc Clin Oncol Educ Book* 2019 Jan;39:454-66; **Lu VM et al:** Hypofractionated versus standard radiation therapy in combination with temozolomide for glioblastoma in the elderly: a meta-analysis. *J Neurooncol* 2019 Mar 27 [Epub ahead of print].

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Sarcoma

Jonathan Trent, MD, PhD, *Director, Bone and Soft Tissue Sarcoma Program, and Associate Director, Clinical Research, Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL*

History: sarcoma first cancer described in history; fossilized remains from 1.7 million years ago found recently in African desert identified osteosarcoma as first human cancer detected; Ebers Papyrus from 1550 BC discusses soft tissue sarcomas; in 260 AD Galen used term *sarcos* for fleshy tumor; John Abernethy separated bone and soft tissue sarcomas as different entities; sarcomas described by mimicry of normal human tissue with development of light microscopy; with development of immunohistochemistry, pathologists further characterized tumors by type of normal tissue they resemble

Pathology: different vascular soft tissue sarcomas include angiosarcoma, hemangiosarcoma, lymphangiosarcoma, and hemangioendothelioma; adipocytic tumors include myxoid-round cell liposarcoma and dedifferentiated liposarcoma; smooth muscle tumors termed leiomyosarcoma; can arise in GI tract, GU tract, or cutaneously, specifically in uterus; bone sarcomas include osteosarcoma with features of bone or chondrosarcoma with features of cartilage-producing cells; >200 different types of unique soft tissue sarcoma and bone tumors; up to 50 different sarcoma types commonly seen at sarcoma centers; most common types include pleomorphic sarcoma, fibrosarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, and synovial sarcoma

Prevalence: unique cancers; rare; estimated 15,000 cases per year in US, compared to ≈200,000 women diagnosed with breast cancer or 180,000 people diagnosed with colon cancer each year; sarcoma can arise almost anywhere in body; ≈50% arise from upper or lower extremity; ≈10% in head and neck; ≈20% in thorax or abdomen; ≈10% in pelvis; some present with unknown primary site

Etiology: sarcomas arise from different embryonic layer than carcinomas; three layers of tissue during embryogenesis; ectoderm — external layer; endoderm — internal layer; mesoderm — middle layer; mesoderm gives rise to bone, cartilage, blood vessels, nerves, and other soft or connective tissues; also called mesenchymal tissue; gives rise to mesenchymal tumors; angiosarcoma resembles blood vessels; liposarcoma resembles fatty tissues; leiomyosarcoma resembles smooth muscle; all arise from mesodermal layer; sarcomas biologically different from carcinomas, which arise from ectodermal and endodermal layers; sarcomas different from other cancers in that there is a distinct molecular origin for many different sarcomas; point mutations in genes such as KIT or PDGF receptor in gastrointestinal stromal tumors (GIST); point mutations in PI3-kinase in myxoid liposarcoma; gene amplifications such as MDM2 or CDK4 found in dedifferentiated liposarcoma and well-differentiated liposarcoma; gene deletions common with osteosarcoma; often have loss of P53 or retinoblastoma; GIST may arise when SDH gene deleted; translocations most common genetic aberration observed in sarcomas; many involve transcription factors; can also be growth factors and developmental pathway molecules; example — Ewing sarcoma involves translocation of EWS to FLI1 protein; translocation product transcription factor turns on genes producing proteins that result in malignant phenotype; dermatofibrosarcoma — type of sarcoma that occurs in superficial tissue below skin; driven by translocation involving collagen promoter in front of ligand platelet-derived growth factor B

Diagnosis: patient may have some discomfort in extremity or notice lump, often believed to be from trauma or injury; standard imaging often performed initially; often X-ray; MRI should be performed; preferred imaging modality for most sarcomas; CT of abdomen good study for sarcoma within chest or abdomen; perform biopsy; gold standard of diagnosis; perform core needle biopsy with multiple biopsy passes through same site to provide adequate tissue; excisional biopsy option in select cases; fine needle aspiration not recommended because adequate tissue not obtained; diagnosis; best made by experienced sarcoma pathologist because of complexity and rareness of sarcomas

Classification: tumors classified using World Health Organization schema; graded using National Cancer Institute or French cancer grading system; staging follows American Joint Committee on Cancer (AJCC) or International Union Against Cancer (IUAC) systems

Discrepancies between primary diagnosis and second opinion: study by Lurkin et al. found 54% full agreement when community pathologist-diagnosed sarcoma reviewed by expert sarcoma pathologist; partial discordance 27% of time; complete discordance 19% of time; Arbiser et al. reviewed 266 sarcoma diagnoses reviewed by community and expert sarcoma pathologists and found 68% full agreement, 7% minor discrepancy, and 25% major discrepancy with complete discordance; change in diagnosis for major discrepancy with complete discordance would dramatically alter treatment and prognosis; recommend patients diagnosed with sarcoma have tissue reviewed by expert sarcoma pathologist

Treatment: may involve surgery, radiation therapy, chemotherapy, or interventional procedure; requires multidisciplinary team; sarcomas best managed at sarcoma centers due to rarity; long-term follow up essential; medical oncologists generally use

systemic therapy dispersed throughout body; includes chemotherapy, targeted therapy, and immunotherapy; active systemic therapy agents include doxorubicin, ifosfamide, dacarbazine, temozolomide, gemcitabine with or without docetaxel, irinotecan; vincristine used in small-cell sarcomas; trabectedin used in liposarcoma or leiomyosarcoma; interferon alpha (now rarely used) shows activity in giant cell tumor of bone; Celebrex, Sulindac, and other anti-inflammatories used in desmoid tumors; tamoxifen has demonstrated activity in low-grade leiomyosarcomas, endometrial stromal sarcomas, and desmoid tumors; high-dose ifosfamide has activity in patients whose tumors have progressed on standard-dose ifosfamide; particularly active in synovial sarcoma, osteosarcoma, and Ewing sarcoma; RANK ligand antibodies such as denosumab have activity in giant cell tumor of bone driven by RANK/RANK ligand interaction; mTOR inhibitors particularly effective in perivascular epithelioid cell sarcoma (PEComa); imatinib FDA approved for GIST and dermatofibrosarcoma; may have activity in other sarcomas; sunitinib active in GIST; also studied retrospectively and shown to have activity in extraskeletal myxoid chondrosarcoma; pazopanib recently FDA approved for variety of soft tissue sarcomas excluding liposarcoma and GIST; eribulin recently approved for liposarcoma

Chemotherapeutic management: determine chemosensitivity of tumor to specific agent; particularly important in adjuvant setting after surgery

Very sensitive histologies: Ewing sarcoma or primitive neuroectodermal tumor, rhabdomyosarcoma, desmoplastic small round cell tumor, GIST, dermatofibrosarcoma, angiosarcoma, myxoid/round cell sarcoma, synovial sarcoma, uterine or extremity leiomyosarcoma, and desmoid tumors

Intermediate sensitivity histologies: fibrosarcoma, malignant peripheral nerve sheath tumor, hemangiopericytoma, solitary fibrous tumor, extraskeletal myxoid chondrosarcoma, and PEComa

Minimal sensitivity histologies: hemangioendothelioma, epithelioid sarcoma, dedifferentiated liposarcoma, and alveolar soft part sarcoma (ASPS)

Resistant histologies: clear cell sarcoma, conventional chondrosarcoma, and GI leiomyosarcoma

Metastasis: metastatic spread of newly diagnosed primary soft tissue sarcoma largely determined by site and type of primary tumor; lung metastasis most common site; rare in GIST, desmoid tumor, dermatofibrosarcoma, or non-malignant giant cell tumor of bone; liver metastasis rare in many extremity tumors but common in GIST, leiomyosarcoma, and angiosarcoma; fatty deposits throughout body susceptible to metastatic deposition in myxoid or round cell liposarcoma; brain metastasis very rare in sarcomas other than angiosarcoma and ASPS; bone metastasis rare in most types of sarcomas but seen in Ewing or primitive neuroectodermal tumor, angiosarcoma, and hemangioendothelioma; lymph node metastases very rare but seen with epithelioid sarcoma, synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma, and angiosarcoma; discovery of lymph node involvement equivalent to finding metastatic deposit in lung, liver, or other distant site; sarcoma more primary tumor or metastatic than regional disease

Goals of chemotherapy: eradicate micrometastatic disease in adjuvant setting or allow resection of metastatic deposits; can use chemotherapy in patients with primary tumors to eradicate microscopic tumor cells, decrease local recurrence rate, downstage unresectable tumors to enable resection and facilitate organ-sparing surgery, and better understand individual patient tumor biology; example — aggressive, chemo-resistant type metastasizing early *vs* chemosensitive tumor

Doxorubicin: discovered in 70s; mainstay of chemotherapy for majority of soft tissue sarcoma histologies; has dose-response rate; higher doses result in higher percentages of tumor shrinkage; response rate ≈15% to 20% in early studies of doxorubicin 45 mg/m^2; rates of 35% to 40% reported by O'Brien et al. when dose escalated to 75 mg/m^2

Ifosfamide: second most commonly used chemotherapy in majority of soft tissue sarcoma histologies; has dose-response relationship; higher doses result in higher probability of shrinking tumor; use of ifosfamide at 6 g/m^2 resulted in ≈15% objective response rates in published studies from Benjamin and Patel; response rates approached 25% at 10 g/m^2; highest response rates observed in 14 g/m^2 given divided in 2 g/m^2 doses daily, q12 hours, or by continuous infusion in study of high dose ifosfamide; continuous infusion ifosfamide at 14 g/m^2 can provide objective response rate ≈25%, whereas bolus provides response rates in excess of 50%

Combination doxorubicin and ifosfamide: many studies; study by Santoro et al. evaluated doxorubicin 50 mg/m^2 plus ifosfamide 5 g/m^2; found objective response rate of 25% in 258 patients; Edmonson et al. compared doxorubicin 60 mg/m^2 with same dose doxorubicin plus 7.5 g/m^2 ifosfamide and found 34% response rate with the combination; doxorubicin 75 mg/m^2 combined with ifosfamide 5 g/m^2 resulted in 45% response rate; Patel et al. published doses of doxorubicin from 75 to 90 mg/m^2 plus 10 g/m^2 of ifosfamide resulting in highest reported response rate of 65%; doxorubicin 75 to 90 mg/m^2 plus 10 g/m^2 ifosfamide most active regimen with highest probability of shrinking tumor and sparing critical organs; consider with patient needing reduction in tumor size to facilitate organ-sparing surgery

Case example: patient with high-grade endometrial stromal sarcoma; recurred at cervix and invaded into vagina; offered surgery involving vaginectomy; presented for second opinion; decided to try chemotherapy; treated with doxorubicin 75 mg/m^2 plus ifosfamide 10 g/m^2; marked reduction of tumor after two cycles; continued to six cycles; performed surgical resection with sparing of vagina; tumor removed with negative margins; 100% necrosis in tumor

Studies: study performed in Europe compared doxorubicin alone to doxorubicin plus ifosfamide; patients enrolled randomized to doxorubicin 75 mg/m^2 as 72-hour continuous infusion or doxorubicin 25 mg/m^2 days one through three and ifosfamide 2.5 g/m^2 days one through four with Neulasta (pegfilgrastim) subcutaneously on day five; overall response rate of doxorubicin 14%; overall response rate of doxorubicin plus ifosfamide 27%; addition of ifosfamide to doxorubicin nearly doubled probability of shrinking tumor; median progression-free survival of doxorubicin 4.6 months;

7.4 months for doxorubicin plus ifosfamide; statistically significant improvement; adding ifosfamide to doxorubicin increased median overall survival from 12.8 months with doxorubicin alone to 14.3 months with doxorubicin plus ifosfamide; 1.5 month increase in median overall survival; 51% 1-yr overall survival for doxorubicin alone in patients with metastatic soft tissue sarcoma; 60% 1-yr overall survival for doxorubicin plus ifosfamide; 9% increase but not statistically significant; combination of doxorubicin and ifosfamide doubles response rate and halves progression[-free] rate; conclusions — doxorubicin plus ifosfamide improves progression-free survival; did not significantly improve overall survival; 9% improvement showed trend toward statistical significance; doxorubicin plus ifosfamide has more side effects than doxorubicin alone

Gemcitabine/docetaxel: combination common second-line therapy for many types of soft tissue sarcoma; provides objective response rate of ≈20%; gemcitabine alone provides response rate of 9%; recent GeDDiS study compared gemcitabine plus docetaxel to doxorubicin; found response rate of doxorubicin alone 66% *vs* 59% for gemcitabine plus docetaxel for objective responses and stable disease; PR plus CR plus stable disease; median progression-free survival for doxorubicin 23 weeks *vs* 24 weeks for gemcitabine plus docetaxel; curve seemed to separate late with hazard ratio of 1.28 favoring doxorubicin; 71-week overall survival with doxorubicin alone on median; median overall survival for gemcitabine plus docetaxel 8 weeks shorter at 63 weeks; hazard ratio of 1.07 also favored doxorubicin; single-agent doxorubicin had much less toxicity than gemcitabine plus docetaxel; doxorubicin considered first-line therapy for metastatic soft tissue sarcoma; gemcitabine/docetaxel second-line therapy

Temozolomide: active in metastatic soft tissue sarcoma; two-arm phase II study with GIST and other types of sarcoma performed; patients received 85 mg/m^2 by mouth daily; zero responses seen in GIST patients; 10% partial response rate in other histologies; nearly 20% (2 of 10 patients) of leiomyosarcoma patients had partial response; well tolerated; overall survival of ≈14 months on median

Pazopanib: PALLETTE study — phase III multicenter, randomized, double-blind, placebo-controlled trial in patients with metastatic soft tissue sarcoma who received prior chemotherapy; had to have received anthracycline or be unsuited to anthracycline therapy; patients randomized to pazopanib 800 mg per day or placebo in 2:1 fashion; no crossover at progression; GIST and adipocytic sarcomas excluded from trial; found overall intent-to-treat median progression-free survival of 4.6 months with pazopanib; 1.6 months with placebo; differences in superiority over placebo stood up in subgroup analysis of leiomyosarcoma, synovial sarcoma, and other soft tissue sarcomas; FDA and EMA (European Medicines Agency) approved pazopanib for use in any soft tissue sarcoma other than GIST and liposarcoma

Trabectedin: recently approved for patients with liposarcoma or leiomyosarcoma; anecdotal activity in Ewing sarcoma, other translation sarcomas, and other types of sarcomas; not FDA approved for those indications; some studies have reported response rates as high as 80% in prolonged progression-free survival in myxoid liposarcoma; patients with metastatic or unresectable liposarcoma or leiomyosarcoma randomized to trabectedin or dacarbazine in 2:1 ratio and followed for median progression-free survival; study found 37% progression-free rate at 6 months for trabectedin; only 14% for dacarbazine; markedly superior outcome with trabectedin over dacarbazine

Eribulin: phase III study of eribulin *vs* dacarbazine in advanced soft tissue sarcoma; eligible patients had leiomyosarcoma or liposarcoma; had two or more prior regimens and measurable disease by response evaluation criteria in solid tumors (RECIST); patients randomized 1:1 to eribulin 1.4 mg/m^2 IV on days one and eight every 21 days or dacarbazine at 850, 1000, or 1200 mg/m^2 IV day one of every 21 days; primary end point was overall survival; secondary end points were progression-free survival, progression-free rate, tolerability; exploratory end point of response rate; patients treated with eribulin had median overall survival of 13.5 months; patients treated with dacarbazine had median overall survival of only 11.5 months; stratified *p*-value of 0.0169 proved superiority of eribulin to dacarbazine by ≈2 months on median

Matching treatment options to specific sarcomas: examples:

- **Non-uterine leiomyosarcoma:** doxorubicin plus dacarbazine front-line therapy at Sylvester; 90 mg/m^2 doxorubicin plus 900 mg/m^2 of dacarbazine; might use 75 and 750 or 60 and 600 in older, frail patients or those with comorbidities; gemcitabine plus docetaxel second-line therapy for metastatic tumors; trabectedin or pazopanib third or fourth line
- **Uterine leiomyosarcoma:** more sensitive to ifosfamide than non-uterine; doxorubicin plus ifosfamide front-line for newly diagnosed metastatic uterine leiomyosarcoma; reserve gemcitabine/docetaxel for second line; pazopanib, trabectedin, and temozolomide next-line therapies
- **Specific sarcomas:**
  - **Synovial sarcoma:** doxorubicin plus ifosfamide front-line therapy for metastatic disease; resistant to gemcitabine/docetaxel combination; do not use as second line
  - **Myxoid/round cell liposarcoma:** resistant to gemcitabine plus docetaxel; do not use regimen
  - **Malignant peripheral nerve sheath tumor:** sensitive to doxorubicin; very sensitive to ifosfamide; some approaches include using high-dose ifosfamide in front-line therapy
  - **Small cell sarcomas:** initial therapy in adults for rhabdomyosarcoma, Ewing sarcoma, and desmoplastic small round cell tumor is combination of vincristine plus doxorubicin plus ifosfamide; high-dose ifosfamide second line; temozolomide plus irinotecan third line; pazopanib fourth line
  - **Solitary fibrous tumor:** relatively resistant; some sensitivity to doxorubicin and ifosfamide; temozolomide plus bevacizumab front line therapy for metastatic solitary fibrous tumor; pazopanib or sunitinib second line; gemcitabine/docetaxel or doxorubicin-based combinations in third and fourth line
  - **ASPS (alveolar soft part sarcoma):** resistant to all chemotherapies; sensitive to multi-targeted kinase inhibitors inhibiting VEGF receptor; also found to respond to immunotherapy checkpoint inhibitors

such as pembrolizumab; clinical trial performed at Sylvester Comprehensive Cancer Center and published in 2019 found axitinib plus pembrolizumab resulted in partial response rate of >50% with some responses durable >2 years of therapy; combination of multi-targeted kinase inhibitor targeting VEGF receptor in combination with checkpoint inhibitor provides highest response rate

Adjuvant chemotherapy: Pervaiz et al. meta-analysis published in *Cancer* pooled multiple randomized clinical trials comparing chemotherapy to no chemotherapy in patients with resected soft tissue sarcoma; demonstrated combination of doxorubicin plus ifosfamide superior to placebo or no chemotherapy; all patients in study had surgery and/or radiation for primary intermediate or high-grade soft tissue sarcoma; patients randomized to chemotherapy or no chemotherapy; patients randomized to doxorubicin plus ifosfamide had five percent absolute risk reduction in local recurrence, 10% absolute risk reduction in distant recurrence, and 11% decrease in probability of death; patients randomized to receive chemotherapy after resection of primary soft tissue sarcoma had probability of survival increased by 11%; important to mention to patients when discussing potential risks and benefits of adding chemotherapy to surgery and radiation for primary soft tissue sarcoma

Conclusion: soft tissue sarcoma rare type of cancer; should be diagnosed by expert pathologist experienced in spectrum of disease; National Comprehensive Cancer Network (NCCN) and other guidelines recommend evaluation at sarcoma center; >50 different commonly seen sarcoma types; increasing therapeutic options; selected based on data and sarcoma center experience; front-line surgery in metastatic setting determined at multidisciplinary sarcoma conference

Suggested Reading

Larrier NA, et al: Radiation therapy for soft tissue sarcoma: indications and controversies for neoadjuvant therapy, adjuvant therapy, intraoperative radiation therapy, and brachytherapy. *Surg Oncol Clin N Am.* 2016 Oct;25(4):841-60; **Ratan R, et al:** Chemotherapy for soft tissue sarcoma. *Cancer.* 2016 Oct;122(19):2952-60; **Tawbi HA, et al:** Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol.* 2017 Nov;18(11):1493-501.

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Neuroendocrine Carcinomas

Daniel Halperin, MD, *Assistant Professor of Gastrointestinal Medical Oncology, University of Texas, MD Anderson Cancer Center, Houston, TX*

Objectives: establish common framework for understanding and classifying neuroendocrine tumors; understand the importance of grading, staging, primary site, and functional status and how these affect patient management and natural history of disease; locoregional therapies; systemic therapy options (bulk of focus for medical oncologists); distinguish between pancreatic and extra-pancreatic neuroendocrine tumors and how this affects management; symptomatic control and special scenarios; examples of particular neuroendocrine tumor types

Framework and classification: neuroendocrine tumors arise from epithelial endocrine cells; distributed throughout digestive tract and pancreas; neuroendocrine tumors used to be carcinoid tumors; in 1890s, the German pathologist Oberndorfer opened an appendix and saw tumor that looked like a carcinoma but not quite, and he called it carcinoid; name stuck but not part of modern nomenclature; tumors characterized by secretory granules that take up many metal salts; granules can be secreted into circulation and cause dramatic functional syndromes

Three groups: 1) poorly differentiated, high-grade neuroendocrine carcinomas are small cell cancers that are beyond the scope of discussion and best dealt with by lung cancer oncologists; 2) well-differentiated neuroendocrine tumors (grade 1, 2 or 3) arising in the pancreas; and 3) well-differentiated neuroendocrine tumors (grade 1, 2 or 3) arising elsewhere

Grading: best reference is 2017 WHO (World Health Organization) Endocrine Handbook, which divides pancreatic neuroendocrine neoplasms into 4 groups; important to understand differences in new classification

Old system of numerical grading (1, 2, and 3): used product of the fraction of cells dividing under the microscope; most accurate way to use this method is with the Ki-67 marker; tumors with Ki-67 less than 3% are grade 1; Ki-67 of 3% to 20% are grade 2; Ki-67 greater than 20% are grade 3

New System: in new system, even tumors that are grade 3 with a division fraction over 20% may be classified based on histologic appearance as well-differentiated; these well-differentiated grade 3 neuroendocrine tumors can be grouped with well-differentiated grade 1 and 2 neuroendocrine tumors for management purposes; instead of saying every cancer with Ki-67 over 20% is poorly differentiated high-grade neuroendocrine carcinoma, we now group well-differentiated neuroendocrine tumors into grades 1, 2, and 3 regardless of Ki-67

Why difference in grading system is important: James Yao's "One Hundred Years After Carcinoid" manuscript in the *Journal of Clinical Oncology* (JCO) in 2008 showed that grade and differentiation, along with stage and primary site, are the key prognostic variables for patients; patients with poorly differentiated grade 3 neuroendocrine carcinomas have a very aggressive malignant course; even patients with localized disease have a steep decline in survival over the first couple of years after diagnosis, with a small proportion (less than 40%) being cured, even with localized poorly differentiated grade 3 neuroendocrine carcinoma; in contrast, patients with well-differentiated grade 1-2 neuroendocrine tumors have a much more indolent natural history, even with metastatic disease (about 20% are long-term survivors [1 to 3 decades]); more recently, data has shown that primary site is an independent predictor of outcome; patients with well-differentiated metastatic neuroendocrine tumors have a median overall survival that varies dramatically based on site of origin; most dramatic comparison would be a patient with a metastatic well-differentiated midgut or small bowel neuroendocrine tumor (median overall survival, 103 months) compared with a patient with metastatic well-differentiated grade 1-2 colon neuroendocrine tumor (median overall survival, 14 months), which is worse than expected for metastatic colon adenocarcinoma; primary site is powerful independent prognostic variable; concept that these tumors are barely cancers is not applicable or correct

Epidemiology: incidence of neuroendocrine tumors rising over time, likely due to improved imaging sensitivity and improved uptake of colonoscopies; single most common primary site is lung (1.5 to 1.6 new cases per 100,000 population per year); approximately three-quarters of neuroendocrine tumors arise in GI tract (3 most common sites are small bowel, rectum, and pancreas); commonly said that gastrointestinal tract is most common primary site for neuroendocrine tumors, but it is the lung; total incidence is at least 7 new cases per 100,000 population per year in United States according to Surveillance, Epidemiology, and End Results (SEER) data

Cancer biology: these cancers can be functional with hormone hypersecretion causing syndromic presentations

Carcinoid syndrome: most common syndrome; triad of wheezing, flushing, and diarrhea; all 3 symptoms almost never present in same patient at same time; eventual right-sided fibrotic valvular heart failure; diarrhea and right-sided heart valvular failure mediated primarily by serotonin; association between wheezing and flushing and serotonin less clear; classic exacerbating factors

are the 5 "E"s, but really just 3 things: 1) ethanol, patients commonly flush after a drink of alcohol; 2) eating specific foods, namely things on the monoamine oxidase inhibitor (MAOI) foods list; and 3) epinephrine, which can be exacerbated by emotion or exercise; most fulminant presentation is carcinoid crisis, which is commonly encountered in operating room when skin incision or other physiologic stress will cause tumor degranulation and serotonin released into circulation to cause hypotension, bronchospasm, and hemodynamic compromise; carcinoid syndrome related to prognostic variables of grade, stage, and primary site; most common with well-differentiated, midgut or small bowel tumors, and with distant disease, particularly liver metastases (serotonin secretion into post-hepatic circulation); large-scale epidemiologic analysis shows that not all 3 necessary for carcinoid syndrome; patients with localized or regional disease outside small bowel can still have carcinoid syndrome, but it is much less likely; impact of carcinoid syndrome is profound; patients have significantly impaired quality of life and shorter life, even when controlling for grade, stage, and primary site; how much of the increased mortality is due to unmeasured co-variates (liver tumor volume) is unknown

- Pancreatic neuroendocrine tumors: produce many hormone hypersecretory syndromes related to pancreatic hormones
  - Gastrinoma: most common; Zollinger-Ellison syndrome; reflux, refractory multifocal peptic ulcers, diarrhea
  - Glucagonoma: causes 3D syndrome of diabetes, dementia, and dermatitis; patients have DVTs
  - Insulinomas: classic Whipple's Triad of neuroglycopenic symptoms associated with low blood sugar that resolves with eating; patients gain weight over time because of chronic exposure to storage hormone
  - VIPoma: from vasoactive intestinal peptide; many liters of diarrhea daily; previously referred to as pancreatic cholera because pancreatic secretion of VIP causes cholera-level diarrhea and fluid loss from gut
  - Other: less common hormone hypersecretory states also exist with pancreatic neuroendocrine tumors
  - Non-functional pancreatic neuroendocrine tumors: 70% to 95%; pancreatic neuroendocrine tumors classified as functional only when clinical syndrome present; elevated laboratory marker without associated clinical syndrome not considered an indicator of functional pancreatic neuroendocrine tumor; some tumors even have granules, degranulate, and secrete products into the blood that are not fully functional hormones; elevated laboratory biomarkers may be present but products are non-functional; diagnosis of functional pancreatic neuroendocrine tumor requires clinical syndrome

Management: for patients with localized and limited metastatic disease, surgical removal advocated when feasible; for patients with advanced disease, priorities are 1) control hormone secretion; 2) control tumor growth; and 3) minimize toxicity; principles very easy to agree with generally, but several of these terms can be variably defined; what qualifies as localized disease or limited metastatic disease varies in clinical practice

- Surgery for localized disease: curative intent, but data for metastasectomy for neuroendocrine tumors is a bit different; unlike other glandular cancers where a resection might be considered curative for minority of patients, resections for patients with neuroendocrine tumors are generally not curative; recurrence rates in surgical series with long-term follow-up show a recurrence rate of 99%; retrospective series and meta-analyses suggest that, compared with locoregional modalities, surgical intervention with complete resection is associated with longer overall survival; in these series, it is impossible to separate out the effect of selection bias from intervention effect, but evidence is strong enough that, in cases where surgery can be safely attempted, it is advocated, regardless of primary site
- Liver-directed therapy: tumors in liver are preferentially fed blood by the hepatic artery, whereas liver parenchyma receives most of its blood from portal vein; leverage this dichotomy to deliver treatments selectively to liver tumors; because liver is by far the most common site of metastatic disease with neuroendocrine tumors, these treatments, while not necessarily driven by randomized, controlled clinical trials, can be employed
- Other therapies: several retrospective series with various technologies (bland embolization, chemoembolization, selective internal radiotherapy, or radioembolization, such as with yttrium-90); if patients well-selected for intervention, they tend to do well; some technical differences in patient selection and adverse event profile, but no randomized comparison of modalities; selection depends on technical expertise and provider preference

Systemic therapy for pancreatic neuroendocrine tumors: some therapies that are FDA-approved and part of guidelines are not options for patients with other types of neuroendocrine tumors, because early phase data were not promising for sites outside pancreas; later randomized studies restricted to patients with pancreatic neuroendocrine tumors

- Alkylating chemotherapy: originally with streptozotocin, developed in 1970s at NCI (National Cancer Institute) as a relatively islet-specific alkylator developed in single center NCI studies and a series of randomized clinical trials in ECOG (Eastern Cooperative Oncology Group), led by Charles Mortell at Mayo; *New England Journal* publication in 1992 with relatively small (100 patient) study with 3 arms: 1) doxorubicin with streptozotocin; 2) 5-FU (5-fluorouricil) with streptozotocin; and 3) chlorozotocin as the control; doxorubicin and streptozotocin arm had better overall survival and progression-free survival with 30% to 40% response rate reported (at a time before consistent CT scans; based on physical exam and biochemical markers); subsequent studies using CT showed lower rates of objective radiographic response; regimen included 5 sequential days of relatively emetogenic streptozotocin and cardiotoxic doxorubicin; more recently, therapy largely replaced with oral capecitabine and temozolomide (cap-tem), which was also evaluated in ECOG in randomized study by Pamela Kunz from Stanford who presented at ASCO (American Society of Clinical Oncology) in 2018; cap-tem associated with confirmed objective response rates of 30% in both arms and clear demonstration of superior progression-free survival for combination arm (40% reduction in risk of progression or death); toxicity profile of regimen is significantly better than IV chemotherapy, with some myelotoxicity and limited gastrointestinal toxicity, but no cardiotoxicity;

in clinical practice, this regimen has largely replaced streptozotocin-based chemotherapy

VEGF (vascular endothelial growth factor) inhibition (sunitinib): relatively specific to pancreatic neuroendocrine tumors; oral VEGF inhibitor FDA-approved based on randomized trial (*New England Journal of Medicine*, 2011) that was conducted in patients with progressive, advanced pancreatic neuroendocrine tumors; comparison with placebo showed a 60% reduction in risk of progression or death; prior phase 2 studies of sunitinib showed no response in patients with tumors outside pancreas; toxicity includes diarrhea and GI distress, hair color changes, hypertension, and some palmar-plantar erythrodysesthesia

Therapies for pancreatic neuroendocrine tumors with broader indications: somatostatin analog (lanreotide)—evaluated in CLARINET study (*New England Journal of Medicine*, 2014); patients had proven somatostatin avid gastroenteropancreatic neuroendocrine tumors with a relatively low Ki-67 (less than 10%); compared with placebo; lanreotide reduced risk of progression or death by 50%; important to note that octreotide was not studied in patients with pancreatic neuroendocrine tumors; population studied with lanreotide is a little bit broader; biochemically, lanreotide and octreotide extremely similar (just a couple of amino acids different); toxicities are primary class effects and include diarrhea (specifically, steatorrhea from pancreatic suppression), cholelithiasis, and hyperglycemia; everolimus—evaluated in randomized RADIANT-3 study (*New England Journal of Medicine*, 2011) back-to-back with sunitinib study; oral mTOR (mechanistic target of rapamycin) inhibitor compared with placebo in patients with advanced progressive pancreatic neuroendocrine tumors (very similar but not identical population to sunitinib study); everolimus reduced rate of progression or death by 65% when compared with placebo; led to its FDA approval for patients with pancreatic neuroendocrine tumors; toxicities include stomatitis (can prophylax with dexamethasone mouthwash), cape-like rash, pneumonitis, some lymphopenia (with occasional related infections), and hyperglycemia

Systemic therapy for extra-pancreatic neuroendocrine tumors:

Octreotide: oldest treatment; evaluated in PROMID study (named for population of patients with midgut neuroendocrine tumors); somatostatin analog that binds somatostatin receptors (SSTRs) 2 and 5 (same target as lanreotide); PROMID trial was a relatively small investigator-initiated study (*Journal of Clinical Oncology* [JCO], 2009) and compared octreotide to placebo in treatment-naïve midgut neuroendocrine tumor patients; octreotide reduced rate of progression or death by 65%

Everolimus: also used for tumors outside pancreas; its development longer and led to slightly different labeling; first randomized trial was RADIANT-2 (launched before RADIANT-3 in patients with pancreatic neuroendocrine tumors); conducted as a study of octreotide with or without everolimus in patients with carcinoid syndrome; tumors had to be growing and progressive within 12 months prior to study entry; study showed no clear demonstrated benefit of everolimus in combination with octreotide in patients with progressive, functional neuroendocrine tumors arising outside the pancreas; however, given success in the pancreas, RADIANT-4 undertaken to compare everolimus with placebo in patients without carcinoid syndrome who had progressive disease in the prior 6 months; population selected to be slightly different from RADIANT-2 (patients did not have carcinoid syndrome and pace of progression a little faster); compared with placebo, everolimus reduced risk of progression or death by 50% to 60%; received FDA approval for patients with extra-pancreatic neuroendocrine tumors without carcinoid syndrome

Peptide receptor radionuclide therapy: most recent therapy, now standard of care; nuclear medicine therapy using a somatostatin analog (octreotate) with inert linker (DOTA) to deliver therapeutic radionuclide (lutetium-177); randomized trial NETTER-1 studied patients with midgut neuroendocrine tumors who had progressed on standard-dose octreotide (30 mg/mo); patients randomized to either high-dose octreotide (60 mg/mo) or to lutetium-177 dotatate; the latter treatment found to reduce the rate of progression or death by 79%; subsequent FDA approval; whereas this study (*New England Journal of Medicine*, 2017) was the first and only randomized, controlled trial with this peptide-receptor radionuclide agent, there is long history of use in Europe in several settings that are far broader than those in the randomized trial; presumably because some of these data are also available and there is fairly extensive experience in patients with non-midgut neuroendocrine tumors, the FDA label reads gastroenteropancreatic neuroendocrine tumors that are progressing; label is a bit broader than randomized data; toxicities are a little different and timing can be different than other routinely used therapies in medical oncology; toxicities in clinical trial included nausea and vomiting (tightly associated with reno-protective amino acid infusion), fatigue (40%), and cytopenias; cytopenias have different time course than those seen with myelotoxic chemotherapy; instead of nadiring at 1 week or so, patients tend to have their counts nadir around 5 or 6 weeks after therapy, which is why this treatment is dosed every 2 to 3 months; for those patients who have significant cytopenias, they can be prolonged and lead to dose delays; 2% or 3% of patients in long-term series develop myelodysplasia or leukemia, but a clear association between many possible risk factors and myelodysplasia has not been found; consider difference in toxicity profile when selecting patients for various therapies

Symptomatic control: oldest intervention for patient whose tumors produced too much hormone was to reduce the size of the tumor; in 1950s, surgeons did R2/debulking (gross debulking leaving residual tumor) to decrease tumor and hormone burden; series suggest that this accomplished goal and patients felt better with lower urinary 5-HIAA (5- hydroxyindoleacetic acid)

Development of minimally invasive techniques and interventional radiology in 1980s; series showed that injection of gel foam and coils into hepatic artery reduced 5-HIAA and patients felt better; there have been comparisons between the 2 techniques, but need to individualize treatment selection based on risk-benefit (patient and their overall clinical scenario)

Medical management: somatostatin analogs available for many years now; initially only available as an IV continuous infusion because of short half-life, but pharmacologic developments in 1970s and 1980s led to availability of intermediate acting, 3 times daily, subcutaneous octreotide, and eventually long-acting, repeatable injections like octreotide LAR and lanreotide depot; these agents (initially octreotide) have been shown to reduce symptom burden and 5-HIAA, which is associated with reduced number of bowel movements in patients with diarrhea; led to FDA indication for octreotide for carcinoid syndrome and VIPoma diarrhea; lanreotide (developed more recently) demonstrated consistent reduction in 5-HIAA and need for rescue octreotide subcutaneous injections (ELECT trial); both drugs indicated for control of carcinoid syndrome diarrhea

Other hormone hypersecretory syndromes in pancreatic neuroendocrine tumors: many unusual syndromes (VIPomas and glucagonomas) can be managed relatively easily with somatostatin analog; gastrinomas can be controlled with somatostatin analog, but proton pump inhibitors are mainstay of therapy if refractory peptic ulcer disease and diarrhea present; gastrinomas were test-case for proton pump inhibitors when first developed; doses quite high (80 mg, 3 times per day) for proton pump inhibitor (omeprazole); often quite difficult to wean; somatostatin analogs can be dangerous in patients with insulinomas; typical somatostatin analogs used for neuroendocrine tumors target somatostatin receptors 2 and 5; depending on balance of somatostatin receptors 1 and 2 on alpha and beta cells, somatostatin analog may block glucagon secretion in patients with insulinoma and cause hypoglycemia; can be catastrophic in patient who already has severe hypoglycemia (sugar in the 20s, then dropped to 5); therefore, do not use in unmonitored outpatient setting; typically begin with frequent small meals, dextrose infusions, and occasionally diazoxide; some reports in *New England Journal of Medicine* that everolimus can control sugar because hyperglycemia is commonly associated with that drug; telotristat can be used for patients with carcinoid syndrome; telotristat is a tryptophan hydroxylase inhibitor that blocks serotonin synthesis in patients with neuroendocrine tumors and carcinoid syndrome; telotristat does not cross blood-brain barrier, which is important because serotonin is really important in the central nervous system; randomized trial was TELESTAR (JCO, 2017) in a very specific patient population with refractory carcinoid syndrome who were receiving standard dose somatostatin analog but had more than 4 bowel movements per day; for these patients, telotristat compared with placebo and showed a.8 bowel movement per day improvement over 12 weeks with associated decreases in urinary 5-HIAA; FDA-approved for patients with refractory carcinoid syndrome with continuing somatostatin analog therapy

Treatment of well-differentiated neuroendocrine tumors: think about available therapies as ladder; as you climb ladder, you get higher response rates and more aggressive therapy, but more risk and higher toxicity; at very bottom of ladder, least toxic thing to offer select patients is observation, which has the side effect of anxiety but is a legitimate choice; discuss with patient whether they prefer anxiety of observation without active treatment or small but modest adverse event rate of active medical therapy; response rate to observation is 0, but can be reasonable for patients with very low-volume indolent disease; a little higher up, a very well-tolerated, treatment with low adverse effects would be somatostatin analogs (octreotide and lanreotide), which cause tumor shrinkage 2% of time; not for debulking, but be used for syndrome control or tumor control (significant reductions in risk of progression or death); next up are targeted therapies like everolimus or, for patients with pancreatic neuroendocrine tumors, sunitinib; response rates less than 10%, but reduce risk of progression or death in patients with progressive disease in randomized controlled trials (highly effective at controlling tumor growth); higher up the ladder, consider peptide receptor radionuclide therapy and, for patients with pancreatic neuroendocrine tumors, chemotherapy (streptozotocin or temozolomide); these have different side effect profiles and would be considered higher risk than targeted therapies; depending on pace of disease and clinical scenario, select patients carefully

Systematic approach: two main questions to consider — 1) is this high-volume or low-volume disease? opinions about whether something is high-volume or low-volume may vary, but this is a reasonable first question as a general way of dividing disease for patients with well-differentiated neuroendocrine tumors; after deciding whether high-volume or low-volume disease, ask 2) is it growing or not? is it progressive or indolent? for patients with low-volume indolent disease, have a conversation about initiating a somatostatin analog versus observation; either choice valid; in control arms of somatostatin analog randomized clinical trials, patients given placebo had relatively long progression-free survival (CLARINET, 16 months for placebo); when patients are well-selected and not at risk from their disease, it is reasonable; for patients with lower volume, but progressive disease, consider sunitinib for pancreatic neuroendocrine tumors and everolimus for everyone; for patients with high-volume disease, think about liver-directed therapies; for patients with pancreatic neuroendocrine tumors, cytotoxic chemotherapy; randomized data in the progressive setting with peptide receptor radionuclide therapy for those with midgut neuroendocrine tumors (label broader for all of GI and pancreas)

Small luminal neuroendocrine tumors:

Appendiceal neuroendocrine tumors: when to refer patients with appendiceal neuroendocrine tumors to surgical oncologists? old analysis by Charles Mortell (*New England Journal of Medicine*, 1987) examined 150 patients with appendiceal neuroendocrine tumors; for 100 patients with tumors smaller than 1 cm, no metastasis observed; for tumors larger than 2 cm, many metastasized; recommendation is that appendiceal tumors larger than 2 cm be resected with right hemicolectomy; simple appendectomy is considered sufficient if tumors are <2 cm, though in the 1-2 cm "gray zone," more aggressive treatment may be considered depending on patient's individual situation

Rectal neuroendocrine tumors: fairly common; in retrospective series, tumors greater than 2 cm often metastasize (up to three-quarters of the time in some series), whereas tumors smaller than 1 cm almost never

metastasize; tumors between 1 and 2 cm are a gray zone; for tumors larger than 2 cm, consider formal resection; for tumors smaller than 1 cm, local intervention

Summary: start with framework; consider grade, stage, primary site, and functional status because each is an independent prognostic factor and helps determine which therapy to employ; grading and grouping patients based on well-differentiated grade 1, 2, or 3 neuroendocrine tumors that can either arise in the pancreas or elsewhere; third group of patients (outside of the scope of discussion) who have high-grade poorly differentiated grade 3 neuroendocrine carcinomas; distinction between high-grade poorly differentiated carcinoma and well-differentiated tumor is crucial in modern nomenclature; locoregional and systemic therapies; therapies uniquely for pancreatic neuroendocrine tumors — alkylating chemotherapy (temozolomide or streptozotocin) and targeted therapy (sunitinib); broader therapies like everolimus, somatostatin analogs, and peptide receptor radionuclide therapy (PRRT); slight difference between randomized level 1 evidence for PRRT and label (broader); symptomatic control, including medical and locoregional interventions to reduce hormone burden and symptoms; special case of patients with insulinomas where somatostatin analogs can be dangerous due to hypoglycemia; small luminal neuroendocrine tumors and special situations, remembering that for tumors over 2 cm we tend to be more aggressive, and for tumors less than 1 cm, we tend to be more conservative

Suggested Reading

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Oncologic Emergencies

Saadia Faiz, MD, *Professor, Department of Pulmonary Medicine, Division of Internal Medicine, University of Texas MD Anderson Cancer Center, Houston, TX*

I. Thromboembolic disease: venous thromboembolism includes deep vein thrombosis (DVT) and pulmonary embolism (PE); common complication in cancer patients; thrombosis regulated by multi-step coagulation cascade involving multiple factors; triggered by Virchow triad — plasma hypercoagulability, changes to blood flow, and endothelial cell dysfunction; two large, population-based, case controlled studies to identify risk factors for venous thrombosis found 4-fold to 7-fold increase in overall risk in cancer patients; highest in non-Hodgkin lymphoma, lung cancer, and GI cancer; estimated incidence 15% per year for venous thrombosis in cancer patients; studies found risk elevated during initial months after diagnosis and in those with metastatic disease; other cancer-associated risk factors in patients include advanced age, comorbidities, immobilization or hospitalization, previous venous thromboembolic event, and hereditary thrombophilia; treatment-related risk factors include chemotherapy, specifically anti-angiogenesis agents such as thalidomide, lenalidomide, and bevacizumab, hormonal therapy, red blood cell transfusion, erythropoiesis-stimulating agents, surgery, radiotherapy, presence of central venous catheter

Mechanism: thrombi form in deep veins in calf and propagate to proximal veins; thrombi above popliteal veins more likely to embolize; ≈80% of patients presenting with PE have evidence of DVT in legs; if absent, likely entire thrombus already detached and embolized; travels through right side of heart after embolization and goes to pulmonary arteries; emboli may break down and lodge into peripheral pulmonary arteries; can remain at main pulmonary artery bifurcation if very large, giving rise to saddle embolism, massive PE resulting in severe hemodynamic compromise, collapse, and severe dyspnea; pulmonary vascular resistance increases due to physical obstruction of vascular bed in patients with very large pulmonary emboli; hypoxic vasoconstriction ensues within pulmonary arterial system; increased pulmonary vascular resistance in turn impedes right ventricular outflow and causes right ventricular dilatation and flattening of intraventricular septum; diminished flow from right ventricle and right ventricle dilatation cause reduction in left ventricular preload, thereby compromising cardiac output; right ventricle fails when unable to accomplish this; results in hemodynamic instabilities such as hypotension

Resolution: in absence of massive PE, PE typically resolves by fibrinolysis or by organization and recanalization or both; occurs most substantially in first week; continues for up to 4-8 weeks; anticoagulation helps to prevent new clots from forming; body will dissolve clot itself; those with elevated pulmonary artery pressures will typically stabilize after treatment within 6 weeks

Presentation: DVT presents with pain, swelling, redness, and warmth in affected extremity or area; physical exam can demonstrate palpable or tender cord or engorged superficial veins; acute painful and cyanotic limb indicates total venous occlusion; emergent; pulmonary emboli can be asymptomatic; large blood clot sometimes seen incidentally on screening computed tomography (CT); many patients can have symptoms, including dyspnea, pleurisy, cough with or without hemoptysis, wheezing, syncope, or presyncope; physical exam can demonstrate tachypnea, tachycardia, rales, or pleural rub; signs of right heart failure seen with severe or massive PE include jugular venous distention, hypotension, hyperdynamic precordium, and loud P2

Workup: EKG findings typically include sinus tachycardia or nonspecific ST-T-wave changes; classic finding of S1, Q3, T3; S waves in lead I, Q waves in lead III, and inverted T waves in lead III; supports right-sided heart strain; laboratory findings can be nonspecific; may include leukocytosis; arterial blood gas could be normal or show hypoxemia or respiratory alkalosis with hypocapnia mainly due to tachypnea; questionable utility of D-dimer in patients with cancer, as D-dimer may be elevated due to cancer itself; cardiac biomarkers used prognostically most valuable laboratory findings; B-type natriuretic peptide (BNP), N-terminal pro–B-type natriuretic peptide (NT-proBNP), and troponin I or troponin T

Imaging: needed to confirm diagnosis; negative chest x-ray with hypoxia highly suggestive of vascular event; Westermark sign demonstration of sharp cutoff of pulmonary vessels with distal hypoperfusion in segmental distribution within lung; relative oligemia, or Hampton hump, can represent lung infarction; shallow hump-shaped opacity in lung periphery with base against pleural surface and hump towards hilum; also described as wedge-shaped opacity; CT angiogram most common confirmatory test; readily available in most centers; very accurate; can provide alternate diagnoses, such as something in lung parenchyma or pleural space; renal insufficiency can limit use due to inability to administer contrast; ventilation/perfusion scanning likely diagnostic in absence of cardiopulmonary disease; normal perfusion lung scan essentially excludes acute pulmonary embolism; can perform further testing with high suspicion; high probability of PE with high clinical suspicion usually confirms diagnosis; further confirmation may be needed in those with intermediate or nondiagnostic studies; other adjunctive tests include lower extremity Dopplers, especially in patients with renal insufficiency or in ICU; presence of blood clot commits to therapy with

anticoagulation; would not change management with PE; echocardiogram can show emboli in transit on right-sided chambers move into lungs; in conjunction with cardiac biomarkers, echocardiogram can stratify patients into low, intermediate, or high risk; other findings that may support hemodynamic instability on echocardiogram include enlarged right ventricle, dilated right ventricle, flattened intraventricular septum, distended inferior vena cava (IVC) with diminished inspiratory collapsibility, and elevated right-sided pressures

Evaluation: perform risk stratification after confirming PE; American College of Chest Physicians, American Heart Association, and European Society of Cardiology have guidelines detailing treatment and risk stratification for PE; break PE down into three main categories; low-risk PE — mortality of 1.1%; intermediate risk (submassive) PE — mortality of 2.8%–8.1%; high risk (massive) PE — mortality of 32%–58%

Low-risk PE: low mortality; patients hemodynamically stable; no imaging or biomarker signs of right ventricular strain; patients will receive systemic anticoagulation except with contraindications; can otherwise receive IVC filter

Massive PE: hemodynamically unstable, critically ill patients; should receive full-dose thrombolysis; may also require additional intervention, such as surgical embolectomy, and supportive care, including intubation, inotropic and vasopressor support, inhaled nitric oxide, or other pulmonary vasodilators, and mechanical circulatory support devices such as VA-ECMO (venoarterial extracorporeal membrane oxygenation)

Intermediate risk or submassive PE: hemodynamically stable, but with imaging and/or biomarker evidence suggesting right ventricular strain; new literature indicates these patients should receive systemic anticoagulation

Thrombolytics: several studies evaluating thrombolytics in this population

Peto randomized multicenter trial (France): largest of these trials; compared thrombolytic therapy with tenecteplase plus heparin with placebo plus heparin in 1005 normotensive patients with acute PE and evidence of right ventricular dysfunction or intermediate-risk PE based on echocardiogram or CT scan; death or hemodynamic decompensation within 7 days primary endpoint; compared with heparin alone, thrombolysis resulted in reduction in primary endpoint of death or hemodynamic decompensation at 7 days following randomization; 6% *vs* 3%; subgroup analysis indicated differences in outcome affected largely by prevention of further decompensation; no difference in 7- or 30-day mortality; administration of thrombolytic agents associated with increased extracranial bleeding; 6% *vs* 1%; major bleeding 12% *vs* 2%; hemorrhagic stroke 2% *vs* 0.2%; benefits of therapy maintained but rates of extracranial bleeding high in pre-specified subgroup analysis of patients >75 years of age — 11% *vs* 0.6%; suggests risk/benefit may be more favorable in those age 75 or younger; long-term follow-up ≈3.5 years showed no difference in mortality and no difference in dyspnea, exercise capacity, right ventricular dysfunction, or chronic thromboembolic pulmonary hypertension

Other studies: half-dose thrombolytics and catheter-directed thrombolysis also evaluated; sample sizes of trials with both modalities limited; have inadequate power to estimate survival benefit; decide clinically on case-by-case basis; submassive PE may need catheter-directed thrombolysis or half-dose thrombolytics; guideline is thrombolysis should only be given for unstable or massive PE

PE response team: multidisciplinary team assembling once PE diagnosed; discusses whether PE intermediate low, intermediate, or high risk or massive; reviews studies, including bedside and pulmonary echocardiogram imaging to detect and diagnose PE, bleeding risk scores, and discusses any contraindication to lysis; team reviews case on conference call; studies have shown this approach improves outcomes and decreases bleeding risk; team usually consists of team attending and representatives of intensive care unit, cardiology, interventional radiology, and relevant subspecialties

Treatment: anticoagulant therapy indicated in almost all cases; removable IVC filter can be considered in those with contraindications

Management: anticoagulation in cancer patients challenging due to risk of recurrent thromboembolic events; bleeding complications higher among cancer patients; low-molecular-weight heparin longtime first-line treatment for cancer-associated thrombosis because it showed lower risk of recurrent thromboembolic events without associated increased risk of major bleeding complications compared to vitamin K antagonists; direct oral anticoagulants (DOACs) have been well established as treatment for venous thromboembolism in those without cancer; two recent trials have evaluated DOACs in patients with cancer; accepted modality; take patient preference, drug interactions, and bleeding risk assessments into account; consider age, previous bleeding episodes, anemia, thrombocytopenia, and renal function; gastrointestinal cancers bled in DOAC trials; use anticoagulation with DOACs in those with caution and close monitoring; trials also excluded those with urothelial tumors or those with nephrostomy tube

Pulmonary tumor emboli: tumor cells can cause occlusion of pulmonary arteries, arterioles, and capillaries; can present similarly to PE or present with right heart failure similarly to massive PE; pulmonary tumor emboli seen in 3%–26% of patients on autopsy series; most commonly seen in adenocarcinoma; other cancers such as sarcoma, leiomyosarcoma, testicular cancer, and choriocarcinoma have also been involved; symptoms can vary from subacute, including cough, dyspnea, or chest discomfort, to acute cor pulmonale; echocardiogram demonstrates elevated right-sided pressures; V/Q scan can show multiple subsegmental matched defects in salt-and-pepper pattern; right heart catheterization confirms pulmonary hypertension; treatment focuses on underlying cancer; supportive therapy with pulmonary vasodilator therapy has been described

II. Hypercalcemia: relatively common in cancer patients; occurs in 15%–30% of patients; associated with solid and hematologic malignancies; most commonly seen with lung cancer, multiple myeloma, and renal cell cancer, followed by breast and colorectal; patients typically have cancer diagnosis; four times more common in those with stage IV cancer; associated with poor prognosis

Mechanism of calcium homeostasis: calcium homeostasis tightly regulated by many hormones, including parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, calcitonin, serum calcium, and serum phosphorus; PTH produced

by parathyroid glands; increases serum calcium and decreases serum phosphorus via direct and indirect stimulation of osteoclasts; increases renal calcium absorption and decreases renal phosphorus absorption; PTH also stimulates conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D in kidneys thorough 1-alpha-hydroxylase; results in increased intestinal absorption of calcium and phosphate; calcitonin secreted by parafollicular C cells in response to hypercalcemia; lowers serum calcium by decreasing renal calcium and phosphorus reabsorption and decreasing bone resorption; calcitonin not significant in overall calcium homeostasis but important therapeutic option

Three mechanisms of cancer-related hypercalcemia:

1. **Humoral hypercalcemia of malignancy:** tumor secretion of parathyroid hormone-related protein (PTHrP); mechanism for ≈80% of patients; most commonly seen in squamous cell carcinoma; results in increased bone resorption and distal renal tubular calcium reabsorption
2. **Osteolytic metastasis with local release of cytokines including osteoclast-activating factors:** accounts for ≈20% of patients; usually associated with extensive bone metastases and skeletal tumor burden; common in metastatic breast cancer and multiple myeloma; increased bone resorption and release of calcium from bone
3. **Tumor production of 1,25-dihydroxyvitamin D:** rare mechanism seen in ≈1% of cases; most common cause in Hodgkin lymphoma; one-third of non-Hodgkin lymphoma; increased intestinal calcium absorption; increasing bone resorption may also contribute

Clinical presentation: mild or indolent hypercalcemia can be asymptomatic or associated with mild nonspecific symptoms such as fatigue and musculoskeletal pain; severe rapidly progressive hypercalcemia can be associated with significant volume depletion, acute renal insufficiency, and dramatic neurocognitive symptoms ranging from altered mentation to coma; degree of hypercalcemia categorized according to serum total calcium; mild hypercalcemia <12 mg/dl; usually no symptoms; moderate 12 to <14; severe hypercalcemia >14, typically symptomatic; symptoms depend on level of calcium and rate of change

Diagnostic testing: confirm hypercalcemia; check serum total calcium; correct for albumin if albumin abnormal; (4 minus serum albumin x 0.8 + serum calcium) gives total estimated calcium; can use ionized calcium; determine whether PTH or non-PTH mediated; measure 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D to evaluate for excess vitamin D production or ingestion; assess for renal function with creatinine; if unclear, can consider further workup for multiple myeloma or vitamin D toxicity

Treatment: goals are lowering serum calcium concentration and treating underlying disease; review medication list and eliminate any medications that could contribute to hypercalcemia, including any calcium-containing medications, vitamin D, thiazide diuretics, and lithium; severity of hypercalcemia and associated symptoms will dictate timing and type of therapy; first goal — promote renal calcium excretion; patients often volume depleted; first line of treatment usually hydration with crystalloid intravenous fluid; loop diuretic such as furosemide may help but should be reserved for patients with heart failure or those volume overloaded; second, reduce bone reabsorption

Bisphosphonates: first-line therapy and mainstay for long-term therapy; should be given within 48 hours of diagnosis; takes approximately 2-4 days to have effect; pamidronate and zoledronic acid acceptable therapies in US; can be associated with nephrotoxicity; use these with caution in those with renal insufficiency; repetitive use of bisphosphonates has been associated with risk of developing jaw osteonecrosis

Second-line agents: include calcitonin; can have rapid onset of action; effectiveness may decrease within 2-3 days due to tachyphylaxis; glucocorticoids have been used to treat hypercalcemia caused by excess extrarenal 1,25-dihydroxyvitamin D in multiple myeloma; steroids essentially inhibit osteoclastic bone reabsorption by decreasing tumor production of locally active cytokines and having direct tumor lytic effects

III. Superior vena cava syndrome: constellation of symptoms and signs resulting from superior vena cava obstruction; ≈15,000 cases per year in US; infectious causes such as syphilitic aortic aneurysm and tuberculosis most common causes until ≈50 yr ago; now rare; 90% of cases now due to malignant tumors; include non-small cell lung cancer, small cell lung cancer, lymphoma, and other metastatic tumors; non-malignant causes can include thrombosis due to implanted intravascular devices, aortic aneurysm, or fibrosing mediastinitis

Clinical presentation: results from increased venous pressure in upper body; causes edema of head, neck, and arms, venous collaterals on chest, neck, and abdomen; patients can have cough, hoarseness, dyspnea, stridor, and dysphagia due to functional compromise of larynx or pharynx; headache, confusion, and coma may signify cerebral edema; cerebral edema rare but potentially fatal; symptoms develop over 2 weeks in approximately one-third of patients and over longer periods in other cases; severity of symptoms depends on degree of narrowing and time of onset

Diagnostic testing: imaging foremost; CT chest with contrast will help to differentiate between vena cava thrombosis and extrinsic compression and define structures within mediastinum, lung parenchyma, and pleural space; tissue diagnosis required to confirm malignancy; peripheral lesion such as palpable supraclavicular lymph node ideal; pleural effusion can sometimes be drained with thoracentesis and sent for cytology; other diagnostic modalities include CT-guided biopsy, bronchoscopy with endobronchial ultrasound, or mediastinoscopy; past concern about bleeding and complications with bronchoscopy; recent data shows bronchoscopy can be safe; perhaps safer than mediastinoscopy

Treatment: goals are alleviation of symptoms, relief of obstruction, and treatment of cancer or thrombosis; immediate interventions can include supportive measures such as head-of-bed elevation and oxygen; loop diuretics commonly used; effectiveness unclear; glucocorticoid therapy commonly prescribed; effects have not been formally studied to suggest benefit; may reduce tumor burden in lymphoma and thymoma; intravascular stent may be considered in those with severe superior vena cava narrowing and to bypass obstruction; in those

with associated thrombus, localized thrombolysis or anticoagulation may also be considered; other treatments may include radiotherapy and systemic chemotherapy

IV. Spinal cord compression: oncologic emergency requiring prompt intervention to prevent permanent paraplegia and reduced quality of life; incidence about 3%–5% of known patients dying from cancer; metastatic spinal lesions can occur at any site; those most commonly associated with spinal cord compression include those with propensity to metastasize to bone such as prostate, lung, and breast; multiple myeloma and non-Hodgkin lymphoma most common among hematologic malignancies; can also be initial manifestation of cancer in ≈20% of patients; mechanistic invasion of tumor into epidural sac; compresses thecal sac; degree of thecal sac compression results in range of presentations from asymptomatic to paraplegia; symptoms can also vary in terms of disease in cervical, thoracic, or lumbar spine; vasogenic edema of white matter early mechanism of injury; vasogenic edema replaced by ischemic hypoxic neuroma injury and onset of cytotoxic edema in later stages

Clinical presentation: pain usually first and most common clinical symptom; present in 80%–95% of patients; typically precedes any neurologic symptoms; patients typically have pain median of 8 weeks or longer prior to diagnosis of spinal cord compression; motor defects occur in 60%–85%; many patients have weakness at time of diagnosis; two-thirds of patients non-ambulatory when diagnosed; pre-treatment neurologic status most important predictor of function after treatment; sensory findings less common but detectable in 40%–90% of patients; patients less aware of sensory deficits than weakness; can include pattern of ascending numbness or paresthesias; area of spinal cord compression not evenly distributed throughout spine; 60%–80% occur in thoracic spine; 15%–30% in lumbosacral spine; <10% involve cervical spine; up to 50% have involvement of more than one area of spine; additional symptoms can also include bowel and bladder dysfunction, ataxia, and cauda equina syndrome

Evaluation: suspected spinal cord compression must be confirmed by imaging to solidify diagnosis and make informed decisions about surgery, radiotherapy, chemotherapy, and other palliative measures; CT and magnetic resonance imaging (MRI) two most useful diagnostic and management tools; CT provides opportunity to diagnose spinal cord compression and to find paraspinal masses; also crucial for planning of management, especially for implantation and instrumentation needed as part of surgical procedures; can also be used to generate dosage plan for radiotherapy; MRI imaging method of choice; management decisions changed by MRI in >40% of patients; noninvasive; has high soft tissue resolution and can image several planes and also allow for reconstruction of images; 95% overall diagnostic accuracy for spinal cord compression; can also distinguish between benign and metastatic causes of vertebral body collapse; imaging of entire spine with or without contrast recommended but may not always be practical

Treatment: goals are preservation of function and mobility, pain relief, local tumor control, and spine stability; patients present in advanced stage; intervention mostly palliative; pharmacotherapy, including steroids and pain control, surgery, radiotherapy, or combination of all three may be used; initially steroids used anecdotally to reduce edema, inhibit inflammatory responses, stabilize vascular membranes, and delay onset of neurological deficit; in randomized comparison of patients assigned radiotherapy with and without corticosteroids, patients assigned dexamethasone had significantly better ambulatory outcomes; consensus to use steroids but not on dosage; dosages of dexamethasone range from 10-100 mg

V. Tumor lysis syndrome: most common disease-related emergency encountered by physicians caring for children or adults with hematologic cancers; most often occurs after initiation of cytotoxic therapy in patients with high-grade lymphoma, particularly Burkitt subtype, and acute lymphoblastic leukemia; can occur spontaneously and with other tumor types; not limited to patients receiving traditional chemotherapy; also occurs in patients receiving steroids, hormonal therapy, targeted therapy, or radiation therapy; patients dehydrated and those with existing kidney dysfunction at higher risk of developing tumor lysis syndrome

Mechanism: tumor lysis syndrome occurs when tumor cells release contents into bloodstream spontaneously or in response to therapy; leads to characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia; electrolyte and metabolic disturbances can progress to clinically toxic effects, including renal insufficiency, cardiac arrhythmia, seizures, and death due to multiorgan failure

Risk factors:

Intrinsic to tumor type: bulky tumor, extensive metastases; the larger the cancer mass or the higher the number of cells lysed with treatment, the higher the risk of clinical tumor lysis syndrome; [indications of high tumor mass may include] organ infiltration by cancer cells, manifested by hepatomegaly, splenomegaly, and nephromegaly; bone marrow involvement; high rate of proliferation of cancer cells; lactate dehydrogenase level can serve as surrogate for tumor proliferation; higher level results in greater risk of tumor lysis syndrome; greater than two-thirds of upper limit of normal; other risk factors intrinsic to tumor type include cancer cell sensitivity to anti-cancer therapy, leukocytosis with white blood cell >50,000, renal infiltration or outflow tract obstruction, specifically cancers that infiltrate or obstruct urine flow

Clinical features that could predispose to tumor lysis syndrome: include acidic urine or oliguria; uric acid has lower solubility in acidic urine; crystallizes more rapidly; patient presenting with acidic urine and hyperuricemia usually already has uric acid crystals or microcrystals in renal tubules; nephropathy before diagnosis of cancer, for example, preexisting nephropathy from hypertension, diabetes, gout, or other causes, or exposure to nephrotoxins such as vancomycin, aminoglycosides, or contrast agents for diagnostic imaging, all increase risk for developing tumor lysis syndrome; dehydration or volume depletion or inadequate hydration prior to treatment can also cause tumor lysis syndrome

Clinical symptoms: may include nausea with or without vomiting, lack of appetite, fatigue, dark urine, reduced urine output or flank pain, numbness, seizures, or hallucinations, muscle cramps and spasm, heart palpitations; kidney failure and death can also occur, especially if syndrome left untreated or undetected

Diagnosis: based on blood tests along with signs and symptoms; onset may be subtle with only a few abnormal laboratory values; can also present with frank kidney and organ failure

Management: maintaining adequate urine output to facilitate excretion of potassium, phosphorus, and uric acid; aggressive intravenous hydration cornerstone of therapy; should be instituted 24 hours prior to chemotherapy and titrated accordingly to maintain urine output of 80-100 ml/hour; fluid management affected by underlying conditions such as heart failure; alkalinization of urine with IV sodium bicarbonate or acetazolamide previously used to prevent formation of uric acid crystals; now thought to increase risk of calcium phosphate crystal deposition and no longer routinely recommended; normalization of serum uric acid level also important; traditional treatment of hyperuricemia included daily administration of allopurinol to decrease production of uric acid; allopurinol ineffective in patients with massive cell lysis; rasburicase converts uric acid readily into excreted allantoin; recommended for initial management of most pediatric and adult tumors at high risk for tumor lysis syndrome; serum uric acid levels often decrease until they become undetectable after rasburicase treatment

Prevention: tumor lysis syndrome can develop even with preventive measures; patients at high risk undergo blood work and clinical monitoring before and during therapy to ensure early diagnosis

Treatment: similar to preventative measures including intravenous fluids, allopurinol, and rasburicase; patients may require admission to ICU; blood work repeated frequently to assess electrolyte levels and kidney damage; heart rhythm and urine output closely monitored; careful correction of electrolyte imbalance required; some patients with severe kidney injury may require temporary hemodialysis or another form of renal replacement therapy

VI. Disseminated intravascular coagulation (DIC): characterized by systemic activation of coagulation; potentially leads to thrombotic obstruction of small and mid-sized vessels, thereby contributing to organ dysfunction; consumptive coagulopathy results in thrombocytopenia and low concentration of clotting factors and may cause profuse hemorrhagic complications; always secondary to underlying condition, which can range from severe infection to trauma to cancer; treating underlying condition cornerstone of therapy; anticoagulation needed to prevent clotting in some cases; in others, replacement of blood products may be needed to prevent bleeding; three different types of cancer-associated DIC; clinical presentations can vary from thrombosis to bleeding or subclinical

Laboratory measurements in cancer-related DIC: in setting of DIC, elevated leukocyte counts, decreased hemoglobin, and elevated D-dimer can be considered as potentially useful, although not very specific; in DIC, decreasing platelet counts or decrease from high normal to normal to low may be more relevant; poor prognostic indicator in malignancy-related thrombosis; abnormal coagulation screen usually considered indicative of DIC; not always true; prothrombin time (PT) and partial thromboplastin time (PTT) may not be prolonged in patients with cancer-associated DIC, especially with subclinical form, when coagulation factor levels only moderately decreased; serum fibrinogen levels rarely decreased in procoagulant type of DIC; in hyperfibrinolytic form, levels can decrease dramatically; most common hemostatic abnormality in one study; abrupt decrease in fibrinogen can be strong risk factor for bleeding in any type of DIC; threshold values have been suggested for replacing fibrinogen to prevent this complication; causes of prolonged PT and PTT other than DIC should be considered in patients with cancer, including liver impairment, vitamin K deficiency, dysfibrinogenemia, paraproteinemias, and acquired inhibitors of coagulation factors

Three types of cancer-related DIC:

1. **Procoagulant cancer-related DIC:** excess thrombin generated causes thrombosis in microvascular and macrovascular fields; seen in pancreatic cancer and other types of adenocarcinoma; thrombosis main clinical feature; different clinical presentations can include features of arterial ischemia; can manifest as uneven patchy discoloration of skin, symptoms of poor digital circulation, cerebrovascular manifestations, peripheral neuropathy, ischemic colitis, venous thrombosis or PE, and unusual form of noninfectious endocarditis; treat underlying cancer and provide anticoagulation with heparin
2. **Hyperfibrinolytic cancer-related DIC:** activation of fibrinolytic system dominates with manifestation of bleeding; patients present with widespread bruising, bleeding from mucosal surfaces, bleeding in central nervous system, lungs, gastrointestinal tract, and from sites of trauma; hemorrhage most common cause of induction mortality in acute promyelocytic leukemia; catastrophic bleeding can occur before diagnosis made in some cases

   Treatment: includes treating underlying cancer and supportive care with blood products; management of patients presenting with acute promyelocytic leukemia and DIC consists of supportive treatment with platelet transfusion aiming at platelet count of >30,000-50,000, fresh frozen plasma and fibrinogen concentrate; should be maintained throughout remission, induction, and disappearance of coagulopathy; invasive procedures such as biopsies or IV line placement should be avoided as much as possible; use of heparin not advocated in view of high risk of bleeding and lack of evidence from clinical studies; adjunctive treatment with fibrinolysis inhibitors beneficial in small clinical trials before introduction of all-trans-retinoic acid and arsenic trioxide in therapy of acute promyelocytic leukemia; coagulopathy quickly subsides with modern treatment modalities and inhibition of fibrinolysis usually not necessary; may even be harmful in view of prothrombotic features of retinoic acid
3. **Subclinical cancer-related DIC:** amounts of thrombin and plasmin generated do not cause obvious clinical manifestations; can have laboratory abnormalities; occurs with many types of solid cancers; laboratory abnormalities may include thrombocytopenia, low levels of fibrinogen, and microangiopathic hemolytic anemia; features may remain longstanding due to continuous thrombin generation as part of DIC; may worsen or improve depending on underlying malignancy; treat underlying cancer and use anticoagulation with heparin

Suggested Reading

Deshwal H, et al: A review of endovascular stenting for superior vena cava syndrome in fibrosing mediastinitis. *Vasc Med.* 2020 Apr;25(2):174-83; **Gupta R, et al:** Long-term mortality after massive, submassive, and low-risk pulmonary embolism. *Vasc Med.* 2020 Apr;25(2):141-9; **Le Trinh H, et al:** Successful chemotherapy management of disseminated intravascular coagulation presenting with metastatic clear cell renal carcinoma: a case report and review of the literature. *J Med Case Rep.* 2020 Apr 21;14(1):52.

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Paraneoplastic Syndromes

Andrew McKeon, MD, BCh, *Professor of Neurology, Associate Professor of Laboratory Medicine and Pathology, amd Co-Director, Neuroimmunology Laboratory, Mayo Clinic College of Medicine and Science, Rochester, MN*

Paraneoplastic neurological disorders: neurological disorders arising in setting of cancer but not caused by metastatic disease or effects of treatment such as chemotherapy, radiation, or surgery; multifarious and sometimes multifocal; can affect any level of nervous system

Pathogenesis: initiated in context of upregulated immune response against neural proteins expressed in regular or mutated form in tumor; immune system recognizes and starts to eliminate proteins; patients often have small and hard-to-detect cancers; immune response ramps up for other reasons; often because of patient autoimmune predisposition; starts attacking nervous system and same protein expressed in native state in nervous system; disorders distinct from paraneoplastic endocrinologic type disorders seen in patients with variety of different cancer types

Symptoms: patients can present with any symptom or sign; need to recognize classical presentations *vs* possible presentations of paraneoplastic disorders; evaluate for suspicious features in history; example limbic encephalitis — disturbance of cognitive function associated with changes in mood, personality, and memory; these patients often have seizures

History: review type of symptoms and timeframe over which they occur; paraneoplastic neurological disorders typically evolve subacutely over days to weeks; many patients present with neurological symptoms for different reasons, but most non-paraneoplastic neurologic disorders occur either less rapidly or, in contrast, hyperacutely, as with stroke; attempt to narrow down population of patients with paraneoplastic disorder or other non-paraneoplastic form of autoimmune disorder for further testing; fluctuating course important; patients may report spontaneous remissions from symptoms for some period; also possible patient may have been administered immunotherapy for other reasons; example — patient may be given corticosteroids for back pain and have subsequent improvement in some other neurological steroid-responsive symptom; inquire about autoimmune background; many patients with paraneoplastic neurological disorders have common autoimmune diseases such as thyroid autoimmunity, type 1 diabetes, pernicious anemia, or non-organ-specific autoimmune disorders such as lupus; no one factor absolutely predictive or specific for paraneoplastic neurological disorder; must consider whole picture

Typical syndromes:

Encephalitis: particularly limbic encephalitis; patients present with onset of memory change, personality change, seizures, and sometimes confusion; condition then rapidly evolves to demented state; contrasts with Alzheimer disease with slow evolution of cognitive symptoms over many years; some patients with encephalitic phenotype can present with more isolated symptoms such as new onset seizures; some patients present with rapidly progressive dementia; are also some non-limbic types of encephalitis; NMDA receptor encephalitis in young women with occult teratoma may present with psychiatric prodrome such as anxiety, mood change, and sometimes psychotic symptoms before development of encephalopathy; autoimmune GFAP (glial fibrillary acidic protein) astrocytopathy patients present with blurred vision, tremulousness, and neuropsychiatric symptoms

Visual disturbances: changes in night vision, increased floaters, or general rapid dimming of vision could represent paraneoplastic retinopathy; associated with recoverin antibody; patients with CRMP-5 autoimmunity present with vision loss, optic neuropathy, and retinopathy with inflammatory infiltrate in anterior chamber; both disorders marker of underlying small-cell carcinoma or occasionally other neuroendocrine cell lineage tumors outside of lungs

Ataxia: among more common manifestations; impairment of cerebellum, brainstem, or both, leading to incoordination of eye movements with nystagmus, dysarthria, or incoordination of limbs with appendicular ataxia and intention tremor; patients often have wide-based gait; appearance similar to severe inebriation

Myelopathy: patients with spinal cord dysfunction; present with variety of symptoms including ascending paralysis, numbness, paresthesias, lower extremity pain, and bowel and bladder dysfunction

Radiculopathies: patients with lumbosacral nerve root involvement with pain radiating down lower extremities; typically multiple nerve roots

Neuropathies: classic sensory neuronopathy of small-cell carcinoma; can have diverse neuropathic manifestations; sensorimotor axon neuropathy among most common

Neuromuscular junction disorders: myasthenia gravis affects postsynaptic membrane; associated with thymoma; small-cell carcinoma usually accompanies presynaptic Lambert-Eaton syndrome; patients typically present with weakness

Peripheral neuropathies: patients present with weakness and sensory loss; sensory loss can affect large fibers, causing balance problems and notable loss of vibration

sense, or small unmyelinated fibers regulating temperature and pain; possible temperature loss and pain in distal extremities

Autonomic nervous system dysfunction: patients present with low blood pressure, orthostatic hypotension, bowel and bladder disturbances, early satiety from GI dysmotility, and heat intolerance; may notice difficulty tolerating bright lights because of pupil mydriasis

Multiple symptoms: many patients with paraneoplastic neurological disorders have multifocal problems; example — combination of movement disorder plus neuropathy

Case example: patient presents with dance-like movements resembling chorea; might consider neurodegenerative Huntington's disease; however, if patient lacks family history or reports other neurological problems atypical for Huntington's disease, such as peripheral neuropathy, presentation might suggest underlying paraneoplastic cause; study published in *Journal of Neurology* on autoimmune chorea found peripheral neuropathy accompanying chorea predictive of paraneoplastic cause

Evaluation: start with neurological and paraclinical neurological measures; document all levels of nervous system involved; may provide clue to diagnosis of paraneoplastic disorder; serves as baseline for future evaluations, after treatments have been started to help with symptoms; neuro-ophthalmological evaluation by retina specialist important for visual symptoms; head MRI can demonstrate classical changes associated with limbic encephalitis or autoimmune GFAP astrocytopathy for evaluating patients with suspected encephalitis; NMDA receptor encephalitis patients typically have normal head MRI but may have abnormal PET scan of posterior regions of brain; obtain baseline cognitive testing; perform at bedside initially; more prolonged and detailed 2 to 4 hour neuropsychometric evaluations can be performed on patients without severe cognitive impairment; EEG testing helpful to evaluate for evidence of accompanying epilepsy with encephalitis; can also demonstrate diffuse slowing in brain; can be remeasured after treatment; obtain MRI of head for brainstem disorders; evaluate for evidence of degeneration of cerebellum characteristic of some paraneoplastic ataxias; sometimes signal abnormality on MRI can be appreciated on T2 images with hyperintensity emanating from brainstem and extending rostrally to involve limbic areas; sometimes seen in patients with Ma2 encephalitis, generally young men with testicular germinoma

Evaluation of myelopathies: MRI imaging can demonstrate characteristic findings; hyperintense white intensity signal noted over full length of spinal cord in central regions or in specific tracts such as corticospinal tracts, lateral spinothalamic tracts, or dorsal columns; restricted abnormality in columns alone has limited neurological differential diagnosis with paraneoplastic syndrome high on list; areas of cord may also enhance; breakdown to blood-brain barrier at T1 sequence post-gadolinium contrast; same columns light up length of cord

Evaluation of nerve roots and radiculopathy: EMG and nerve conduction studies can help confirm clinical findings; MRI imaging can help evaluate for inflammation of nerve roots; general imaging helpful for differential diagnoses; causes include metastatic disease, viral infections, or other infiltrative disorders such as sarcoidosis

Evaluation of neuromuscular junction disorders: readily identifiable by clinical examination; fatigable weakness may be appreciated for myasthenia gravis; augmentation of muscle strength, reflexes, or compound motor action potentials on EMG by exercise facilitation

Evaluation of peripheral neuropathies: clinical exam important; evaluate for evidence of loss of deep tendon reflexes, distal loss of sensation, and some distal-predominant loss of strength; in contrast with paraneoplastic myelopathies, increase in muscle tone seen, brisk reflexes; extensor planters may be observed; some distal or more proximal sensory loss with sensory level across thorax or abdomen; for neuropathies and neuromuscular junction disorders such as Lambert-Eaton syndrome, EMG and nerve conduction studies can demonstrate characteristic findings

Evaluation of autonomic neuropathies: abnormalities can be documented clinically; measure sitting, lying, and standing blood pressures; examine pupils; perform transit studies of gut to evaluate for hypomotility; perform specialized autonomic testing such as quantitative sudomotor axon reflex testing, thermoregulatory sweat test, tilt table testing, and measurements of heart rate and blood pressure responses to deep breathing and Valsalva

Workup: demonstrate immunological abnormalities; serum and CSF paraneoplastic neurological autoantibody testing; can also perform testing of spinal fluid for more generic inflammatory markers such as cell count, protein, IgG index and synthesis rate, and oligoclonal bands

Autoantibody testing: test serum and spinal fluid based on profile of autoantibodies relevant to clinical neurological presentation; has been gradual increase in number of antibody markers of paraneoplastic neurological disorders; difficult for clinicians to keep track of current antibody tests relevant to particular patient presentation; recommend testing on basis of profile of antibodies that represents, eg, encephalopathy, myelopathy, movement disorder, or peripheral neuropathy; has been found that physician-selected individual antibody tests ordered based on clinical phenotype have low hit rate; better to test for whole profile of autoantibodies upfront due to possibility of occult cancer and response to immunotherapy; some cancers have multifaceted immunological response; particularly true for small-cell carcinoma; example — woman with ANNA2 antibody could represent breast or small-cell lung cancer; profile restricted to ANNA2 or anti-Ri antibody with breast adenocarcinoma; patients with underlying lung cancer tend to have multitude of autoantibodies targeting calcium channels or other small-cell carcinoma-specific markers such as anti-Hu, amphiphysin, or CRMP-5 antibodies; no longer a situation of one antibody, one disease

Serum *vs* CSF: largely depends on clinical presentation; might only test for serum CRMP-5 antibody in patient presenting with isolated anterior chamber inflammatory eye disease; may need to profile approximately 15 antibodies in serum and CSF to optimize sensitivity and specificity of findings in patient presenting with encephalitis; some autoantibodies such as LGI1 or CASPR2 associated with thymoma; antibody optimally detected in serum; in contrast, NMDA receptor antibody optimally detected in CSF in terms of sensitivity and specificity

Autoantibodies: two types; some target extracellular domains of plasma membrane-bound proteins such as ion channels and receptors; example — NMDA receptor autoantibody causes downregulation of receptor in animal models; receptors can repopulate cell surface and gradually patient can recover over time once antibody removed by plasma exchange or other treatments; this is example of antibody that is good biomarker in clinical laboratory and indicative of antibody mediated disorder from pathological and therapeutic standpoint; other autoantibodies generated in context of paraneoplastic disorders are indicative of T cell-mediated disorder; in such cases, antibodies are reactive against linear epitopes of intracellular proteins in cytoplasm, nucleus, or nucleolus; these proteins processed in proteasome; degraded proteins expressed on cell surface of neuron or other nervous system cell type, such as astrocyte or oligodendrocyte; proteins are presented on MHC class I in degraded state as polypeptides; recognized by cytotoxic T lymphocytes that bring about degeneration of nervous system; autoantibodies generated in this context would not be reactive in vivo with intracellular proteins because they cannot cross plasma membrane; probably have some other effect such as debris opsonizing; these antibodies excellent biomarkers in clinical laboratory; such antibodies, generated in context of upregulated MHC class I and T-cell effectors, are the more common biomarkers encountered in laboratory for classical paraneoplastic neurological disorders

Markers: many of these antibodies reactive with transcription factors such as Hu, Ri, and Yo proteins; many associated with small-cell carcinoma, including ANNA1 or anti-Hu, ANNA2 or anti-Ri, AGNA or SOX1, MAP1B also known as PCA-2, CRMP-5 also known as CV2, amphiphysin-IgG, and neuronal intermediate filament light chain

Thymoma: commonly associated with paraneoplastic syndromes; many patients have benign thymomas; some have thymic carcinomas; these patients can have CRMP-5 antibody biomarker; can occur in isolation or as part of profile of autoantibodies, which could include myasthenia gravis antibodies such as acetylcholine receptor binding and modulating antibodies, striational antibody, and also cell membrane-directed antibodies such as AMPA receptor antibody

Ma2 antibody: may be accompanied by Ma1 antibody; patients with Ma2 antibody or both Ma1 and Ma2 typically have brainstem or limbic encephalitis; patients with brainstem encephalitis can have ataxia, eye movement problems, sleep disorders; some have phenotype with limb and neck rigidity and postural instability with eye movement problems mimicking some rare forms of Parkinsonism, such as progressive supranuclear palsy

Targeted intermediate filament proteins: include GFAP and neuronal intermediate filaments; GFAP antibody associated with teratoma and other cancer types; neuronal intermediate filament antibodies associated with neuroandrogenic carcinoma, particularly neurofilament light chain antibody

Reactive autoantibodies: all antibodies just described are processed intracellular antigens; biomarkers of cytotoxic T cell-mediated disorder rather than pathogenic in themselves; tend to have highest predictive value for cancer; generally >50%; most 70% or higher

Antibodies targeting plasma membrane proteins: these proteins include receptors and ion channels; some autoantibodies have good predictive value for cancer; 50% of patients with NMDA receptor antibodies have ovarian teratoma; 70% of patients with AMPA receptor antibodies have neoplasias, including thymoma, lung carcinoma, and breast carcinoma; 50% of patients with GABA B receptor autoimmunity have small-cell lung cancer; PCATR (or DNER) associated with Hodgkin lymphoma in 70% of patients; many other autoantibodies have idiopathic autoimmune cause; cancer not found in most of these patients; exceptions include LGI1/CASPR2 antibodies, associated with thymoma in ≈20%; glycine receptor occasionally detects thymoma or other cancer types

Duplicative nomenclature: historical reason; many autoantibodies identified initially by staining pattern by indirect immunofluorescence assay; antibody detected by using mouse or rat brain, applying patient serum or spinal fluid, and using secondary anti-human antibody with fluorophore attached; assay could be read under indirect immunofluorescence; example — Purkinje cell cytoplasmic antibody type I also known as anti-Yo; first name — tissue pattern description name; second name — protein name; antibodies increasingly named according to target protein

Neurological autoantibody accompaniments: classical paraneoplastic antibodies may have multitude of different phenotypes associated with antibody; patients may have multifocal disorders; example — ANNA1 or anti-Hu patients may have anything from limbic encephalitis to brainstem encephalitis, peripheral neuropathy, or combination; plasma membrane-directed syndromes have antibodies that may be pathogenic with more restrictive clinical phenotype; example — encephalitis only phenotype of note in NMDA receptor autoantibody

Laboratory detection: indirect immunofluorescence assay useful for screening for presence of neuronal antibodies; allows progression to protein-specific assay to confirm presence of antibody; report with accompanying comment regarding neurological and cancer significance

Confirmatory assays: can be done by western blot or immunoprecipitation assay; good for linear intracellular epitopes; perform cell-based assay to confirm presence of plasma membrane protein-directed antibodies, because epitopes are 3D conformation-dependent; protein expressed on cell surface of testing substrate in 3D conformational state; for some antibodies, better to screen for specific antigen such as LGI1, CASPR2, because sensitivity higher than on tissue-based immunofluorescence assays; flow cytometry used for antibody aquaporin-4 antibody for neuromyelitis optica; occasionally accompanied by cancer, particularly in patients >50 years

Differential diagnosis: patients present with neurological symptoms in neurological practice; serum and spinal fluid result should initiate evaluation or search for de novo cancer; in oncological practice, neurological disorders may have been diagnosed as paraneoplastic and patient may have been referred for cancer workup; alternatively, patient may already have been diagnosed with cancer and developed some form of neurological complication in context of treatment; differential diagnosis for brain or eye disorders includes possibility of infiltration from carcinomatosis, lymphomatosis, or metastases; same

is true for ataxic disorders and spinal cord disorders; some chemotherapy treatments such as methotrexate or ifosfamide can result in encephalopathy; patients may develop vitamin deficiency for unrelated reasons; also common cause of myelopathy such as vitamin B12 deficiency; copper, vitamin E, or folate deficiency often seen in setting of gut malabsorption; consider metastatic disease and metastatic leptomeningitis for radiculopathies and lumbosacral disease; consider chemotherapy-related side effects in presence of peripheral neuropathies; time course and relation to chemotherapy useful; can be difficult to tease out; sometimes providers order paraneoplastic autoantibody testing; consider effects of whole-brain radiation for encephalopathies or rapidly progressive dementias, particularly in patients with frontal subcortical type of dementia with cognitive problems, urinary difficulties, and gait problems; patients with symptoms of neuromuscular junction disorders such as myasthenia gravis or Lambert-Eaton syndrome could have myopathy; myopathies can arise occasionally as paraneoplastic necrotizing autoimmune myopathy (NAM); associated with HMG-CoA reductase antibody or SRP antibody; could also be result of steroid treatment used in some chemotherapy treatment regimens

Further evaluation: sometimes autoantibody finding may indicate de novo or recurrence of very specific cancer type; very selective or narrow cancer evaluation may be required; example — small-cell, extrapulmonary small-cell, or extrapulmonary neuroendocrine carcinoma should be considered for positive ANNA1 or anti-Hu antibody; PET/CT of trunk ideal screening test; targeted biopsy of tissue could follow screening; for thymoma, consider high resolution CT of chest or MRI of chest; for suspected breast cancer, mammogram, breast exam, and sometimes more focused evaluations of breasts, such as MRI; PET/CT for lymphoma; for lymph node disease, PET/CT also useful to help target lymph node biopsy; cancers may be small and occult; unusual for patients with metastatic disease to present with paraneoplastic disorder; tends to occur earlier in disease course or may be representative of very aggressive anti-tumor response; clinical exam, ultrasound with transvaginal views, or MRI of pelvis for gynecological cancers; upper and lower endoscopy for GI cancers; ultrasound or PET imaging of thyroid can indicate presence of malignant nodule; dermatologic exam appropriate in patients with Merkel cell skin carcinomas of neuroendocrine lineage or occasional melanomas

Following autoantibodies over time: important to note that negativity for paraneoplastic autoantibodies does not exclude diagnosis; diverse cancer workup in some cases due to high suspicion clinically for paraneoplastic disorder; undertake general routine age- and sex-appropriate cancer screening going forward if cancer not found; if something else later found in history or examination, this may warrant repeating antibody testing; some patients have autoantibody highly predictive for cancer but negative cancer tests with nothing to biopsy; example — cancer found in ≈80% of patients ANNA1 or anti-Hu, usually associated with small-cell carcinoma; generally recommended patients to have repeat imaging every 6 months for up to 3 years after initial detection of autoantibody; following autoantibodies over time not helpful in predicting outcomes or response to treatment; may be worth repeating autoantibody profile if patient in remission from cancer in context of paraneoplastic neurological autoimmunity has recurrence of neurological problems, either same or different from previous; antibody profile may have expanded, indicating specific cancer; marked increase in antibody titer may indicate recurrence of cancer, prompting further testing

Treatment: typically initiate right away, particularly for severe neurological symptoms; could consist of methylprednisolone treatments intravenously 1g daily for 5 days; followed by 1g weekly for 6 to 12 weeks in addition to or instead of plasma exchange; plasma exchange administered as one treatment every other day for five to seven treatments over 10 to 14 days; easy to administer in addition to chemotherapy or radiation therapy; when considering surgery, be careful about corticosteroids and wound healing; discuss timing of steroid administration with surgical colleagues; sometimes taking break for few perioperative and postoperative weeks; also sometimes anticipated improvement with paraneoplastic disorders from effects of chemotherapy itself due to removal of tumor antigen or because of immunosuppressive effects of drugs such as cyclophosphamide, which are frequently part of chemotherapy regimens; reasonable to try further treatments when patient has completed oncological therapy and returns to neurologist with relentless progression of severe neurological symptoms; includes corticosteroids, plasma exchange, intravenous immune globulin, or cyclophosphamide for those seriously affected; no class I evidence from rigorous controlled trials to support recommendations; all on basis of clinical experience and recommendations of experts and small retrospective case series

Outcomes: generally poor outcomes for classical paraneoplastic disorders; some individual patients have responses to immunotherapy; immunotherapy should be attempted in patients with reasonable performance status who might tolerate treatment; PCA1 (anti-Yo) autoimmunity has poor neurological outcomes, though some patients stabilize with treatment but do not improve; pattern of poor responsiveness typical for patients with classical paraneoplastic antibodies reactive with intracellular antigens such as Yo, Hu, and Ri; patients with antibodies targeting plasma membrane proteins such as AMPA and NMDA receptors often have very robust responses to immunotherapy; generally require much treatment and supportive care, often in hospital, particularly for NMDA receptor encephalitis; recovery can be quite slow; some patients have good recoveries even with paraneoplastic encephalitis; always some patients who do not do well because treatments may cause immune suppression and opportunistic infection or increased severity and aggressiveness of disease; treat potentially antibody-mediated disorders with early corticosteroids, IVIG or plasma exchange; follow up if needed with B lymphocyte-directed therapy such as rituximab; may be pertinent for NMDA receptor encephalitis; cyclophosphamide frequently utilized in severe cases

Prognosis: long-term prognosis for small-cell carcinoma-associated paraneoplastic disorders generally quite poor; usual 1-year prognosis; some long-term treated survivors with limited initial disease; some may have severe neurological deficits from original paraneoplastic disorder

Checkpoint inhibitors: monoclonal antibodies have revolutionized treatment of previously hard-to-treat cancers, including melanomas and metastatic carcinomas; carry neurological implications; patients can develop autoimmunity; rheumatologic autoimmunity common; neuromuscular disorders such as necrotizing myopathies, myasthenia gravis, neuropathies, and central nervous system disorders including encephalitis, movement disorders, and myelopathies observed at Mayo Clinic; antibody targeting phosphodiesterase 10A in patients with metastatic adenocarcinoma treated with checkpoint inhibitor drug targeting PD1 subsequently developed form of encephalitis with chorea; anticipate immunologic neurological complications with increased use of immunotherapies for treatment of cancer; attempt to treat with corticosteroids while balancing treatment of cancer and considering potential for neurological harm; change of treatment may be needed for severe neurological consequences

Suggested Reading

Baizabal-Carvallo JF, et al: Autoimmune and paraneoplastic movement disorders: an update. *J Neurol Sci.* 2018 Feb;385:175-84; **Lancaster E:** Paraneoplastic disorders. *Continuum.* 2017 Dec;23(6, Neuro-oncology):1653-79; **Zoccarato M, et al:** Diagnostics of paraneoplastic neurological syndromes. *Neurol Sci.* 2017 Oct;(Suppl 2):237-42.

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Pain Management for Cancer Patients

Keith Swetz, MD, *Professor of Medicine, Medical Director, Supportive Care and Survivorship Clinic, and Ambulatory Clinical Core Leader, Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama School of Medicine, Birmingham, AL*

Cancer pain: affects up to 60% of patients receiving therapy for cancer; between 70% and 90% in advanced stages; major factor impacting overall quality of life; can impair social function and functional status and lead to lack of desire to continue with tumor-directed therapy; challenges include assessing and optimally managing pain safely; complicated by opioid crisis in US and scrutiny for prescribing controlled substances

Evaluation: history and physical to evaluate previous exposure to opioids and other controlled substances that might impact tolerance and overall symptom management; workup with labs and radiographs to understand source of pain; radiographs include x-rays, plain films, CT scans, PET scans, and MRIs; some specific pain syndromes come from tumors themselves

Therapies: include chemotherapy, radiation therapy, orthopedic interventions, and neuropathic pain treatment

- Chemotherapy: shrinks tumors and relieves oncologic pain from tumors invading structures; efficacy depends on sensitivity of tumor type
- Radiation therapy: external beam radiation, nuclear medicine, or radioisotope approach; certain tumors radiosensitive, others less so; majority of tumors causing pain treated with external beam radiation; given over multiple fractions, such as 5 or 10 fractions, or single fraction, particularly for painful bony metastasis in appendicular skeleton; single fraction does not have as durable response, but may have excellent palliation of pain and be more consistent with patient goals of care, especially when patient close to end of life or struggling with trips to and from treatment center
- Orthopedic interventions: considered for underlying bone or muscle structures invaded by tumor; could treat impending fracture with pinning or internal fixation, resections, or other types of stabilizing procedures; vertebral compression fractures may not require surgical intervention; might respond to vertebroplasty or kyphoplasty — using balloon to expand vertebral body and insert cement to preserve integrity of vertebral body and prevent collapse
- Neuropathic pain interventions: differentiate pain caused by tumor-directed therapy *vs* pain from tumor involvement, such as brachial plexopathy or other infiltrative process

Goals of pain management: preserve dignity and improve overall quality of life; manage otherwise intractable symptoms to help patients live best lives for as long as possible

Pain management: common three-tiered approach associated with World Health Organization (WHO) pain ladder

First tier of WHO pain ladder: treat mild pain with anti-inflammatory drugs, over-the-counter analgesics, or non-opioid analgesics

- Acetaminophen: effective at treating patients with musculoskeletal pain; concern of masking of fever in patients receiving myelosuppressive chemotherapy; consider cumulative daily dose and underlying liver structure and function
- Nonsteroidal anti-inflammatory drugs: effective at treating bone or muscle pain; over-the-counter naproxen or ibuprofen readily available; once-a-day agents enteric diclofenac or meloxicam inexpensive and well-tolerated; increased risk of bleeding and renal insufficiency; monitor coagulation tests, platelets, and risk of underlying gastrointestinal hemorrhage; follow renal function
- Topical nonsteroidal anti-inflammatory drugs: topical diclofenac most common; works well for large joints; no broad evidence for treating neoplasm-associated pain
- Gabapentinoids: gabapentin and pregabalin; used with neuropathic component of pain

Second tier of WHO pain ladder: add short-acting opioid to tier one treatments; often immediate-release opioids in lower doses — hydrocodone, oxycodone, morphine, or hydromorphone most commonly used agents; little evidence for opioid-acetaminophen combination tablets; patients sometimes report combination tablets work well and oxy-acetaminophen even at lower dose more effective than oxycodone immediate release and separate acetaminophen; no evidence in literature; avoid combination tablets to stay below maximum dose of acetaminophen out of concern for liver function; 4000 mg daily might be acceptable boundary for patients with normal liver function; decrease to 3000 mg daily if patients have some impaired liver function; decrease to 2600 mg daily if concerned for intraparenchymal metastases or risk of decreasing hepatic function; codeine: has fallen out of favor; activated in liver through cytochrome P450 system to produce its active component, morphine; using morphine skips need to have codeine activated; oxycodone, morphine, and hydromorphone come as individual short-acting preparations; hydrocodone does not come as single agent in US; always partnered with acetaminophen or ibuprofen

Third tier of WHO pain ladder: evaluate adding long-acting opioids to short-acting opioids for more steady pain

relief overall; long-acting opioids include long-acting or extended-release morphine, extended-release oxycodone, transdermal fentanyl patches; methadone — longer acting agent but not extended-release preparation; use methadone in consultation with pain or palliative care specialist; variable pharmacokinetics can be exploited to potentially use two or three times daily

Other options: consult NCCN (National Comprehensive Cancer Network) treatment guidelines for cancer pain and symptom management; treatments utilized for all types of cancer-related pain; include mindfulness, physical therapy, TENS (transcutaneous electrical nerve stimulation)

Opioids: go-to for severe pain; widely available and reasonably inexpensive in US; good blood levels obtainable when used on regular basis; consider patient's past opioid or sedative-hypnotic use or history of substance abuse during evaluation; currently an opioid epidemic in US; despite scrutiny on prescriptions, these drugs not going away, will continue to be mainstay of approach to cancer-related pain; important for hematologist-oncologist to be familiar with these drugs and understand how to approach their use

Pharmacology: opioids versatile; effective whether used orally or parenterally; important to recognize how quickly to expect drug to take peak effect; immediate-release agents such as oxycodone, hydromorphone, or immediate-release morphine have time to peak effect of ≈1 hour taken orally in liquid or tablet form; consider redosing if pain not controlled by 1 hour, though half-life can vary; consider using same dose of oral or parenteral opioid if dose effective; if given dose has no effect on overall pain severity, generally recommended to double dose at time expecting peak effect; IV effect depends on agent; peak effect of ≈6 to 10 minutes if using highly lipophilic drug like fentanyl; might expect peak effect between 10 and 15 minutes if using hydromorphone or morphine; house staff sometimes treat with fentanyl q2 or q3 hours; might be unmitigated symptoms in that interval between doses if drug peaking at 6 or 10 minutes; intramuscular injection of opioids discouraged due to erratic dispersion within muscles and associated pain; subcutaneous injection of opioids works well; achieves better time to peak effect than oral medications; not as fast as IV; expect peak effect of ≈20 to 30 minutes for patients receiving subcutaneous dose of morphine or hydromorphone; useful for patients with difficult IV access or failure of long-term catheter

Dosing: starting dose of morphine for opioid-naïve patient between 5 and 15 mg orally and 2 and 5 mg IV; equianalgesic tables widely available; 1 mg of IV morphine equivalent to 3 mg oral morphine; 123 rule — 1 mg of IV morphine equal to ≈2 mg of oral oxycodone equal to ≈3 mg of oral morphine; 123 analogous to 30-20-10; add 7.5 and 1.5 to 30-20-10 ratio for hydromorphone; next most commonly used agent; IV more potent than oral; 30 mg of oral morphine equals 20 mg of oral oxycodone equals 10 mg of IV morphine, 7.5 mg oral hydromorphone, 1.5 mg IV hydromorphone; start at appropriate dose and double dose as needed to find correct dose for opioid-naïve patient; consider total opioid in past 24 hours for patients in pain crisis already on long-acting and/or short-acting opioids; try to convert everything into morphine, oxycodone, or hydromorphone equivalents; bolus or breakthrough dose somewhere between 10 and 20 mg [percent? See below] of total daily dose

Case example: patient taking 30 mg of extended-release morphine twice daily; using 6 doses of oxycodone immediate-release 20 mg; had two 10 mg oxycodone immediate-release with long-acting morphine; 200 oral oxycodone equivalents; 100 mg of IV morphine equivalents or 300 mg of oral morphine equivalents using 123 rule

Redosing and restructuring: consider at least 10% of total daily dose of long-acting medicine in emergency room or acute care setting; ≈10 mg of oral morphine as first dose represents ≈10% of total daily requirement; might increase to 15% or 20% if pain severe; often switch over to more potent agents such as hydromorphone rather than using 15 or 20 mg of IV morphine; be cautious when considering going from 1-2 mg of IV morphine to 1 mg of hydromorphone; different by factor of 5 to 6; going directly to 1 mg of hydromorphone significant increase relative to morphine; consider switching to another agent when one opioid becomes less effective or toxicity develops; take about half to two-thirds of overall daily opioid use and put that into sustained release; have reasonable amount of breakthrough medication available based on 10% to 20% of total daily dose for individual doses; goal of three or less breakthrough doses per day if managing pain well with long-acting agent; sometimes patients use every 4 hours

Adverse effects: use caution with morphine in renal insufficiency; glucuronidated metabolites can linger; morphine-3 and morphine-6-glucuronide more lipophilic and may cross blood-brain barrier better; some cause prolonged effect; patients with renal insufficiency may have longer lasting glucuronidated morphine causing more sedation or symptoms of neurotoxicity; include twitching, myoclonus, or more severe hyperalgesia, hallucinations, or seizures

Allergy to opioids: IgE-mediated anaphylaxis to morphine exceedingly rare; itching associated with mast cell degranulation locally from use of morphine common; improved by giving drug slowly or using antihistamines; some patients on opioids experience nausea, constipation, and sedation; constipation usually chronic problem; sedation or nausea may improve over time

Hydromorphone or oxycodone: superior to morphine for renal insufficiency; hydromorphone has lower propensity for forming active metabolites; also preferred for elderly patients

Fentanyl: useful in hepatic or renal insufficiency; parenteral fentanyl — 1 mg of IV morphine = ≈10 **mcg** of IV fentanyl; one to 10 ratio though units differ; lipophilic; rapidly taken up; does not have long half-life; cannot have long intervals between doses; transdermal patch allows medicine to move from vehicle on patch into capillaries, from capillaries into bloodstream, and then into CNS; because of lipophilic nature, moves into fat before crossing into bloodstream; extremely cachectic patients have less fat for drug to move into; may have erratic, unpredictable absorption; suboptimal absorption of transdermal patch also seen in dehydrated patients with skin tenting as volume shunted away from periphery and kept central to keep organs perfused; fentanyl patches affected by temperature; temperature potentially changes drug composition within matrix on patch; warmth causes vasodilatation and erythema, leads to increased blood flow to that area, and more fentanyl taken from patch; remove

patch when patients present with sepsis, neutropenic fever, and increased confusion; switch to different agent in interim

Codeine: useful with cough and upper respiratory infection; not useful for cancer-associated pain; activated by CYP2D6; hormonal agents and antineoplastic agents use same pathway; best to avoid drugs impacting activation of agents like tamoxifen to endoxifen

Meperidine: rarely indicated given risk of neurotoxicity or seizure; regular morphine can treat rigors; class effect

Tramadol: avoid for cancer pain unless dealing with mild pain; combination mu-opioid agonist; has some serotonin–norepinephrine reuptake inhibition; also impacts 2D6; can interact with other drugs, particularly other antidepressants; puts patients at risk for serotonin syndrome and reduces seizure threshold; risk of withdrawal with cessation or switching from moderate or high dose tramadol to opioids; reported cases of hypoglycemia; avoid unless dealing with relatively healthy patients not on many other agents concurrently

Radiation: consider radiation oncologist for treating bony metastasis or soft tissue metastasis; use shortest effective course of treatment

Treatment of neuropathic pain: agents associated with neuropathy include vinca drugs, platinum, taxanes, and newer small molecule inhibitors; drugs such as pregabalin or gabapentin anticonvulsants studied in diabetic neuropathic pain; little evidence to support regular use for chemotherapy-associated pain; often used to spare opioids

Gabapentin and pregabalin: act on alpha 2-delta ligand binding to alpha 2-delta subunit of voltage-gated calcium channel; calcium second messenger system; calcium influx passes signals along; calcium influx modulated by gabapentin; decreases downstream neurotransmitter activity; similar adverse effect profiles for gabapentin and pregabalin include sedation, dizziness, and peripheral edema; be aware in older patients or those with risk of pathologic fracture; adjust doses of both drugs in patients with underlying renal insufficiency; peripheral edema underrecognized for some patients; important if patient concurrently on corticosteroids or nonsteroidal agents; patients feel similar to alcohol intoxication in terms of sedation, confusion, and dizziness

Pharmacokinetics and dosing: gabapentin has more saturable pharmacokinetics; non-linear, similar to how enzymes work; pregabalin has more linear pharmacokinetics; highly bioavailable at all doses, even higher ones; decrease in bioavailability with higher doses of gabapentin; some patients tolerate up to 3600 mg gabapentin while others cannot tolerate 600 mg daily without side effects; gabapentin given three times daily; titrated up slowly to avoid adverse effects; pregabalin given twice or three times daily; more rapid onset due to high bioavailability; pregabalin controlled substance by FDA; gabapentin controlled substance at state level in many places

Antidepressants: sometimes help with neuropathic pain; tricyclic antidepressants effective when tolerated; anticholinergic side effects of nortriptyline or amitriptyline limit use; more indications for use of serotonin–norepinephrine reuptake inhibitors (SNRIs); duloxetine FDA approved for diabetic neuropathic pain; not for chemotherapy-associated neuropathic pain; FDA approved for improved functional status in patients with underlying osteoarthritis, particularly of knee; patients with chronic musculoskeletal pain and concurrent anxiety or depression might benefit from nonopioid approach with duloxetine; start at low dose of 20 to 30 mg in evening; target maximum of 60 mg daily; be aware of potential drug interactions, underlying transaminases, and hepatic function

Procedures: important to know specific procedure availability at home institution

Neuraxial approach: strategies to mitigate pain within spinal column

Intrathecal system or pump: evidence of economic benefit and improved quality of life for patients with refractory pain; Thomas Smith in 2002 *Journal of Clinical Oncology* demonstrated patients with intrathecal drug delivery systems used less overall systemic opioid and had less side effects; requires experienced operator to manage, refill, and implant pumps

Epidural injections: consider placing epidural catheter for refractory pain; done with both anesthetic and/or opioid; simple epidural steroid injection may be beneficial for patients with underlying discogenic or malignancy-associated pain from nerve root compression within spinal column

Ablative procedures: alcohol-based ablation — absolute alcohol or phenol injected in tumor to cause cell rupture and death of neoplasm; cryoablation — uses multiple probes to deliver cold temperatures and cause tumor destruction by freezing; radiofrequency ablation; method determined by operator; not curative procedure; focused on improving quality of life for patients with pain or other symptoms from tumor

Nerve blocks: injecting anesthetic with or without steroid to help control pain; particularly helpful for patients with pain syndromes associated with nerve groups within sympathetic nervous system; celiac plexus block — commonly used in abdominal or visceral malignancies; often with pancreatic cancer; performed via endoscopic ultrasound; sometimes gastroenterologist injects alcohol through echoendoscope after visualizing celiac plexus; sometimes radiologist or anesthesia pain clinician proceduralists use para-axial approach — enter through back near vertebral body around L1 and perform bilateral splanchnic nerve block with same effect; superior hypogastric plexus block — helps mitigate deeper pain within pelvis or rectum; sacrococcygeal or ganglion impar block — used for perineal or perianal pain; lumbar sympathetic blocks — used for severe leg pain; cervical or thoracic ganglion blocks — for thoracic or upper extremity pain in setting of malignancy

Neurolytic procedures: used in setting of limited life expectancy or desire for more durable response to pain; ablation of nerve group using injectable alcohol or phenol and anesthetic to destroy nerve group; used with life expectancies of 6 months or less; can be repeated if performed earlier; risk of increasing pain over time due to deafferentation pain — nerves resprout in abnormal patterns and cause pain to recur

Suggested Reading

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Gastrointestinal Symptoms

Keith Swetz, MD, *Professor of Medicine, Medical Director, Supportive Care and Survivorship Clinic, and Ambulatory Clinical Core Leader, Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama School of Medicine, Birmingham, AL*

Constipation: common side effect of pain management; manage proactively when starting patients with cancer-associated pain on opioid therapy; can be distressing symptom leading to preventable emergency room trips

Etiology: caused by opioids, thalidomide, and other drugs; underlying mechanism associated with motility; opioids slow gastrointestinal motility; allows for more water absorption and results in harder stools

Stimulant laxatives: use with opioid and chemotherapeutic-associated constipation; senna among most common stimulants; consider bisacodyl given orally or as suppository; counteracts effect of medications slowing motility; side effects include cramping; senna or bisacodyl sometimes perceived as ineffective; often caused by improper dosing; senna usually 8.6 mg per tablet; provide patients adjustable range; sometimes between 8.6 mg once daily up to four tablets twice daily; substantially higher dose could be required, such as 37.4 mg twice daily for severe constipation; for patients struggling to swallow, bisacodyl suppository stimulates colonic nerves to contract and evacuate distal colon; consider other approaches when stimulants ineffective

Osmotic agents: include ionic and nonionic agents

Ionic agents: include magnesium hydroxide or Milk of Magnesia; use caution in setting of renal insufficiency; magnesium citrate; phosphorus products include oral Phospho-Soda; keep water in intestinal lumen and cause profound fluid shift; minimize phosphorus load in patients with heart failure or kidney disease

Non-ionic agents: effective; polyethylene glycol 3350 most commonly used over-the-counter osmotic agent; small moiety of polyethylene glycol not absorbed; anything not absorbed pulls water in to flush it out; pulls water in and softens stool; typical dose 17g in 8oz of water; patients can split dose; half a capsule or 8.5g twice daily in 4oz of water; helpful if patient on fluid restriction; sometimes 17g twice daily needed for severe constipation; one of safer osmotic laxatives available over the counter; does not cause dramatic fluid shifts *vs* magnesium citrate, magnesium hydroxide, or Phospho-Soda

Non-absorbable non-ionic compounds: keep water in colon lumen

Lactulose: non-absorbable sugar; cannot be broken down and absorbed earlier in gut; bacteria that break it down produce gas, causing flatulence; diarrhea possible side effect; compliance often difficult due to numerous bowel movements in given period, as also seen in hepatic encephalopathy population; does not always occur

Sorbitol: sugar alcohol; both sorbitol 70% solution and lactulose require prescription; generally safe if dose appropriate and patients hydrated

Enemas: conventional sodium phosphate enema available over the counter; effective with stool in distal colon and rectum; use caution with phosphorus in heart and renal failure; avoid electrolyte shift issues and limit to one 4oz enema per day; bisacodyl or mineral oil enemas potentially effective for disimpaction; using non-ionic contrast such as gastrografin can be diagnostic to rule out obstruction and therapeutic from resulting mass laxation; use of soap suds or tap water enema for patients with renal or cardiac issues precluding use of phosphate enema; puts volume and distention within distal colon; stretching will sometimes cause laxation

Bulking agents: psyllium or calcium polycarbophil — over-the-counter fiber products; effective in bulking stool when colon working at baseline; adding fiber adds mass to stool; colon stretch causes myenteric plexus to contract and move stool forward; patients taking opioids or agents that negatively affect motility have impaired automatic contraction with stretching of colon; patients using fiber products and opioids simultaneously have large stools without motility; develop distention and become obstipated; require more osmotic or stimulating agents

Docusate: very effective stool softener if patient has normally functioning gastrointestinal tract; not effective if patient on medications like opioids that slow motility; clinical trial in patients on hospice evaluated benefit of senna alone *vs* senna plus docusate; docusate did not add benefit to constipation relief; added to pill burden and cost

Peripherally acting mu-opioid receptor antagonists (PAMORAs): use with opioid constipation; agents like naloxone only act at gastrointestinal level and not at CNS to cause opioid withdrawal

Methylnaltrexone: injectable and tablet forms; mostly used by injection; effective for patients with refractory opioid-associated constipation; quaternary amine structure restricts passage across blood/brain barrier; relatively low risk of opioid withdrawal; laxation occurs within ≈4 hours after dose; cost ≈$40 per dose; less expensive than emergency room copay for disimpaction or abdominal flat plate; keep available at home if proven effective in patient; subsequent meta-analyses confirm methylnaltrexone effective for opioid-associated constipation; not appropriate agent for multifactorial chronic constipation

Naloxegol: first commercially available oral PAMORA in US; still available; indicated for patients with chronic

non-cancer associated pain; some off-label use; may be effective in patients physically active with better performance status than those predominantly bedridden

Linaclotide or lubiprostone: affect chloride channels within intestines; chloride channels put chloride into main lumen; draw water and move stool along; use only when other agents have failed

Bowel obstruction: sometimes difficult to determine if patient constipated, obstipated, or showing signs and symptoms of malignant bowel obstruction; challenging and controversial supportive care management issue; treatment often depends on underlying etiology; is it large bowel obstruction, which might require stent? small bowel obstruction? complete or partial? controversy within literature about efficacy of some treatments

Management: avoid operative intervention when possible; initial conservative measures include nasogastric tube for decompression; often uncomfortable; helps with removal of fluid and gas; IV fluid resuscitation; balance acid-base status and electrolytes like sodium and potassium; conservative measures only work ≈20% of time; if approach fails, move to other options; patients frequently deal with high degree of colicky pain; parenteral opioid analgesics often needed to control pain; controversy due to potential for slowing gut motility

Dexamethasone: parenteral steroids gold standard for high-grade or partial malignant small bowel obstruction; anti-inflammatories might help with inflammation caused by adhesive process or tumor itself extrinsically compressing intestinal lumen; aids with gut edema resulting from obstruction; antiemetic and anti-inflammatory properties; avoid interfere with sleep cycles by administering during day

Other issues: patient may need acid suppression for prevention of gastrointestinal hemorrhage; parenteral proton pump inhibitors and histamine-2 blockers; nausea managed with antiemetics

Metoclopramide: frequently referenced treatment for incomplete malignant or partial malignant small bowel obstruction; potential for prokinetic effect; avoid metoclopramide or methylnaltrexone with more high-grade bowel obstruction due to risk for perforation, though there is little evidence

Octreotide: somatostatin analog; decreases enteric secretions; evidence shows octreotide superior to using anticholinergics or anticholinergic antihistamines like scopolamine or hyoscyamine to quiet gut; controversial whether truly gold standard; less benefit there is effective nasogastric tube decompression; makes more sense if patient cannot tolerate nasogastric tube; counteracts action of vasoactive intestinal peptide; decreases fluid retention within intestinal lumen; inhibits gastric secretions, motility, and biliary flow; slows fluid creation within gastrointestinal tract and crampy, colicky pain

Anticholinergics: include scopolamine and hyoscyamine; glycopyrrolate or meclizine can be considered; can all be used in combination; weak evidence

Diarrhea: less common than constipation in oncology patients

Carcinoid or other vasoactive processes: cause increased secretion and gut motility; important to treat carcinoid or neuroendocrine tumor primarily with octreotide or lanreotide in standard oncologic practice

Treatment-induced diarrhea: diarrhea can be caused by treatments like FOLFIRI (folinic acid, fluorouracil, irinotecan) for colorectal cancer; irinotecan causes diarrhea and intestinal cramping; atropine usually used with that regimen; has potent anticholinergic properties; sometimes not as effective after infusion; consider scopolamine or hyoscyamine; hyoscyamine used sublingually; provides relief of intestinal cramping; little evidence for support; match pharmacology with pathophysiology; use least sedating and best tolerated agent for patient

Infusions causing gastrointestinal lining breakdown: patients commonly treated with combination atropine and diphenoxylate or over-the-counter loperamide; atropine not well-absorbed orally but provides some anticholinergic activity to help with cramping; diphenoxylate weak opioid analog; loperamide weak opioid analog without pain-relieving effects; diphenoxylate and atropine or loperamide may add to opioid effects if patient taking opioids for pain

Colitis: infections with clostridium difficile, immunotherapy, or autoimmune colitis cause diarrhea; consider cause before treating

Anorexia: NCCTG (North Central Cancer Treatment Group) study published in late 1980s by Aminah Jatoi and Charles Loprinzi evaluated megestrol acetate *vs* dexamethasone *vs* fluoxymesterone, an anabolic steroid; side effects with fluoxymesterone unacceptable; fell out of favor; megestrol acetate studied; fairly well-tolerated; risk of venous thromboembolic disease fairly low; more likely risks related to edema; may improve weight and appetite, but does not affect quality of life according to Cochrane and other meta-analyses; dose choice challenging; from 160 mg to 800 mg daily; dexamethasone similarly effective to megestrol but does have steroid side effects; consider patient prognosis and other symptoms; for patient with low energy, bone pain, or other inflammatory processes, consider dexamethasone; use of dexamethasone has changed due to rise of immunotherapy and potential impacts on antineoplastic activity

Nausea and vomiting: consider cause of nausea when selecting pharmacologic agents

Vomiting from brain chemoreceptor trigger zone (CTZ): responds to serotonin antagonists, neurokinin 1 inhibitors, corticosteroids, and dopamine antagonists; serotonin antagonists include palonosetron and ondansetron; neurokinin inhibitors include aprepitant or fosaprepitant; dopamine antagonists include prochlorperazine, metoclopramide, and promethazine; metoclopramide predominantly antidopaminergic; has some antiserotonergic activity; promethazine has some weak antidopaminergic activity and some antihistaminic activity; sometimes more useful for other types of nausea; helps patients fall asleep but wake up still nauseous; haloperidol — potent dopamine antagonist effective with D2 receptors in CTZ; coupling dopamine antagonists with serotonin antagonists like ondansetron can prolong QT interval; be mindful about interactions of different agents

Nausea associated with mass effect or brain bleed: comes from stimulation of intracranial pressure receptors; corticosteroids treatment of choice

Nausea from vestibular center: infarction or metastatic disease within posterior fossa, particularly within

cerebellum in oncologic setting; agents include anticholinergic antihistamines like meclizine, scopolamine, or diphenhydramine; superior to ondansetron, which has no effect on vomiting from vestibular center in posterior fossa

Cortical or emotional input: anticipatory nausea; triggered by pain or anxiety; benzodiazepines, dopamine antagonists, or cannabinoids used; cannabinoids include THC, prescription dronabinol, medical or recreational marijuana (where legally available)

Gastrointestinal distention or irritation: can come from radiation, chemotherapy, obstruction, peritonitis, visceral inflammation, ischemia, perforation, carcinomatosis, or pain; dopamine antagonists and peripherally acting serotonin antagonists most effective; enterochromaffin-like cells within gastrointestinal tract stimulated by radiation and liberate serotonin; ondansetron or metoclopramide can be helpful; ondansetron makes patients more constipated and decreases motility; ondansetron monotherapy reviewed in *JAMA* (*Journal of the American Medical Association*) paper from Gordon Wood and colleagues in 2007; olanzapine effective; hits multiple receptors depending on level or dose; mirtazapine similar; olanzapine more effective antiemetic due to antidopaminergic properties; has good evidence for initial and delayed chemotherapy-associated nausea and vomiting; also very effective in stimulating appetite in anorexia; evidence from large clinical trials not available

Management: select agents based on source of nausea; history and physical important; synergize by picking drugs from different classes; example — partnering antidopaminergic drug with corticosteroids, benzodiazepines, or antihistamines; little evidence picking two drugs from same class increases efficacy; can increase side effects; example — promethazine weakly antidopaminergic; increased risk of dystonic reaction or other extrapyramidal symptoms when used with metoclopramide

Oral mucositis: Mucositis Study Group of Multinational Association for Supportive Care and Cancer and International Society of Oral Oncology (MASCC/ISOO); suggests pain control first; additional symptoms in gut might be substantial; might require days of patient-controlled analgesic pump in presence of severe mucositis discomfort

Etiology: multifactorial process; direct cytotoxic tissue injury from radiation or chemotherapy; proinflammatory cytokines; upregulation of inflammatory signals and amplifications of TNF alpha and other factors leading to inflammatory process and causing ulceration; healing phase takes time; managing symptoms appropriately early on important; lesions associated with stomatitis heal somewhere between 2 and 4 weeks after last dose of chemotherapy or radiation therapy; be mindful of immunosuppressed individuals or those at risk for superinfections

Oral decontamination: MASCC/ISOO's second point; cleaning mouth of normal oral flora or other bacteria challenging; patients at risk for bacteremia and other types of infections from organisms within oral cavity with breakdown in integrity of mucosal barrier; non-medicated rinses mix saline and sodium bicarbonate (salt and baking soda); avoids difficult brushing regimens or flossing; difficult to handle chlorhexidine mouthwash; may not change severity of mucositis; not routinely recommended; recognize secondary causes of infection such as oropharyngeal thrush or HSV viral infections superimposed on mucositis; treat active fungal infection with systemic azole antifungal; many patients at risk for viral infection on prophylactic acyclovir or valacyclovir

Nutritional support: important when patients struggle with eating; have nutritionist work with patient early; use soft or liquid diet; better tolerated than regular food requiring chewing; some patients with severe mucositis, such as those receiving protracted courses of chemotherapy and radiation, may require gastrostomy tube; use tube when bridging to improvement, not because patient unable to get calories in at given point; use intravenous fluids if necessary to appropriately hydrate patients; total parenteral nutrition (TPN) available; not routinely recommended due to risk of infection; patients receiving TPN at increased risk for bloodstream infections

Management: bleeding can be an issue; monitor platelet counts for those receiving myelosuppressive chemotherapy; topical hemostatic agents include fibrin glue or gelatin sponges; can be helpful with focused bleeding; struggle with transient xerostomia associated with treatment, permanent xerostomia, or hyposalivation associated with long-term difficulties from treatment; have patients keep water available to sip; recommend sugarless gum, xylitol, or other sugar alcohols to stimulate salivary flow; guidelines allow cholinergic agents; not commonly used; baking soda, table salt, and warm water rinses and sugar-free gum and candy support secretions; consider commercially-available artificial saliva products; certain growth factors like palifermin reserved for worst cases; not typically used in supportive-care setting; patients with severe mucositis in setting of hematopoietic stem cell transplant may be candidates

Suggested Reading

Farmer AD, et al: Pathophysiology, diagnosis, and management of opioid-induced constipation. *Lancet Gastroenterol Hepatol.* 2018 Mar;3(3):203-12; **Villa A, et al:** Pharmacotherapy for the management of cancer regimen-related oral mucositis. *Expert Opin Pharmacother.* 2016 Sep;17(13):1801-7; **Walsh D, et al:** 2016 Updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. *Support Care Cancer* 2017 Jan;25(1):333-40.

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Other Acute and Chronic Toxicities of Cancer and Cancer Treatment

Keith Swetz, MD, *Professor of Medicine, Medical Director, Supportive Care and Survivorship Clinic, and Ambulatory Clinical Core Leader, Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama School of Medicine, Birmingham, AL*

Fatigue: National Comprehensive Cancer Network (NCCN) definition of cancer-related fatigue focuses on distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment; not proportionate to recent activity and interferes with usual functioning; 60% to 90% of cancer patients, especially those undergoing chemotherapy, experience fatigue; may be pervasive and last for months or years after therapy is discontinued

Etiology: not simply effect of chemotherapy on body; complex issue with dysregulation in homeostasis in hypothalamic-pituitary-adrenal axis and inflammatory pathways; determine if fatigue caused by cancer, cancer treatment, or other conditions

- Anemia or iron deficiency: associated with restless legs, which might interfere with sleep
- Thyroid function: check TSH and free T4 for hypo- or hyperthyroidism; seen more with immunotherapy-associated endocrinopathies; issues related to hypothalamic-pituitary-adrenal axis or thyroid axis
- Vitamin D: check levels; no large clinical trials; low levels particularly important if patient on bisphosphonates, which increase risk of hypocalcemia; role of vitamin D in energy, pain, and mood not well understood; not many side effects from use
- Sleep hygiene: most important confounder with fatigue; determine if poor sleep hygiene, insomnia, history of poor sleep, swing shifts, abnormal sleep patterns, or untreated sleep apnea exist
- Other causes of cancer-related fatigue: uncontrolled or undertreated pain, anxiety, or pervasive mood symptoms

Pharmacologic treatments: many confounding factors; no strong evidence; benefit seen for some patients, particularly with concurrent depressive symptoms; psychostimulants generally used

- Methylphenidate family: psychostimulants; include long-acting or immediate-release methylphenidate and dexmethylphenidate; fairly safe; used without substantial cardiac toxicity; most studies suggest some improvement, but little of statistical significance; use determined by patient-specific profile in terms of overall survival; evaluate for concurrent depression with vegetative symptoms and underlying cardiac toxicities; anxiety, poor sleep, or anorexia possibly exacerbated by psychostimulants; use time-limited trial to evaluate efficacy
- Amphetamines: include dexamphetamine and mixed amphetamine salts; studies have not shown dexamphetamine beneficial for cancer-related fatigue; many patients still using these drugs believe they provide some benefit; difficult to determine if confounding factor or dependence; manage other symptoms, such as depression if or when weaning patients; put risk mitigation strategies in place with continued use
- Modafinil or R-modafinil: typically used for patients with narcolepsy; little evidence for benefit with fatigue; sometimes difficult getting medicines covered by insurance
- Antidepressants: SSRIs or bupropion; paroxetine most commonly evaluated; challenge due to anticholinergic properties and substantial issues with dependence and withdrawal; no specific antidepressant recommended for cancer-associated fatigue
- Reversible acetylcholinesterase inhibitors: include donepezil; used to treat dementia; studies have not shown benefit

Nutritional supplements: form of Wisconsin ginseng promising; clinical trials have shown varying results; L-carnitine or CoQ10 do not appear effective; commercially available caffeinated guarana-based products; predominantly vitamins and caffeine; likely to have short-lived effects, if any

Nonpharmacologic treatments: most promising, based on clinical studies for treatment of cancer-related fatigue; includes varying forms of exercise; stretching or yoga-type activity, posturing, relaxation, and deep breathing; cognitive behavioral therapy, energy conservation, or other supportive therapy with counseling potentially beneficial in reframing overall fatigue and what it means in course of illness and survivorship journey

Management: many studies with little evidence supporting one treatment over another; treat confounding electrolyte or metabolic deficiencies, such as iron, thyroid, vitamin D; appropriately regulate sleep cycles and insomnia; treat pain; consider graded exercise, other types of mindfulness, or yoga relaxation-based therapies

Sexual side effects: may relate to cancer treatment or other specific hormonal issues; determine if libido present; evaluate ability to become aroused or achieve erection; determine ability to ejaculate or orgasm; anorgasmia — great difficulty achieving orgasm — different from inability to become aroused; points to possible vascular or endocrine issues *vs* mental health issues

- Relationship issues: changes in roles within relationships in cancer treatment and survivorship can impact patient libido, self-worth, and overall perception of desirability

to their partner or ability to please their partner; often intimacy issues; procreative urge not always maintained when patient facing death

Psychogenic causes: include depression, anxiety, and self-worth issues; may or may not be related to underlying cancer; uncertainty about prognosis often causes anxiety or pervasive mood symptoms; address unresolved guilt or other types of self-worth issues; use counselors to provide appropriate therapy for deeper-seated problems

Hormonal causes: seen with patients on breast cancer estrogen-modulating therapy or testosterone-modulating therapies for prostate cancer; check for suppressed testosterone levels and PSAs; GnRH analogs eliminate pulsatile release of GnRH; constitutive presence of GnRH decreases LH, FSH production and ultimately decreases production of testosterone overall; patients on long-term opioid therapy at risk for hypothalamic hypogonadism even with non-androgen-based cancers and patient not on androgen deprivation therapy; for patients on chronic opioids with difficulty achieving erections or low libido, check morning testosterone or testosterone panel; evaluate issues related to androgens within endocrine system; might replace estrogens or androgens; depends on underlying malignancy and survivorship plan

Physiologic causes: blood flow issues or surgery that has altered ability to achieve erection even under optimal circumstances; discuss with urologist if patient unable to achieve erection; something anatomic or neurologic may need to be addressed

Complications in women: include vaginal lubrication and atrophic vaginitis; use higher-grade, water-based lubricants rather than low-grade, generic, over-the-counter lubricants; allows for comfort; in post-operative setting, particularly with gynecologic malignancies or radiation therapy within pelvis, what worked previously might not work after treatment

Survivorship issues: patients treated with antineoplastic drugs, radiation, surgery, or combination at risk for complications, especially neuropathy; recognize overall situations commonly encountered, including secondary malignancies, late effects of treatment, and cardiovascular side effects

Myocardial dysfunction: anthracyclines such as doxorubicin increase risk for dilated cardiomyopathy; dose-dependent and usually non-reversible; ABCDs of non-ischemic cardiomyopathy — alcohol, beriberi, cocaine, coxsackie, and doxorubicin or other anthracyclines; HER2 receptor antagonists include trastuzumab, pertuzumab, and lapatinib; cause non-dose-dependent and potentially reversible myocardial dysfunction; standard echocardiogram evaluating left ventricular ejection fraction (LVEF) alone not sufficient; requires markers of longitudinal strain

Accelerated atherosclerosis: mantle radiation to chest can cause issues with heart; head and neck radiation increases carotid atherosclerosis and stroke risk; follow appropriate lipids

Hypertension: seen with platinum therapy for testicular cancer; most frequently seen with anti-angiogenesis therapies, which include sunitinib, sorafenib, pazopanib, and bevacizumab; bevacizumab used in colon, brain, and other cancers

Conduction system dysfunction: previous radiation places patient at risk for atrial fibrillation, early pacemaker requirement, and valvular heart disease of mainly mitral and aortic valves; evaluate with echocardiogram

Pericardial disease: affects smaller number of patients; restrictive pericarditis, chronic effusion, and other issues; predominantly related to fibrosis from previous treatments like radiation, chemotherapy, or cancer itself; fibrosis from radiotherapy major underlying mechanism for coronary arteriopathy, valvular disease, constrictive pericarditis, conduction abnormalities, restrictive heart disease, and some forms of myocardial dysfunction; less fibrosis with anthracyclines or HER2 receptor antagonists

Coronary artery disease: left-sided breast cancer, history of circulatory disorders, diabetes, chronic obstructive pulmonary disease (COPD), current smoking, obesity, and other ischemic heart disease greatly increase risk for subsequent coronary events in setting of previous cancer-directed therapy

Heart failure: patients with history of pediatric malignancies subsequently at risk for developing heart failure; ≈5% incidence of clinical heart failure between 15 and 20 years for patients treated for childhood cancers, according to prior studies; many childhood cancers, particularly sarcomas, treated with anthracyclines; some studies following patients over 6 to 10 years have suggested 7% incidence of development of clinical heart failure; probably higher; issues to be explored include evaluation of groups developing longitudinal strain *vs* dilated cardiomyopathy, reversibility or non-reversibility, dose-dependent or not dose-dependent; surgery, stress, pregnancy, and secondary malignancy might precipitate heart failure

Contractility and cardiac output: negatively affected by sorafenib, sunitinib, and pazopanib

Evaluation: screen prior to and intermittently during and after cardiotoxic treatment; baseline echocardiogram for all patients receiving anthracycline for leukemia, acute myeloid leukemia, or sarcoma; consider concurrent factors such as hypertension, dyslipidemia, diabetes, sedentary lifestyle, nicotine use, and obesity

Management: field of cardio-oncology — experts from cardiology and oncology making sure patients receive appropriate screening after cancer therapy, whether following radiation, chemotherapy, or targeted therapy, or if patients on maintenance, trastuzumab, or pertuzumab therapy; complications of cancer treatment related to cardiovascular system tend to occur 10 or 20 years after treatment; make sure patients have good survivorship plan and cardio-oncologist

Radiation therapy: associated with fibrosis; major factor for coronary disease; likely major factor for conduction disorders and other chronic pericardial diseases; risk depends on method of radiation administration, total dose, technique, other risk factors for cardiac disease, and administration of chemotherapy with cardiotoxic effects

Secondary malignancies: include development of contralateral breast cancer or myelodysplastic syndrome or leukemia if exposed to alkylating agents, topoisomerase inhibitors, or radiation; radiation also associated development of secondary malignancies of head and neck, lung, breast, and thyroid; smokers at much higher risk of developing secondary malignancies

Chemotherapy-associated neuropathy: see longer discussion in Dr. Swetz's "Pain Management" lecture; most prevalent with taxanes, vincas, and platinum-based therapies; oxaliplatin and paclitaxel most associated with acute neuropathic pain during infusions

Calcium, magnesium, and glutathione infusions: studies have not shown benefit in treating chemotherapy-associated neuropathy

Alpha-lipoic acid and acetyl-L-carnitine: studies have not shown benefit in treating chemotherapy-associated neuropathy

Gabapentinoids: most common treatment for chronic chemotherapy-associated peripheral neuropathy; gabapentin and pregabalin most common; gabapentin has dose-dependent ceiling; less bioavailable as dose increases; pregabalin highly bioavailable at all doses; more linear pharmacokinetics; adjust both in renal failure; both can be given three times daily; pregabalin has indication for twice daily; pregabalin federally controlled substance; gabapentin controlled only on state level

Serotonin–norepinephrine reuptake inhibitors (SNRIs): some evidence suggests benefit; duloxetine beneficial in neuropathy associated with diabetes; data extrapolated and used for patients with chemotherapy-associated neuropathy, particularly with musculoskeletal pain; venlafaxine can be used; less clear evidence that venlafaxine has as much potential analgesic effect *vs* duloxetine; might be due to powering of studies and study design

Topical treatments: proprietary agents include baclofen, ketamine, amitriptyline, lidocaine, and nonsteroidal agents like ketoprofen; no large studies to show benefit; helpful for some patients; avoids potentially challenging situations with toxicity

Scrambler therapy: new treatment for chronic chemotherapy-associated neuropathy; supported by works out of Europe and smaller studies within US; different frequency and duration of treatment from transcutaneous electrical nerve stimulation (TENS) unit

Suggested Reading

Fanous I, et al: Cancer treatment-related cardiac toxicity: prevention, assessment and management. *Med Oncol.* 2016 Aug;33(8):84; **Fehrenbacher JC:** Chemotherapy-induced peripheral neuropathy. *Prog Mol Biol Transl Sci.* 2015;131:471-508; **Mohandas H, et al:** Cancer-related fatigue treatment: an overview. *J Cancer Res Ther.* 2017 Oct-Dec;13(6):916-29.

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Symptom Management for BMT Patients

Muzaffar H. Qazilbash, MD, *Professor, Department of Stem Cell Transplantation, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX*

Mucositis: tissue injury caused by chemotherapy or radiation; cells lining oral or gastrointestinal mucosa damaged and sloughed off; common complication of high-dose chemotherapy and autologous or allogeneic stem cell transplantation; incidence varies from 50% to 80% in patients undergoing high-dose chemotherapy; regimens more commonly associated with mucositis include total-body irradiation and allogeneic transplants, especially when methotrexate used for graft *vs* host disease (GVHD) prophylaxis; risk factors include poor oral hygiene, dental disease, and periodontal disease; peak incidence occurs ≈1 week from start of high-dose chemotherapy; patients present with severe mouth pain; may lead to difficulty swallowing, which may interfere with oral nutrition; can also lead to mouth ulcers and infections with viruses and fungi

Prevention: chlorhexidine or other mouthwashes used to reduce tissue injury and risk of superinfection; cryotherapy prevents severity of mucositis; efficacy shown in clinical trials, especially with alkylators like melphalan; patients given ice chips preceding melphalan infusion; use as cryotherapy for ≈30 minutes; reduces incidence of mucositis by causing vasoconstriction in oral mucosa; growth factors tested in clinical trials; palifermin — keratinocyte growth factor; expensive; only reduces severity of oral mucositis with intense regimens, including total-body irradiation; not commonly used due to cost and lack of efficacy beyond oral mucositis; used before or with high-dose regimen before stem cell transplantation; use anti-infective prophylaxis, especially viral, as tissue injury promotes herpes simplex viral infections

Management: oral mucositis can lead to severe mouth pain, odynophagia, dysphagia, and compromised nutrition; treat with antiseptic mouthwash with chlorhexidine, salt, and soda; mucosal protective agents include amifostine; analgesics other component of treatment; many patients require intravenous opioids; patient-controlled analgesia, including morphine or hydromorphone infusion sometimes needed to control pain; topical analgesics like viscous lidocaine also used to reduce severity; sucralfate coats lining of pharyngeal and esophageal mucosa and may reduce severity; clinical trials have not shown significant benefit; hypothesis that glutamine for nucleotide synthesis and cell integrity may reduce severity of mucositis; conflicting results in clinical trials; several trials show lack of efficacy; only one pediatric trial showed effectiveness; local glutamine may have some activity; based on clinical trial data, no unequivocal benefits of total parenteral nutrition (TPN) in setting of high-dose chemotherapy and stem cell transplantation, especially with autologous stem cell transplantation, where complication reversible; TPN can be considered in patients with allogeneic transplantation who have received methotrexate for GVHD prophylaxis and where oral intake has been severely affected

Severity: graded from one to five; NCI (National Cancer Institute) common terminology criteria; grade one — asymptomatic or mild symptoms; grade two — moderate pain and ulcers that do not interfere with oral intake; grade three — severe pain interfering with oral intake; grade four — life-threatening consequences requiring urgent intervention; grade five — death

Diarrhea: common problem in patients undergoing high-dose chemotherapy and stem cell transplantation; most commonly caused by epithelial damage induced by alkylating agents or total-body irradiation; can occur in 50%-80%; no effective preventive therapy; mostly secretory diarrhea; patients lose large amounts of fluid because of epithelial damage interfering with intestinal absorptive capacity; diarrhea generally begins within 1 to 2 days of start of high-dose chemotherapy; peaks ≈7 days after start of chemotherapy; ≈50% overall incidence of diarrhea in stem cell transplant setting; delayed diarrhea in allogeneic transplant setting could be from acute GVHD

Presentation: begins with increased frequency of bowel movements and decrease in stool consistency, which becomes increasingly watery; sometimes associated with increased flatulence and abdominal cramping; watery diarrhea can be debilitating and potentially life-threatening due to severe dehydration and electrolyte imbalances; TPN required in rare cases; severity described by NCI common terminology criteria; increased severity with greater frequency and volume or decreased stool consistency; severity varies according to regimen used; no effective preventive strategy

Infectious etiologies: possible infection with *Clostridium difficile* if patients have received prior *antibiotics* or receive prophylactic antibacterial therapy; send stool samples to rule out *C. difficile*-induced diarrhea; if positive, treat accordingly; CT of abdomen warranted to rule out neutropenic enterocolitis if diarrhea associated with blood in stool, intense cramping, or peritoneal signs; If positive, treat with broad-spectrum antibiotics

Management: chemotherapy-related diarrhea self-limiting; requires treatment due to severity and duration; IV hydration and electrolyte replacement; TPN occasionally needed; treat *C. difficile* or neutropenic

enterocolitis with appropriate antibacterial therapy; loperamide or diphenoxylate with atropine can be used for initial therapy and symptomatic management
- Loperamide: more commonly used; given orally; can be repeated after each loose bowel movement to reduce peristalsis by inhibiting release of acetylcholine through activation of the mu-opioid receptors; reasonably effective anti-diarrheal agent; helps mitigate symptoms and reduces severity of diarrhea; frequency can be increased according to severity and frequency of diarrhea
- Diphenoxylate: synthetic opioid clinically related to meperidine; inhibits peristalsis and GI motility; associated side effects include drowsiness, flushing, dry mouth, rash, and nausea; no randomized trials comparing loperamide with diphenoxylate; loperamide considered more effective and associated with fewer side effects; loperamide preferred treatment in published guidelines for treatment of chemotherapy-related diarrhea
- Octreotide: used for patients with severe diarrhea refractory to loperamide or diphenoxylate; synthetic somatostatin analog effective in control of diarrhea associated with carcinoid syndrome and gastrin-secreting tumors, among others; given subcutaneously three times daily; dose can be escalated in patients with loperamide- or diphenoxylate-resistant diarrhea; several clinical trials have shown efficacy of octreotide with dose titrated to response; side effects mild and include bloating, cramping, and flatulence; hypersensitivity reactions sometimes occur
- Alternative options: tincture of opium widely used; not much published data; refer to gastroenterology for endoscopy to rule out other infectious causes including cytomegalovirus when diarrhea persists for more than 14 days after stem cell transplantation, especially in autologous stem cell transplantation setting where GVHD not concern

Nausea and vomiting: common side effects in patients receiving high-dose chemotherapy; feared by patients; no objective measurements for nausea; subjective; vomiting measured in volume; both nausea and vomiting divided into acute, chronic, or anticipatory; based on time related to administration of chemotherapy; acute nausea or vomiting happens within 24 hours of start of chemotherapy; delayed nausea or vomiting occurs >24 hours after administration of chemotherapy; peaks in 48 to 72 hours in patients who do not receive antiemetic preventive therapy; anticipatory nausea or vomiting occurs in patients with nausea and vomiting in previous treatments, especially with severe symptoms; conditional reflex happening before chemotherapy administered

- Mechanisms and pathophysiology: structural components of nervous system and neurotransmitters two different components resulting in nausea and vomiting; structurally, three areas in brainstem play important role in emetic reflex; mostly in lower brainstem; area postrema and nucleus tractus areas play role in development of acute nausea and vomiting; also mediated by afferent and efferent stimuli and certain neurotransmitters; in GI tract, enterochromaffin cells or damage to epithelial cells can release neurotransmitter, which can stimulate CNS in brainstem or cerebral cortex to stimulate nausea and emesis reflex; three most critical neurotransmitters include dopamine, 5-hydroxytryptamine (5HT3), and substance P and neurokinin-1 axis; inhibited by effective anti-nausea medications; 5HT3 or serotonin system associated with acute nausea and vomiting; substance P and neurokinin-1 system associated with delayed nausea and vomiting
- Risk factors: chemotherapy agent most important; cisplatin, anthracyclines like doxorubicin, and anthracyclines combined with cyclophosphamide highly emetogenic; others less emetogenic but dose-dependent; cyclophosphamide moderately emetogenic drug in lower or moderate doses; becomes highly emetogenic in higher doses as in stem cell transplant patients as part of a conditioning regimen; younger and female patients tend to have more severe nausea and vomiting than older patients; patients with prior history of heavy alcohol use tend to have less nausea and vomiting with emetogenic medications
- Antiemetic therapy: many different highly effective agents; divided into several broad categories
  - 5HT3 (5-hydroxytriptamine 3) inhibitors: include ondansetron, granisetron, and palonosetron; work through blocking 5HT3 receptors; available orally, intravenously, and some in transdermal patch; great efficacy and safety; side effects include QT interval prolongation; use caution when combining with agents that can cause QT prolongation to avoid cardiac arrhythmias; debilitating but not life threatening side effects include headache, constipation, and malaise
  - Neurokinin inhibitors: work on substance P/neurokinin pathway; important in acute and delayed nausea; especially delayed; include aprepitant, fosaprepitant, and rolapitant; very effective in combination with 5HT3 inhibitors and corticosteroids; highly efficacious; good safety profile; side effects mainly fatigue and malaise; not associated with QT prolongation seen with 5HT3 inhibitors
  - Corticosteroids: dexamethasone most common agent; clinical trials have shown combining dexamethasone with 5HT3 and/or neurokinin inhibitors improves efficacy and control of nausea and vomiting in all kinds of chemotherapy; especially in high-dose chemotherapy and conditioning regimens in autologous and allogeneic stem cell transplantation
  - Olanzapine: antipsychotic drug; demonstrated highly effective in anticipatory, acute, and delayed nausea and vomiting when used with chemotherapy regimens of high-to-moderate to low emetogenesis in phase three randomized trial; works by antagonizing 5-hydroxytryptamine-2 and dopamine-2 receptors; associated with neurological side effects, including drowsiness, extrapyramidal reactions, and orthostatic hypotension; safety well documented when used with proper monitoring
- Management: guidelines by American Society of Clinical Oncology and European Society of Medical Oncology (ESMO) recommend various antiemetic combinations to counter emetogenic potential of chemotherapy drugs; highly emetogenic regimens that have >90% incidence of nausea and vomiting — include cisplatin and high-dose chemotherapy, anthracyclines with high-dose cyclophosphamide; treat with combination of all major groups of antiemetics; example — 5HT3 inhibitor like ondansetron in combination with neurokinin inhibitor

like fosaprepitant in combination with dexamethasone and addition of olanzapine; guidelines published by American Society of Clinical Oncology recommend how to administer these agents; reference and review articles and meta-analyses; use combinations on day one; can be repeated on subsequent days or certain agents like steroids or olanzapine may be given on subsequent days depending on regimen; all four agents may not be necessary with moderately emetogenic chemotherapy; combination of 5HT3 inhibitor like ondansetron with steroids or 5HT3 inhibitor with neurokinin inhibitor like fosaprepitant and steroids can be given depending on intensity of nausea and vomiting; single-agent antiemetics like 5HT3 inhibitor ondansetron or single-agent dexamethasone may be used effectively in chemotherapy of low emetogenic potential; not often encountered with conditioning regimen

Delayed nausea and vomiting: less data on patients with delayed nausea and vomiting; most effective agents like 5HT3 inhibitors less effective in delayed nausea and vomiting; corticosteroids, olanzapine, and neurokinin inhibitors like fosaprepitant or aprepitant show significant activity in delayed nausea and vomiting; cannabinoids not incorporated in guidelines; relatively low efficacy; poorer safety profile than accepted agents; may be used in individual patients; generally not very safe or effective approaches; not enough validated data to recommend one experimental or dietary approach over another

GVHD: classically divided into acute vs. chronic, based on timing; acute GVHD seen within first 100 days and chronic GVHD starting thereafter; caused by cells of donor immune system, mainly T lymphocytes, which react against recipient organs and tissues as foreign and initiate inflammatory reaction; mainly T-lymphocytes and cytokines; classically divided into acute and chronic types based on timing; acute GVHD previously defined by appearance within first 100 days; chronic GVHD previously defined by manifestation after 100 days; NIH Consensus Criteria now identifies four subcategories; 1) classic acute GVHD — manifestations seen within first 100 days of allogeneic stem cell transplantation; 2) persistent, recurrent or late-onset acute GVHD — classical symptoms of acute GVHD seen after 100 days of allogeneic stem cell transplantation; 3) classic chronic GVHD — features of chronic GVHD can be seen at any time after allogeneic transplantation, but patient does not have any features of acute GVHD; 4) overlap syndrome — patients may present at any time post-allogeneic transplantation with features of both acute and chronic GVHD

Incidence: varies in literature from 10% to 50% or higher; depends on type of transplant and other factors

Acute GVHD:

Risk factors associated with acute GVHD: degree of HLA mismatch between donor and recipient among most important factors; disparity in gender; eg, higher risk when donor female and recipient male; intensity of conditioning regimen; myeloablative regimens, which cause more tissue injury, associated with higher risk; acute GVHD varies according to prophylactic regimen used; calcineurin inhibitor and methotrexate most common regimen; source of graft — peripheral blood, bone marrow, or umbilical cord blood; type of donor — related, unrelated, or partially matched related donor

Clinical manifestations of acute GVHD: skin, GI tract, and liver most commonly affected organs; skin and GI involvement most common; one prospective study showed almost 60% of patients presenting with skin and/or GI; remaining 40% had liver involvement, mostly in combination with skin or GI tract; maculopapular rash classic skin presentation; generally starts after white blood cell or neutrophil engraftment; roughly 2.5 to 3 weeks after allogeneic stem cell transplantation; rash can be generalized; may start at back of neck, involving ears, shoulders, palms of hands, and soles of feet; degree of skin involvement graded according to extent of skin involved; stage 1 — maculopapular rash involves <25% body surface area; stage 3 — generalized erythroderma; stage 4 — bullous formation and desquamation; GI tract involvement can be upper or lower; watery diarrhea most common manifestation of lower GI involvement; associated with cramping or excess gas and sometimes diarrhea mixed with blood; severity graded according to volume of diarrhea; stage 1 — volume between 500 mL to 1 L daily; stage 4 — >2 L of diarrhea associated with pain or ileus; upper GI involvement may present with nausea, indigestion, anorexia, or vomiting; liver involvement by itself relatively rare; reported in fewer than 5% of patients; generally involved with skin and/or GI tract; liver involvement graded according to bilirubin level; stage 1 — bilirubin of 2 to 3 mg/dL; stage 2 — bilirubin of 3 to 6 mg/dL; stage 3 — bilirubin of 6 to 15 mg/dL; stage 4 — >15 mg/dL; involvement of other organs much less common; includes eyes, kidneys, and lungs; photophobia with eye involvement; nephritis or nephrotic syndrome with kidney involvement; interstitial pneumonitis with lung involvement

Diagnosis of acute GVHD: highly suspected in patients undergoing allogeneic stem cell transplantation who develop skin, GI, or liver manifestations after neutrophil engraftment within first 100 days; can be seen later; histological confirmation with tissue biopsy can corroborate clinical impression; skin and GI biopsies with endoscopies relatively accessible; liver biopsies recommended, but carry risk of bleeding in patients already thrombocytopenic and with bleeding diatheses; intense research in use of biomarkers to diagnose GVHD; these include separation of tumorigenicity 2 (ST2), a member of IL-1 family, regenerating islet-derived 3-alpha (REG3 alpha), expressed by regenerating cells in gastrointestinal epithelium, and tumor necrosis factor receptor 1 (TNFR1) reflecting inflammation associated with TNF; these are three most commonly studied biomarkers in clinical trials; not yet affecting clinical decision making

Grading of acute GVHD: two popular grading systems; Glucksberg grading system oldest and most commonly used; takes stage of skin, GI, and liver into consideration; grades patients from grade one to four; grade one — lowest severity with early skin involvement and no liver or GI involvement; grade four — highest severity with advanced liver or GI

involvement; grading can help determine response and risk of treatment-related or GVHD-related mortality

Prevention of acute GVHD: no universally agreed prevention strategy for allogeneic stem cell transplantation; transplant centers have developed their own guidelines based on type of transplants they perform; 1) commonly used regimen includes a calcineurin inhibitor, either cyclosporine or tacrolimus, given in combination with methotrexate in fixed doses; methotrexate generally four doses at one, three, six, and 11 days after allogeneic transplantation; calcineurin inhibitors continued for up to several months after allogeneic transplantation; combination of calcineurin inhibitor and methotrexate most commonly used for myeloablative allogeneic transplantation; 2) calcineurin inhibitor with mycophenolate mofetil (MMF) second most common combination used for prevention; generally used for reduced intensity or non-myeloablative transplants; MMF replaces methotrexate for fixed duration; 3) use of T-cell depletion from graft being explored; no approach considered standard or superior to another; approaches include physical separation of T-cells from graft, *ex vivo* removal of T-cells from graft with agents such as monoclonal antibodies, or *in vivo* depletion of T-cells with pharmaceutical agents such as anti-thymocyte globulin or alemtuzumab; patients receiving immunosuppressive treatment at risk of infection; give appropriate bacterial, viral, and fungal prophylaxis

Treatment of acute GVHD: immunosuppression basic principle; choice of treatment depends on severity of disease; topical steroids can be used without systemic therapy for grade one GVHD; may achieve control in significant proportion of patients; systemic steroids used for patients with higher grade with more extensive involvement of skin, GI tract, or liver; high-dose systemic steroids standard of care; methylprednisolone most common agent; 2mg/kg body weight; steroids in grade two or higher GVHD continued for several weeks in responders; gradually tapered over period of months; this is time when disease flare may happen; 25% to 40% complete response rate with single-agent methylprednisolone; randomized phase three trial showed futility of combination of glucocorticoids with mycophenolate; trial closed; methylprednisolone or prednisone alone at 2 mg/kg body weight remains standard of care for treatment of grade two or higher disease; some guidelines suggest use of nonabsorbable steroids locally active in GI tract in addition to systemic steroids; example — budesonide in combination with systemic methylprednisolone; octreotide recommended to control severity of diarrheal symptoms in patients with severe diarrhea that has not responded to steroids

Second-line therapy: no consensus on second-line therapy for steroid-refractory or resistant acute GVHD; patients should be enrolled in clinical trials; some empiric evidence of efficacy for some agents used based on small phase two studies; include MMF. etanercept — recombinant TNF alpha receptor fusion protein, pentostatin — purine analog which inhibits T-cell proliferation, alpha-1 antitrypsin — circulating protease inhibitor which protects tissues from proteolytic degradation; ruxolitinib, selective JAK1/2 inhibitor used in treatment of primary myelofibrosis, has shown some efficacy; sirolimus also tested and used; extracorporeal photopheresis (ECP) has shown activity, especially in skin and liver acute GVHD; treatment consists of infusion of ultraviolet A-irradiated autologous peripheral lymphocytes collected by apheresis and incubated with 8-methoxypsoralen; approach also used for treatment of cutaneous T-cell lymphoma; phase two trials and retrospective analyses have shown activity of this treatment; monoclonal antibodies against T-cells, including alemtuzumab, brentuximab, and anti-thymocyte globulin antibodies directed against CD25; mesenchymal stromal cells have been used; hypothesized to reduce inflammation and promote tissue healing; failed to meet efficacy criteria in large clinical trials; may still be explored in refractory patients or in clinical trials

Chronic GVHD: classic with clinical manifestations seen at any time after allogeneic stem cell transplantation or as part of overlap syndrome with concurrent presence of acute and chronic GVHD manifestations, according to NIH consensus criteria; also occurs after allogeneic stem cell transplantation, most likely mediated by donor T-lymphocytes, cytokines, and other immune cells; overall incidence unknown; estimated from clinical trials and reports ≈40% of long-term survivors of allogeneic stem cell transplantation develop chronic GVHD; incidence varies from 5% to 80% in various studies

Risk factors for chronic GVHD: greater disparity between donor and recipient of allogeneic transplantation; gender disparity between donor and recipient, especially with female donor and male recipient; prior acute GVHD; use of peripheral blood stem cells *vs* bone marrow stem cell at graft

Most commonly affected organs: skin reported in >65% of patients; oral mucosa in ≈60%; liver in 52%; lungs in 50%; eyes in ≈50%; joints and fascia in ≈48%; lower GI tract in ≈30%; genital mucosa and skin in ≈12%

Skin involvement: most common feature of chronic GVHD; different from acute GVHD; classic manifestations include poikiloderma — combination of atrophy and hypopigmentation or hyperpigmentation in skin appearing as patches; lichen planus-like features — red-to-purple papules or plaques; sclerotic features — cellulite-like rippled appearance in skin due to thickening of fibrous septae within fat; morphia-like features — firm, hyperpigmented or hypopigmented skin-colored plaques

Eye involvement: includes dry eyes, cataracts, and corneal epithelial staining in about one-third of patients

Liver involvement: presents as liver function abnormalities; cholestasis with elevation in total bilirubin and serum alkaline phosphatase

Gastrointestinal involvement: dry mouth with oral ulceration and sometimes gingival inflammation and erythema; patients may present with dysphagia or esophageal ulcers; radiographic findings include esophageal webs and ring-like narrowing

Pulmonary involvement: may present as obstructive and restrictive changes; bronchiolitis obliterans characteristic, diagnostic finding; patients may show

abnormalities on pulmonary function tests; include decrease in FEV1 to FVC ratio; evidence of air trapping on high-resolution CT; histologic evidence of bronchiolitis obliterans on biopsy diagnostic of chronic GVHD

Musculoskeletal involvement: seen in ≈50% of patients with chronic GVHD; may manifest as fasciitis with limitations in joint mobility and skin changes; may present as myositis with muscle weakness with or without myalgias; muscle abnormalities can be manifested on electromyography; can demonstrate inflammatory myopathy; biopsy generally needed to confirm myositis

Hematopoietic involvement: hemolytic anemia and immune thrombocytopenia

Diagnosis of chronic GVHD: suspect in patients with risk factors and characteristic symptoms who have undergone allogeneic stem cell transplantation; criteria created by NIH consensus panel in 2005; chronic GVHD can be seen at any time after allogeneic stem cell transplantation as long as patients have characteristic findings according to criteria; identify signs and symptoms of chronic GVHD; divide into diagnostic or distinctive; no additional confirmation needed with diagnostic features; example — poikiloderma or esophageal web; distinctive features must be confirmed by skin biopsy; include skin depigmentation or sicca syndrome

NIH grading system for chronic GVHD: grades severity of chronic GVHD in every organ; chronic GVHD divided into mild, moderate, or severe types; mild — generally involves two or fewer organs with no clinically significant functional impairment; moderate — involves three or more organs with no clinically significant functional impairment or at least one organ with clinically significant functional impairment but no major disability; severe — involves major disability; according to data collected, ≈10% of patients had mild chronic GVHD; 60% had moderate; 30% had severe; severity associated with worse survival and quality of life

Prevention of chronic GVHD: unlike acute GVHD, no standard or agreed-upon regimen for prevention of chronic GVHD; number of agents have been used; anti-thymocyte globulin shown to reduce incidence of chronic GVHD in prospective, randomized trials; especially in patients undergoing unrelated allogeneic transplantation; consider in patients receiving unrelated donor transplantation

Treatment of chronic GVHD: depends on severity of involvement; no standard agreed-upon treatment; systemic treatment recommended for patients with three or more organs involved, thrombocytopenia, or severe involvement of individual organ; prednisone most commonly used treatment; usually given at 1mg/kg body weight; goal of tapering in 2 weeks and lowering dose to 1 mg/kg every other day in next several weeks; other agents have been tested in combination with prednisone without showing additional benefit; patients severely immunocompromised; require prophylactic antimicrobial therapy for bacterial, viral, and fungal infections; supportive care for each site important due to chronic symptoms and involvement of multiple organs; dry skin, oral and dental hygiene, dry eyes, vaginal dryness and sexual dysfunction, GI motility problems and dysphagia, shortness of breath due to bronchiolitis obliterans, and joint and musculoskeletal problems, including fasciitis and myositis

Second-line treatment: in patients with suboptimal response to prednisone or who failed to respond; calcineurin inhibitors only group of drugs that have shown activity; cyclosporine or tacrolimus can be started and continued for extended time; other therapeutic options with some activity include ECP, PUVA for skin involvement; MMF, sirolimus, ruxolitinib, ibrutinib, a Bruton tyrosine kinase inhibitor, rituximab, and low-dose IL-2; ursodeoxycholic acid for liver involvement; enroll patients in clinical trials if available

Suggested Reading

Bowen JM, et al: Advances in the understanding and management of mucositis during stem cell transplantation. *Curr Opin Support Palliat Care.* 2017 Dec;11(4):341-6; **Nassereddine S, et al:** Acute graft versus host disease: a comprehensive review. *Anticancer Res.* 2017 Apr;37(4):1547-55; **Zeiser R, et al:** Pathophysiology of chronic graft-versus-host disease and therapeutic targets. *N Engl J Med.* 2017 Dec;377(26):2565-79.

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Communication Challenges with Oncology Patients

Timothy Gilligan, MD, *Associate Professor of Medicine, Department of Hematology and Medical Oncology, Cleveland, and Vice-Chair for Education, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

How to Build Strong Relationships

Get to know patients as human beings: many oncologists like to start with social history rather than pushing it until later in the interview; benefits of this approach with seriously ill patients; when people are seriously ill, they often lose elements of their identity that are important to them; for instance, they may be unable to play with their kids, participate in an important hobby, work, or have sex; things that are important to how they think of themselves can be threatened; by finding out about who the person was before they were sick and what is important in their life, identity, and social support system, we can see them as they were and as they want to think about themselves; allow them to symbolically reclaim identity; thus, taking time to find out who the person is before we find out about their disease can be helpful

Listening: we spend a lot of time talking, and patients often spend a lot of their visit listening and having huge amounts of information delivered; make sure that we are listening as much as we are talking, if not more; listen actively to hear and understand rather than to plan a response; we can listen in a way that allows patient to tell story in own terms, not medicalized version that we often demand from them; for example, with pain, we might say, "How bad it is on a scale of one to 10?" or "Where it is located? Does it radiate? What makes it better? What makes it worse?" an alternative approach is to use open-ended questions — "Tell me more about your pain" or ask about impact on their life; "How has this symptom changed your life? Are there things you have had to give up? Are there things you no longer can do?" if we find out that pain is keeping someone from working, sleeping, or participating in an activity, that may be more important than whether it is a 6, 7, or 8

Assess patient's view of their condition: helpful to ask what ideas they have about what is going on; more and more patients are looking things up on the internet; they may have family members or friends who are telling them things; or maybe they know someone who had a similar condition; these past experiences may be enlightening or confusing; patient may have false or misunderstood information; if we learn this, we can speak to them in a way that is more helpful to them; it is helpful to know what the patient expects from us; What does success look like? What are they hoping for? What are they most worried about? these questions give much more humanistic picture of the impact of illness on patient than simply asking the more typical medical questions

Empathy: try to imagine what it is like to be this person; What would it be like to have cancer? What would it be like to have your doctor tell you that your cancer had come back or had spread to your liver or that additional chemotherapy would not be helpful? If we can start to imagine what it would be like to hear that, try to imagine what the patient is feeling, we can connect with them in a more meaningful way; part of the goal is for patient to feel heard and seen, that their oncologist gets it, has some sense of what they are going through even if we cannot fully understand it

PEARLS mnemonic for empathy: "P" stands for partnership, a reminder to align ourselves with patient; we are on same side; we want the best for them; sometimes they can start to feel in a visit that we are adversaries if we recommend one thing and they want something else; positioning ourselves on the same side may sound something like, "I want to make sure you get the best treatment," or, "I want to find an effective and safe treatment for your pain"

"E" is for emotion: naming the emotion; if someone is upset, it is important to notice it and let the patient know that we have noticed it; "You seem sad today. You seem frustrated today. You seem angry with me;" naming the emotion allows us to make progress in understanding it and moving forward; if we ignore the emotion, it will often escalate and get out of control; people may be scared to name emotions, particularly anger, thinking it will cause the person to boil over; in fact, the opposite is true; if we pretend it is not there, they are likely to become more angry; naming the emotion is like lancing an abscess because it allows it to drain; it may not drain immediately, but at least it allows the process to start

"A" is for acknowledgement: it sucks to have cancer; we need to find a way to say to our patients that we get it; "You're going through a hard time. This has been a terrible year for you. I know you are upset about this;" get it out in the open so it can air out, and the patient can feel seen and heard; they know we cannot make everything better, but it is important for them to know that we see what they are going through

"L" is for legitimation (validation): it is upsetting to be a cancer patient; a lot of frustrations can develop; sometimes when people get upset, they worry that it means something is wrong with them, that they should not be getting upset; for instance, my patients coming in for surveillance scans, even if they are in remission, often get very nervous the week before their scans because they are worried what they might show; the

week before CT scans is often a very unpleasant week for cancer patients; I try to normalize this for them — "many patients tell me that the week before scans is really tough;" they may or may not agree, but if it has been tough for them, it normalizes their feelings, and patients report that this is helpful

"S" is for support: "I want to help you. I want to do what I can for you;" it is similar to partnership; regardless of strategy we use, it is important to find some way to convey empathy to patients and it is important to say it out loud so that they can hear it; one thing that makes me sad at times is to see how much my colleagues care about patients and to realize that the patients do not see it; patients do not realize how much work is going on behind the scenes, conversations with colleagues, reviewing of scans and records; expressing empathy is a way of showing the patient that we care so that they can see it and feel it; it is a way of building stronger relationships with patients

Educating patients: the literature on patient retention of information from physicians is very disappointing; patients remember less than half of what they learn in physician visits and less than half of what they remember is accurate; our attempts to educate our patients are often not successful; if someone told me that less than 50% of the chemotherapy I prescribed ended up in the patient's body, I would see that as a major safety issue; I am also not satisfied if less than half of the information I am trying to convey is retained and only a quarter is accurately retained

Limit the amount of information given; think about what patients really need to know and what they want to know; try to be concise; focus on the key aspects that we want them to retain; shift from giving little 5- or 10-minute lectures on a subject and, instead, turn it into a conversation with back-and-forth; check with the patient about whether they are keeping up and what they are understanding; if I am going to be teaching about chemotherapy, I might start by asking what the patient knows about chemotherapy; Do they know anyone who has been through chemotherapy? What concerns do they have about chemotherapy? by engaging them more actively, we retain their attention and can frame the information in a way that is relevant to their interests and concerns

Teach-back: a powerful tool; can sound something like, "When you go home and talk to your family, what are you going to tell them I told you today?" or, if I have educated them about chemotherapy and febrile neutropenia, I might ask them, "What are you going to do if you have a fever? And what temperature would constitute a fever?" if they do not give me accurate answers to those questions, then I know I need to go back and do further education; if they can tell me, "If I have a fever, I'll go to the emergency room, and a fever is above 100.5 degrees," then I know we are on the same page

Shared decision-making: an intersection of three different things; 1) the medical literature or evidence-based medicine; what are the findings of studies that can guide our practice? it is the information database that we draw from; 2) our expertise as clinicians, the art of medicine; how do we apply that data to the individual patient? 3) the patient; they have expertise in terms of their bodies, their experience, their values, and their priorities; we want an overlap of the patient's values and priorities, the physician's expertise in terms of what makes the most sense medically for the patient, and the evidence from the medical literature; none of these three things alone is adequate to make decisions for patients; shared decision-making is particularly appropriate where there are multiple options, not a single best medical option; if someone comes in with acute appendicitis, we do not spend a lot of time on shared decision-making; with cancer, when someone is deciding on whether or not to have chemotherapy, especially in a non-curative setting, or when someone is trying to decide between surgery or radiation therapy for a cancer that can be treated either way, or if someone is trying to decide between a lumpectomy and a mastectomy, shared decision-making can have an important role; shared decision-making is particularly relevant when it comes to clinical trials

Informed consent: three key elements; one is voluntarism, that is, the person should have a free choice; the second is information disclosure; they need to have adequate information upon which to make a choice; it cannot be informed consent unless the patient is informed; information transfer is important and it needs to be done in a way that the patient or the decision-maker can understand it; the third piece is decision-making capacity; if this is lacking, the patient cannot truly consent to treatment; there are a number of things that can compromise capacity, including illness, age, and other factors; when we consent a patient for a treatment or a trial and when we participate in shared decision-making, one approach is to make a list of pros and cons of the various choices that could be made; we then want to apply the patient's priorities and goals to those pros and cons; pros and cons may be based on the medical facts, literature, and data, but how to choose or prioritize among pros and cons will be heavily influenced by who the patient is, what they want, what is most important to them; goal is to end up with a decision that is matched to the patient's priorities and goals, given the various options and what they have to offer

Clinical trials: several necessary steps; the patient needs to understand their current situation; do they understand their diagnosis, stage of disease, prognosis, and natural history of their illness? What will happen if we do not do anything, and what will happen if we intervene? What is the benefit that the treatment has to offer? It is hard for patients to make a sound decision about whether to consent for treatment if they do not understand what they are faced with and what will happen as a result of their choosing one of their options; secondly, they need to know what the standard-of-care options are; if the patient did not participate in a trial, what would we do and what would the expected outcome be? once the patient understands this, it will make more sense to them why we are looking at trials in their particular situation

Trial details: the ethical steps; 1) what is the purpose of the trial? 2) the type of research, what is being studied? 3) who will participate, who are the subjects in this trial? 4) it needs to be entirely clear that participation in the trial is voluntary, and that they will still be able to get care from us and our system whether or not they participate in a trial; they need to know that they can

withdraw from the trial if they want to, at any time, for any reason; they need to know the procedures and protocol involved, risks, benefits, and costs; those are the minimum requirements for informed consent for participation in human research trials

Giving bad news: in oncology, we regularly give people bad news, often the worst news they have ever heard, and in some cases, the worst news they can imagine; there are ways to do this more or less skillfully, and it is important to have a plan and a structure for how we have these conversations; these are not conversations in which to just wing it or follow our instincts; one framework for bad news conversations, called SPIKES, can help organize the conversation

"S" is for setting: where are we going to have the conversation? a hospital hallway is a terrible place to have a bad news conversation; it can also be very awkward to have a bad news conversation in a shared patient room, where there is a roommate; ideally, we can all be seated at eye level and have some privacy and quiet; planning for the conversation to take place at an appropriate time and place is important

"P" is for perspective: it is helpful to start the conversation with finding out what the patient already knows; I might ask them, "What have the other clinicians you've seen told you about what's going on?" or, "What information have you been given about your illness and the stage of your disease?" I do not want to make it sound like a test, so I don't ask them, "What do you know about your illness?" I think the burden is on us, in the healthcare system, to have educated them, so I tend to frame it as, "What have you been told?" if their perspective is very unrealistic, that gives me a warning that I am going to have to do some careful education about the patient's situation; it is possible that what I am going to say is going to be a real shock, and it is also possible that they already know what I am going to say; if they already know it, then I am going to frame it differently than if I think it is going to be a shock

"I" is for invitation: I want to give the patient some control over the conversation, so I might ask, "I have some results I would like to go over with you. Is now a good time for you?" maybe there is someone they want to be there (spouse, children, loved ones), who is not there, so there is a need to reschedule; it also gives them a little bit of control in a situation where they feel that they have none

"K" in is for knowledge: at that point, I am going to start giving information; I have chosen an appropriate time and place, found out what they already know, gotten their permission to have the conversation, and now I am going to give them the information; one of the key things about giving bad news is to give it as concisely and clearly as possible; sometimes we talk for a long time at this point in the conversation, and when I watch this happening, what I see is our hope that if we just talk long enough, we can somehow turn the bad news into good news — "I am afraid your cancer has spread to your liver, but I have this really great clinical trial I want to talk to you about that is very promising;" this is trying to distract them from the fact that we have given them bad news and that the consolation information we are using to try to make them feel better is really little consolation; it can be hard, because patients get upset when we give them bad news, and we may feel bad that we have made them cry, we have made them upset, but what has actually made them upset is the fact of their situation; if a patient starts crying in a situation like this, it often simply means that they understood what we said; crying is a normal human response to bad news, so it is important for us as oncologists to feel comfortable sitting quietly with someone who is upset; we do not do the patient any favors if we make it our goal to make them not upset

"E" is for emotions: this is a key time for empathy; if the patient starts to cry or gets angry, we cannot fix that, but we can empathize — "I know that was really hard to hear. I wish I had better news to offer. I can see that you are very upset;" these are much better responses than trying to cheer them up or distract them

"S" is for summary: the key here is that the patient needs to know the next steps; where do we go from here? when are we going to talk again? when are we going to talk about options for treatment? we do not want to leave them hanging and wondering what comes next, so tying things up is very important

Goals of care: unfortunately, we often wait until quite late in the course of disease before we start to have these conversations; it can be helpful to have them earlier; goals of care relate to shared decision-making; hard to make sound medical decisions for the patient if we do not know what their priorities are; if we wait until a crisis, we are making our lives and the patients' lives harder, because it is hard to discuss difficult issues during a crisis; I remember seeing a patient once who was at the end of the road in terms of treatment options; we had given him multiple lines of chemotherapy and he had ended up living longer than I had ever expected, but we were reaching the end; I went in to see him feeling very sad that I was not going to be seeing him much longer, and that we were going to have to transition to hospice; the patient looked at me and said, "Dr. Gilligan, you told me this day would come at the very beginning;" it made our relationship much easier at that point, that he had been operating from a clear understanding of what he was faced with from day one; when the time came, it was disappointing and it was sad, but it was not unexpected; those sorts of experiences motivate me to try to have these conversations earlier, so that patients know what is ahead of them, even if it is hard to hear

REMAP: a mnemonic for goals of care

"R" stands for reframe: this is an invitation to take a step back and look at the big picture; patients may be focused on moving from treatment to treatment to treatment while their condition is gradually declining, and I might say, "I'm wondering if it would be okay to take a step back and look at the big picture;" if we have talked about scan results and progression of disease, "I'm wondering if this would be a good time for us to talk about what this really means, in terms of the course of your disease?" or we might say, "What I hear from you is that you are getting more tired and you are not able to do as many of your activities as you used to. I am curious what you think is going on?" patients are often scared to have these big picture conversations because they are worried about what it means; but they are thinking about it, and it is easier for them if we allow that conversation to come out from inside their head and take place out loud with us so that we can help and support them

"E" stands for emotion: talk about their feelings; "What are you most worried about? What are you scared of? What are you concerned about?" allowing them to get it out in the open allows them to process it and, again, allows us to support them

"M" stands for map: moving towards a plan; we might ask, "What is most important to you at this point, given where things are with your illness? What are your priorities?" maybe the priority is to fight the cancer as aggressively as possible, but maybe the priority is to spend more time at home and have time with children or loved ones; or maybe the priority is to reach a certain milestone; we are charting a path forward, and that path is, to some extent, dictated by the patient's priorities

"A" stands for align: the purpose here is to try to align our plan with the patient's priorities, what is important to them

"P" is to propose a plan: to sum that up, we are reframing; Can we take a step back, look at the big picture? emotion naming; how are you feeling? What are you worried about? mapping out what is most important to you at this point; What are your priorities? then try to align their priorities with our options and propose a plan based on that; no need to use this structure if it is unhelpful to you, but it is very important to find a way to have those conversations with patients, so that the decisions we make about their treatment are lined up with what is important to them; one of the things driving the push to have these conversations earlier is that a lot of patients receive very aggressive care at the end of life that does not seem to offer meaningful benefit to them; if patients do not want to die in the ICU or do not want to die in the hospital, if we have these conversations about what they do want and what is important, we can make choices that are appropriate

End-of-life issues: having early conversations can be very helpful; if we know a patient has a cancer that is incurable and likely or expected to take their life, having early conversations about goals of care, code status, what is important to them is very important; it makes it easier when we get to the point of transitioning to hospice, because we have a sense of what is important to them and we can have that conversation in a way that is informed by our knowledge of their priorities and their values; they can feel that the care is more individualized; these are scary topics and it is easy to avoid them, but we can take better care of patients if we address them directly

Code status: the purpose of the code status conversation is not to arrive at a particular outcome, but to arrive at an outcome that is appropriate for the patient, given their condition, their values, and their priorities; best to frame it in terms of aligning with the patient; we want to give them the care that is most consistent with what they want; we do not want to put them through ACLS if that is not what they want; we do not want them to end up in the ICU on a ventilator or vasopressors if that is not what they want; if it is what they want, then having a plan for them to be full code makes sense for that patient; if they are making choices that seem terribly inappropriate to us medically, it is easier to have that conversation with the patient if we have done the things described earlier in this talk and established a trusting relationship in which the patient feels that we have some understanding of what they are going through and that we care about it

Summary: those are the main issues that I see in our challenging conversations with oncology patients; we owe it to ourselves to reflect on the fact that in this field, we have extraordinarily difficult conversations with patients; there are few professions in which people have to have such high stakes, difficult conversations with other human beings on a regular basis; there are few jobs in which people give so much bad news in such a short period of time as we often are called on to do; it is important to find ways to recharge our own batteries so we do not get burned out; I have found that investing in building stronger skills in this area has helped me to enjoy my job more and feel better about the work that I do; I hope you will find the same

Suggested Reading

Gilligan T et al. Patient-clinician communication: American Society of Clinical Oncology Consensus Guidelines. *J Clin Oncol.* 2017 Nov;35(31):3618-32; **Storm C et al.** Informed consent for chemotherapy: ASCO member resources. *J Oncol Pract.* 2008 Nov;4(6):289-95; **Childers JW et al.** REMAP: a framework for goals of care conversations. *J Oncol Pract.* 2017 Oct;13(10):e844-50. Doi:10.1200/JOP.2016.018796.

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Infectious Disease and Oncology

Steven M. Lipkin, MD, PhD, *Professor of Genetic Medicine, Gladys and Roland Harriman Professor of Medicine, and Vice-Chair of Genetic Research, Weill Cornell Medical College, Cornell University, New York, NY*

Cytotoxic chemotherapy: kills rapidly dividing cells; includes cancer cells and normal bone marrow, gastrointestinal epithelial, and skin epithelial transit-amplifying cells; lower gastrointestinal epithelial cells lining colorectum divide fastest of any cell type; once approximately every 3 days; bone marrow hematopoietic stem cells turn over once approximately every 10 days; skin cells about once every 14 days; thus, gastrointestinal epithelial, bone marrow, and skin epithelial cells are common locations for complications from chemotherapy cytotoxicity; bone marrow immune suppression generally results in a low of <500 cells/microliter (µL) a median of 10 to 14 days after initiation of chemotherapy

Immune system: divided into innate and adaptive immune arms; innate immunity comprised largely of neutrophils, macrophages, and monocytes; express pattern receptors to fight common bacteria or fungal gene products such as lipopolysaccharide (LPS) — major constituent of bacterial cell membranes, particularly of Gram-negative bacteria; innate immune response typically what signals bacterial and fungal infection through release of pyrogens — molecules promoting fever; adaptive immune system consists of T, B, and dendritic cells; takes weeks to months to mature; in neutropenic fever, focus is on neutrophil and myeloid cells from innate immune system

Neutropenia: arises when patients have suppressed neutrophils after cytotoxic chemotherapy; oncology patients with hematologic malignancies and solid tumors treated with cytotoxic chemotherapies have impaired myeloid and neutrophil cell numbers and reduced barrier integrity of gastrointestinal, skin mucosal, and pulmonary barriers; have elevated risk for bacteria and fungi to translocate across mucosal surfaces and promote sepsis; longer duration of neutropenia associated with higher risk of infection in cancer patients; risk particularly acute for patients with hematologic malignancies, who are extremely immunosuppressed at baseline, and patients in pre-engraftment stage for hematopoietic stem cell transplantation

Sepsis: systemic, bloodborne infection with bacteria or fungi; can often progress with minimal symptoms in neutropenic patients, because they have fewer immune cells to release cytokines, chemokines, and other pyrogen-signaling molecules; fever or rigors — involuntary shaking — can sometimes be only signs; can quickly progress to hypotension and circulatory shock; treat patients showing new organ dysfunction such as altered mental status, hypotension, or tachypnea urgently for sepsis; important to have high degree of suspicion for neutropenic fever early in patients having recently received cytotoxic chemotherapy; have low threshold for starting broad-spectrum antibiotic therapy

Neutropenic fever: commonly defined by two major features — absolute neutrophil count (ANC) <1000 and single oral temperature reading greater than or equal to 38.3°C/101°F; alternate criteria include temperature >38°C/100.4°F lasting >1 hour; oral or otic tympanic thermometry reliable methods for measuring body temperature; recent studies suggest body temperatures have decreased over past century in US and Europe because of changes in diet, sedentary lifestyle, and obesity; may provoke revision to thresholds

ANC: calculated by multiplying total white blood cell count by percentage of polymorphonuclear cells and bands; neutropenia — ANC <1500 cells or 1000 cells per µL; severe neutropenia — ANC <500 cells per µL; profound neutropenia — ANC <100 cells per µL; risk of clinically significant neutropenic fever infection increases as ANC falls below 500 cells per µL and with duration; example — >1 week increased risk factor for neutropenic fever; risk for bacterial sepsis further increases as ANC falls below 100 cells per µL

Fever: medical emergency in patient with neutropenia; broad-spectrum antibiotics first line of defense; administer <1 hour after arrival at healthcare setting such as clinic or emergency room; adjust antibiotic doses for impaired hepatic or renal function if present; monitor febrile neutropenic patients frequently for blood pressure, heart rate, respiratory rate, and temperature; healthcare workers should also assess mental performance status and ability of patients to take in oral fluids and medicine, particularly for patients with chemotherapy-induced mucositis; administer oral or IV fluids to maintain urine output >0.5 ml/kg of patient weight per hour in patients with normal renal function; obtain blood cultures before initiating antibiotic therapy, so antibiotics do not influence growth of blood cultures

Empiric coverage: gram-positive, gram-negative, and anaerobic bacteria and fungi; gram-positive bacteria from gastrointestinal tract or skin most frequent infections in neutropenic fever patients; gram-negative bacterial infections also prevalent; anaerobic microbiota common in colorectum but specific anaerobic antibiotics typically not empirically administered; anaerobic bacterial sepsis occurred in <4% of cancer neutropenic fever patients in recent meta-analysis; also increased risk of invasive fungal infection, most notably with candida, aspergillus, or fusarium; initial empiric coverage for fungal infections

typically not given without high index of suspicion, such as if patient has had recent fungal infection

Empiric therapy: typically consists of antipseudomonal beta-lactam agent such as ceftazidime, cefepime, meropenem, imipenem/cilastatin, and piperacillin/tazobactam; ceftazidime monotherapy also can be efficacious, but ceftazidime monotherapy has rising resistance rates among gram-negatives and limited efficacy against gram-positive bacteria such as streptococci; ceftazidime alone should not be used with risk of gastrointestinal tract translocation and mucositis by streptococci; standard doses of agents for initial monotherapy include cefepime 2 grams IV every 8 hours; meropenem 1 gram IV every 8 hours; imipenem/cilastatin 500 mg IV every 6 hours; piperacillin/tazobactam 4.5 grams IV every 6 to 8 hours; ceftazidime 2 grams IV every 8 hours

Other antibiotics: vancomycin, antifungals, aminoglycosides, or fluoroquinolones added when patients have sepsis, hypotension, and mental status changes, especially in cases where patients have invasive disease such as cellulitis or pneumonia; modifications used for patients at risk of infection with specific antibiotic-resistant organisms from recent infections; metronidazole or clindamycin alternatives for anaerobic coverage of patients with neutropenic fever with sinusitis, necrotizing mucositis, periodontal or perirectal cellulitis, intraabdominal infection, or pelvic disease; cephalosporins not typically used for patients allergic to penicillin; patients with immediate-type hypersensitivity reaction causing wheezing or skin hives should not receive beta-lactam antibiotics or carbapenems; alternatives include aztreonam plus vancomycin or ciprofloxacin plus clindamycin; fluoroquinolones such as ciprofloxacin should not typically be used in patients recently receiving them orally for prophylaxis before chemotherapy or preparation for bone marrow transplant; study of 14 randomized trials showed gram-positive antibiotic coverage added to standard empiric therapy did not reduce all-cause mortality in patients with cancer and neutropenic fever

Summary: longer patient has neutropenia (ANC <500 or <100) after cytotoxic chemotherapy the higher the risk of neutropenic infection; early recognition of neutropenic fever in cancer patients critical to successful outcomes; rapid initiation of antibiotic therapy in vulnerable patient population with high mortality and morbidity extremely important; can be life-saving

Fungal infections in cancer patients: interest in antifungal prophylaxis for high-risk cancer patients receiving chemotherapy driven by poor treatment outcomes with delayed initiation of therapy; rising incidence of life-threatening invasive fungal infections in cancer patients overall, particularly in those with hematologic malignancies; difficulty in establishing differential diagnosis early in course of infection among critical parameters; oncology patients at highest risk for fungal infections those with greatest degree of immune suppression; often include hematological malignancy patients, those receiving allogenic bone marrow transplant, or both

Etiology: aspergillus has become most common [fungal?] infection in cancer patients; candida second leading cause of invasive fungal infections in cancer patients; attributable to increasing use of antifungal prophylaxis targeting candida species; aspergillus most common mold pathogen in patients with malignancies; highest rates in patients with acute myelogenous leukemia (AML); invasive aspergillosis ranges from 5% to 10% of patients over course of disease; patients with relapsed or refractory AML receiving salvage chemotherapy among those at highest risk; inhalation into respiratory tract most common mechanism of infection by aspergillus; pneumonia and sinusitis most frequent manifestation of invasive aspergillosis

Candida species: account for second-most common cause of fungal infections and leading cause of invasive fungal infections in cancer patients; incidence of invasive candidiasis in patients with hematologic malignancies not receiving antifungal prophylaxis ranges from 10% to 25%; gastrointestinal tract primary route of infection; caused by mucosal injury after concomitant cytotoxic chemotherapy and translocation through gastrointestinal epithelium to abdomen; candida also common fungal cause of central venous catheter-associated infection; candida subspecies causing infections include *Candida albicans*, *Candida glabrata*, and *Candida tropicalis*

Fusarium species: another important cause of fungal infection in cancer patients; *Fusarium solani* most frequent; other causes include *Fusarium oxysporum*, *Fusarium verticilloides*, and *Fusarium proliferatum*; fusarium colonizes skin; dermal infections most common

Preventative therapy for fungal infections: depends on specific organism and susceptibility characteristics; a recent meta-analysis of four randomized trials comparing different types of systemic antifungal prophylaxis using fluconazole, itraconazole, posaconazole, clotrimazole, and placebo in cancer patients receiving myelosuppressive chemotherapy showed antifungal prophylaxis reduced all-cause mortality by ≈38% and invasive fungal infections by 67%; fluconazole most commonly used regimen for high-risk patients before allogenic stem cell transplant; alternatives include voriconazole and posaconazole

Effective antifungal therapy in cancer patients: depends on specific organism and patient ANC as important marker of immune status; for non-neutropenic patients with infection, candida and aspergillus most common; initial therapy includes an echinocandin; choices include anidulafungin, caspofungin, or micafungin; fluconazole alternative in patients not critically ill and those unlikely to be infected with fluconazole-resistant organisms such as *Candida glabrata* or *Candida krusei*; oral fluconazole can be used in most patients; patients unable to take oral medications or with poor gastrointestinal absorption can use fluconazole IV; lipid micelle amphotericin B another alternative if patients resistant to other antifungal agents; amphotericin B less well-tolerated; problematic in patients with renal insufficiency; echinocandins, including anidulafungin, caspofungin, or micafungin indicated for neutropenic patients infected with candida or aspergillus species

Second-line therapy: includes lipid micelle amphotericin B; fluconazole indicated next as alternative; should not be used in critically ill, hemodynamically-unstable, or recent azole exposure patients, such as with prophylaxis; for those situations, echinocandins such as anidulafungin, caspofungin, or micafungin, or amphotericin B preferred as frontline therapy; for neutropenic patients infected with *Candida glabrata* or *Candida krusei*, voriconazole

preferred over fluconazole; for patients infected with *Candida krusei*, resistance to fluconazole common; treatment with voriconazole or echinocandins preferred

***Candida auris*:** important emerging pathogen in US and Europe; infections multidrug-resistant; associated with high mortality rates on multiple continents; for patients with systemic or invasive fungal infections with Candida auris, initial therapy includes echinocandins such as anidulafungin, caspofungin, or micafungin; drug-resistance to other antifungal therapy classes, including azoles, frequent; because of multidrug resistance and potential for infection spread, infection control precautions such as used for Mycobacterium tuberculosis-infected patients similarly used for patients colonized or infected with Candida auris

Summary: many cancer patients at high risk for fungal infections; patients at highest risk include those with hematologic malignancies, neutropenic patients, and those who have recently received cytotoxic chemotherapy or allogenic bone marrow transplants; effective prophylaxis and therapies available, but fungal infection must be recognized early

Central line infections in cancer patients: central venous catheters increasingly used in inpatient setting for oncology patients; use recently increasing in outpatient setting; central venous catheters provide long-term venous access for administering drugs and taking frequent diagnostic blood specimens; bloodstream infections important cause of overall morbidity and mortality; ≈90% of catheter-related bloodstream infections annually in US occur with central venous catheters; 24,265 central line-associated bloodstream infections in 2017; incidence of nosocomial bloodstream infections in cancer patients ≈60 cases per 10,000 hospital admissions; ≈51% of cases occur in ICU; ICU most frequent healthcare facility site for patients carrying venous catheters; all intravascular devices confer risk of infection; non-tunnel central venous catheters and pulmonary artery catheters carry greater risk compared to peripheral venous catheters

Site of catheter placement: affects risk of infection; risk of bloodstream infection in cancer patients elevated with femoral or internal jugular placement compared to subclavian vein placement in neck; other important factors increasing infection risk include duration of central venous catheter placement, type of catheter material, acute *vs* non-acute insertion, and skills of inserter

Etiology: prior to 1990s, gram-negative anaerobes predominant organisms associated with central venous catheter infections; gram-positive aerobes and candida species have since increased; most common organisms include coagulase-negative staphylococci, staph aureus, enterococci, candida fungal species, klebsiella, *E. coli*, enterobacter, and pseudomonas; in patients with hematologic and non-hematologic malignancies, gram-negative pathogens have increased in prevalence; fungi, most commonly candida colonizing skin, comprise ≈25% of central venous catheter infections; especially problematic in patients with high glucose-containing fluids going through indwelling catheters; enhanced recognition and reporting as pathogens most likely reason for increased rates of coagulase-negative staphylococcal infections; widespread community use of broad-spectrum antibiotics and increased use of intravascular devices have also increased prevalence

Treatment: removal and replacement of offending indwelling catheter first step in clearing catheter infection; catheter removal especially important with staph aureus, *Pseudomonas aeruginosa*, drug-resistant Gram-negative bacilli, and fungi such as candida

Antibiotic lock therapy: injection of concentrated antibiotic solution into catheter lumen to achieve drug level high enough to kill bacteria within biofilm of catheter; biofilms — dense aggregations of bacteria in extracellular matrix; useful adjunctive therapy administered with systemic antibiotic therapy in situations where catheter cannot be removed

Empiric antibiotic therapy for catheter-related infections: guided by gram stain results; IV vancomycin for gram-positive organisms; isolates with vancomycin minimum inhibitory concentrations of >2 mcg per ml preferred for hospitals with high rates of methicillin-resistant staph aureus; additional agents include daptomycin, ceftaroline, tedizolid, telavancin, dalbavancin, oritavancin, and others; cornerstones of empiric therapy for gram-negative bacilli include monotherapy with ceftazidime, cefepime, piperacillin-tazobactam, imipenem, and meropenem; for candidemia, empiric therapy includes monotherapy with echinocandins such as caspofungin, micafungin, or anidulafungin; fluconazole or amphotericin B can also be used; patients known to be colonized with drug-resistant organisms should receive empiric antibiotic therapy selected accordingly

Summary: central line infections common in oncology patients whether or not immunosuppressed; infections usually treatable; patients expected to make full recoveries if offending indwelling catheter removed, and appropriate antimicrobial therapy quickly initiated

Viral infections in cancer: cytotoxic antineoplastic chemotherapy frequently suppresses myelopoiesis and developmental integrity of mucosal surfaces such as gastrointestinal tract, lungs, and skin; causes cancer patient risk for invasive infections due to viruses; intensity of innate immune component of inflammatory response typically muted in neutropenic patients with ANC <1000; fever may be earliest and sometimes only sign of infection; effectively prevented with antiviral prophylaxis; especially for human herpes viruses

Herpes viruses: most herpes simplex virus 1 and 2 infections caused by reactivation of latent infections; likelihood of reactivation influenced by intensity of chemotherapy regimen and relative impact upon virus-specific cytotoxic T-lymphocyte immune response; example — reactivation occurs in >50% of seropositive AML patients who have had induction chemotherapy; similar numbers of herpes simplex virus 1 and 2 reactivation seen in patients with hematopoietic stem cell transplant in absence of antiviral prophylaxis; infection can cause wide variety of symptoms; include encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular disease; physical exam will often also reveal vesicles on lips, genitalia, skin, and perianal areas; ulcerations of oral and upper gastrointestinal mucosa frequent and often manifest as pain

Herpes zoster: related virus; caused by varicella zoster virus; often presents in atypical disseminated pattern involving multiple dermatomes and widespread skin rash; median time to reactivation for herpes zoster infection in

lymphoma patients ≈5 months following chemotherapy; immunocompromised patients with disseminated varicella zoster virus infection can also frequently have pulmonary involvement; patients can be placed on respiratory precautions to prevent aerosolized transmission to susceptible individuals and hospital staff

Management: most patients with herpetic infections respond well to acyclovir and valacyclovir-containing regimens; typically very effective if administered promptly; adoptive T-cell therapy being pursued for refractory infections; only performed in specialized centers; adoptive immunotherapy also performed for other viruses such as Epstein–Barr virus

Immunization in cancer patients: immunosuppressive mechanisms promoted by different malignancies and cytotoxic chemotherapy regimens that deplete leukocytes; preventing infection with immunization extremely important for almost all cancer patients; even routine infections can result in substantial morbidity and mortality in immunosuppressed patients; antimicrobial therapy often less effective than in unimpaired hosts without cancer; immunization important modality to prevent these infections; number of cancer patients unable to display protective immune response when vaccinated; live virus vaccine immunization can also drive unchecked viral proliferation of even attenuated strains that would be safe in patients without cancer; probability of being infected and inability to prevent infection by immunization highly correlated to state of immune compromise; when cancer patients vaccinated, vaccine-promoted immune response cannot be taken for granted; successful immunization may require additional testing, example — antiviral drug prophylaxis during influenza season; United States Advisory Committee on Immunization Practices and Infectious Disease Society of America provide detailed instructions for vaccinations of immunocompromised patients

Inactivated vaccines: administer in non-pediatric cancer patients before initiation of chemotherapy or radiation by at least 2 weeks; when splenectomy performed as surgical therapy, vaccinations should be given at least 2 weeks prior to surgery; vaccinations should occur at least 2 weeks prior to therapies when chemotherapy includes immunosuppressive drugs, which can include cytotoxic chemotherapy and other immune agents, such as methylprednisolone; if inactivated viruses administered during chemotherapy, follow-up antibody tests should be performed with titering to be considered protective; vaccines can be re-administered after completion of chemotherapy, radiation therapy, or immunotherapy; typical to wait at least 2 to 4 weeks after completion of these treatments

Live vaccines: for chemotherapy, radiotherapy, immunotherapy or splenectomy patients, live virus vaccines should be given at least 4 weeks prior to planned procedure; if patients have already initiated chemotherapy before consideration of vaccination, live vaccines should be avoided at all times during course of cancer chemotherapy due to potential for vaccine-derived infections

Patients with B-cell cancers: monoclonal antibodies such as rituximab frequently given to deplete all normal and malignant B cells; for patients with leukemia, lymphoma, and other malignancies in remission who have received monoclonal antibodies or chemotherapy, inactivated vaccines should not be given for at least 3 months following completion of therapy; in patients who have received anti-B-cell antibodies, administration of live vaccines should be delayed for at least 6 months following radiotherapy, immunotherapy, or splenectomy

Bacterial inactivated vaccines: include tetanus toxin, diphtheria toxin, and pertussis; administer booster immunization for all solid and hematologic malignancy patients; Tdap vaccine generally preferred; like viral inactivated vaccines, administer at least 3 months prior to immunosuppressive or cytotoxic chemotherapy

Pneumococcal pneumonia: important cause of death in many cancer patients; particularly important for pneumococcal vaccination to be given prior to starting treatment; different pneumococcal vaccines have different epitope coverage; PPSV 23-23-valent polysaccharide vaccine recommended for immunocompromised adults; PCV 13-13-valent pneumococcal conjugate vaccine also recommended for oncology patients; vaccines have several non-overlapping components and can be used together; for patients who have not previously received either PPSV 23 or PCV 13, PCV 13 should be given first followed by PPSV 23 8 weeks later; for patients who have previously received one or more doses of PPSV 23, single dose of PCV 13 should be given 12 months or more after last PPSV 23 dose; for patients requiring additional doses of PPSV 23, first such dose should be given no sooner than 8 weeks after PCV 13 and at least 5 years after most recent dose of PPSV 23; PPSV 23 tends to produce more robust response; pneumococcal IgG2 concentrations in serum correlate well with vaccine efficacy; PPSV 23 immune response typically diminished after chemotherapy; vaccine responses lowest in patients with leukemia, head and neck cancer, and Hodgkin lymphoma; with Hodgkin lymphoma, vaccine responses can remain impaired for up to 7 years following chemotherapy; priming with PCV 7 seven-valent pneumococcal conjugate vaccine improves response to later vaccination with PPSV 23 and PCV 13

Meningococcus vaccination: recommended for cancer patients; evidence vaccine response hypoactive in some patients

***Haemophilus influenzae* vaccine:** not routinely recommended for adult cancer patients; however, is indicated for patients having hematopoietic cell transplant or adult oncology patients at significant risk of developing Haemophilus influenza B

Influenza vaccine: adults with cancer should receive inactivated influenza vaccine annually; however, for patients receiving anti-B-cell antibodies such as rituximab, vaccine administration should be delayed for at least 6 months; immunization of family members for influenza strongly recommended; presently less evidence to justify giving second dose of influenza vaccine within same season; best to administer >2 weeks before chemotherapy, immunotherapy, or radiation therapy; alternatively immunize at least 3 months after completion of chemotherapy; if neither option possible, immunize patients 1 week after first chemotherapy cycle; observational data from patients with solid tumors receiving chemotherapy showed immunization on day four or five of chemotherapy cycle more immunogenic than that administered on day 16; conflicting results regarding immunogenicity of immunization on first day of chemotherapy — some evidence shows worst

immunogenicity; data controversial; patients with hematologic malignancies particularly in acute B- and T-cell leukemias at greatest risk of death from influenza; reported seroconversion rates to inactivated influenza vaccine in patients with cancer range between 25% and 70%; two-dose regimen does not improve response further; meta-analysis of smaller studies regarding influenza seroconversion and seroprotection after vaccination showed approximately one-third of patients with cancer had strong response compared to control subjects; likelihood of response affected by intensity and type of chemotherapy and timing of vaccine administration in chemotherapy cycle; for patients receiving B-cell-depleting therapies after vaccination, concern of weakening immune system; example — zero of 67 patients receiving rituximab within previous 6 months developed seroprotective titers against influenza in one study of non-Hodgkin lymphoma patients; 82% of controls developed seroprotective titers following vaccinations; intranasally administered live attenuated influenza virus not recommended in immunocompromised individuals; live attenuated influenza virus can be used to vaccinate family members of oncology patients

Hepatitis B vaccine: important consideration for cancer patients because of frequent exposure to blood products; vaccine is recombinant, so there is no risk of live virus; all unvaccinated cancer patients should receive hepatitis B vaccine; regimens that include doubling standard antigen dose or administrating additional doses may further increase response rates

Hepatitis A vaccine: can be co-administered with hepatitis B vaccines at same time to cancer patients; often effective strategy because many risk factors for hepatitis A and B overlap

Human papillomavirus vaccination (HPV): also important for cancer patients; HPV vaccination very effective to prevent cervical, anal, and penile cancer; cancer patients with indication for HPV vaccination should be immunized, typically before chemotherapy; if not possible, vaccination should occur after completion of chemotherapy

Herpes zoster vaccine: herpes zoster illness more common in immunocompromised patients; vaccine is recombinant; used for prevention of shingles; recombinant zoster vaccine given as two doses 1 to 2 months apart; safe and immunogenic in randomized trial of cancer patients with solid tumors receiving chemotherapy; humoral and cell-mediated immune responses persisted at least 1 year after vaccination

Summary: patients with cancer at increased risk for many serious infections preventable by vaccination; patients with hematologic malignancies generally immunosuppressed to greater degree than those with solid tumors; for patients with solid tumors, immunosuppression more likely to result from poor performance status, malnutrition, or anatomic obstruction; example — liver masses obstructing biliary drainage; almost all cancer patients can benefit from vaccination with minimal side effects; considered important aspect of cancer care and immunoprevention

Suggested Reading

Bell T, et al: Prevention of central line-associated bloodstream infections. *Infect Dis Clin North Am.* 2017 Sep;31(3):551-9; **Gustinetti G, et al:** Bloodstream infections in neutropenic cancer patients: a practical update. *Virulence.* 2016 Apr;7(3):280-97; **Shah MK, et al:** Immunizing cancer patients: which patients? which vaccines? when to give? *Oncology (Williston Park).* 2018 May;32(5):254-8.

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Management of Brain Metastases

Adam Sonabend Worthalter, MD, *Assistant Professor of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL*

Brain metastases: most common malignant brain tumors; particularly for patients with lung cancer, breast cancer, and melanoma; melanoma patients have 20% to 50% lifetime risk of developing brain metastasis; triple-negative breast cancer has high incidence of brain metastasis; non-small cell lung cancer has ≈15% to 20% risk; because there are more patients with lung cancer than melanoma, there are more patients with lung cancer-related than melanoma-related brain metastasis; renal cell carcinoma can also lead to brain metastasis; histologies rarely leading to brain metastasis include colon, esophageal, and pancreatic cancers

Intracranial *vs* brain metastasis:

- Metastases in brain parenchyma: penetration of blood-brain barrier; can occur inside brain, cerebellum, brainstem; rarely spinal cord; ventricular metastasis sometimes occurs
- Dural metastasis, particularly meningeal metastasis: metastases grow in dura mater and can extend into and arise from bone; example — prostate cancer rarely or never manifests as brain metastasis but often manifests as dural-based lesions that can be confused with meningioma; involve bone and dura; can put pressure on brain and cause symptoms; dural metastases not beyond blood-brain barrier; can receive treatment via systemic circulation
- Leptomeningeal disease: distinct from dural or meningeal metastasis; disease in subarachnoid space; poor penetration of systemic chemotherapy; intrathecal chemotherapy possible; often presents in context of advanced breast cancer; can manifest as hydrocephalus and cranial neuropathies, including chin numbness and weakness, facial pain, and double vision; manifests radiographically as enhancement in cerebellar vermis near lower cranial nerves or in brain sulci; does not necessarily mean thickened dura; hydrocephalus can lead to nausea, vomiting, lethargy, papilledema; when affecting spinal cord, can cause painful radiculopathy, cauda equina syndrome, weakness in arms and legs, tingling, and numbness
  - Diagnosis of leptomeningeal disease: clinical diagnosis; changes prognosis; sometimes made with MRI or obtained by performing large volume lumbar punctures; negative large volume lumbar puncture that does not reveal positive cytology does not rule out leptomeningeal disease; often requires two taps
  - Management: active treatment or palliative approach; some chemotherapeutic agents penetrate blood-brain barrier into cerebrospinal fluid compartment; prognosis very poor; survival usually months; two methods of managing symptomatic hydrocephalus; 1) ventriculoperitoneal shunt — cerebrospinal fluid diverted into abdominal cavity; 2) Ommaya reservoir — does not drain anywhere but remains in plastic bubble underneath skin connected to ventricular catheter; patient tapped intermittently; shunting leads to less intervention later, as patient does not need to be constantly tapped; inevitably leads to seeding of peritoneal cavity with tumor cells; tumor cells can also occlude shunt valve and shunt system; advantage of Omaya reservoir is possibility of liver and intrathecal chemotherapy; nuanced decision depending on histology and agents considered; hybrid approach places shunt valve that can be turned off to prevent distal runoff; off-setting mechanical by pushing over skin without surgery or magnetic approach; allows shunt to transiently be turned into tapping reservoir where one can inject chemotherapy in liver and directly into brain; leptomeningeal disease in brain often handled with whole-brain radiation; spinal radiation in palliative setting when disease is in spine

Screening: recommendations for breast cancer do not involve screening MRI for brain metastasis; asymptomatic brain metastasis diagnoses often take place in context of advanced cancer, when patient involved in clinical trial requiring screening MRI; patients at high risk should be evaluated carefully; high-risk conditions include triple-negative breast cancer, melanoma, renal cell carcinoma, and patients with neurological symptoms and history of cancer

Diagnosis of single brain metastasis: consider performing biopsy when brain metastasis suspected based on imaging; 89% of patients with history of cancer and single enhancing lesion have brain metastasis; means that 11% of lesions different from initial cancer diagnosis; biopsy or resection indicated in newly diagnosed single brain lesion, but depends on clinical context; do not perform on candidates with poor performance status

Diagnosis of multiple brain metastases: histological confirmation often unnecessary; in presence of two different systemic cancers, occasionally necessary to biopsy brain metastases to determine which of cancers is active

Diagnosis of brain metastasis without history of cancer: surgical resection first choice if patient symptomatic from single intracranial lesion, for example, if there is seizure or weakness related to mass effect; helpful diagnostically and therapeutically; can relieve patient symptoms, improve performance status, and lead to better outcome; surgery for single intracranial brain metastasis in patients with otherwise good systemic control or amenable to systemic

therapy can prolong survival; craniotomy for resection of single, symptomatic brain lesion first step even if CT or PET shows easily biopsied, less invasive foci outside brain; can likely avoid additional, unnecessary procedures; example — systemic treatment can evolve quickly if patient receives craniotomy for resection and histology consistent with non-small cell lung cancer; biopsy of lung lesion afterwards might be obviated, as diagnosis already made

Imaging: CT often reveals mass effect or brain edema, but not best choice for evaluating disease; CT with contrast can be helpful if patient not amenable to MRI; MRI gold standard for diagnosis; small cell lung cancer and non-small cell lung cancer often present as several lesions; renal cell carcinoma and melanoma often produce single lesions, which are often hemorrhagic and present as blood clots first diagnosed on CT; can manifest as seizures and acute deterioration, because bleeding brain metastases can grow rapidly

Options for management of brain metastasis: depends on multiple factors; surgical resection with microsurgical techniques if necessary, radiosurgery, whole-brain or other types of radiation, immunotherapy, laser interstitial thermal therapy (though there are not many randomized, controlled studies supporting its use), and some chemotherapies exhibiting brain penetration; immunotherapy has taken new role in context of brain metastasis, particularly for systemic diseases such as melanoma and renal cell carcinoma and sometimes lung cancer; chemotherapeutic drugs include newer agents and targeted therapies; osimertinib novel-generation tyrosine kinase inhibitor for EDFR-mutant non-small cell lung cancer; exhibits good penetration to CNS

Management strategies: depends on tumor size, mass effect and symptoms, number of lesions, location/accessibility of tumor, and whether tumor hemorrhagic; clinical correlation indicated; symptoms related to mass effect or pressure on brain generally improve with short course of steroids; good indicator that removing lesion will lead to symptomatic improvement; however, resection of tumor or control of disease will not lead to improvement of symptoms if tumor has destroyed brain tissue; consider number and placement of metastases; hemorrhagic tumors tend to rebleed and cause seizures; often patients with Trousseau's syndrome in need of anticoagulation due to deep vein thrombosis, pulmonary embolism, or high risk of developing thrombotic complications elsewhere; hemorrhagic brain metastasis increases risk of poor outcome if patient requires anticoagulation; resection of surgically accessible hemorrhagic lesion advised in most cases

Comorbidities and surgical risk: complication avoidance relates to surgical indications based on patient performance and systemic status; be more aggressive in patients with high Karnofsky performance status living independently; patients with poor functional status, requiring-24 hour assistance, wheelchair bound, or comatose not ideal candidates for aggressive treatment

Systemic disease status: among most important determinants of treatment strategy for brain metastasis; clinical trials for resection of brain metastasis have sometimes shown prolongation of survival; sometimes have not; systemic disease status relates to difference between trials showing benefit in survival and trials that do not; primary histology also important; example — patient with small cell lung cancer, even if symptomatic, should undergo whole-brain radiation therapy; tumors extremely radiosensitive; surgery not indicated; check for molecular features for targeted therapy; example — EGFR mutation status and use of osimertinib in non-small cell lung cancer

Case example one: 45-year-old female with history of non-small cell lung cancer and no evidence of systemic disease presented with headache; CT revealed lesion; MRI revealed left temporal-occipital ~6 cm greater diameter enhancing tumor with local mass effect; physical exam found right homonymous hemianopia, poor balance; tumor superficial on occipital pole; right homonymous hemianopia due to destruction of calcarine fissure on left side; no disease elsewhere in body or brain; tumor too large for treatment with conventional radiosurgery; stereotactic craniotomy performed for release of mass effect for local control and for confirming histology; surgery uneventful; discharged 3 days after surgery; underwent radiosurgery to resection cavity few weeks later; histology confirmed non-small cell lung cancer; use of radiosurgery avoided whole-brain radiation therapy

Important trials:

Randomized, controlled trial by Patchell: published in *New England Journal of Medicine* in 1990; evaluated surgery in treatment of single metastasis to brain; inclusion criteria — single brain metastasis, Karnofsky performance status of 70 or greater; patients randomized to resection plus radiation *vs* biopsy plus radiation; 48 patients included; local recurrence in case of surgery 20% *vs* 52% for cases with radiation and biopsy; study showed overall median survival significantly longer for patients with resection, 40 weeks, as compared with 15 weeks for those with biopsy and radiation; functional independence much greater for patients receiving craniotomy for resection of tumor *vs* biopsy; no difference in systemic death between groups; 30% of patients had extracranial disease

1993 *Annals of Neurology* study: by Vecht et al.; for treatment of single brain metastasis; radiation alone *vs* radiation plus resection — very similar conditions to Patchell study; Karnofsky performance status 50 or greater; 63 patients stratified by extracranial disease; surgery associated with longer and functionally independent survival; benefit not seen in 30% of patients demonstrating progressive extracranial disease

1996 *Cancer* study: randomized trial assessing surgery in addition to radiation for patients with single brain metastasis with Karnofsky performance status of 50 or greater; evaluated resection plus radiation *vs* biopsy plus radiation; no difference in survival; extracranial disease highly predictive of mortality; ≈45% of patients had extracranial disease; three studies together suggest surgery for resection plus radiation leads to prolongation of survival and functional status with single brain metastasis if patient has controlled systemic disease

Post-surgical radiation: 1998 study; patients randomized to surgery *vs* surgery plus radiation; recurrence less frequent in patients with radiation overall; 18% *vs* 70%; neurological death lower in patients with radiation; however, no difference in survival or time with functional independence

More recent (2011) radiation trial: phase three trial published in *Journal of Clinical Oncology* by Sun et al. compared radiation to observation in patients with locally advanced non-small cell lung cancer; neurocognitive and quality of life analysis; study showed prophylactic whole-brain radiation for non-small cell lung cancer brain metastasis led to greater cognitive decline in immediate and late recall; clear evidence radiation leads to more local control; older class one evidence that whole-brain radiation prolongs survival for patients with brain metastasis; However, is associated with cognitive decline; recent literature suggests hippocampal-sparing whole-brain radiation might have better cognitive outcomes; however, study did not compare cognitive outcomes to those in patients not receiving radiation or patients receiving radiosurgery; lecturer prefers to reserve whole-brain radiation for special cases

Radiosurgery (as used by lecturer in case example): randomized, controlled trial published by Mahajan et al. in *Lancet Oncology* in 2017 for postoperative radiosurgery *vs* observation for patients with complete resection of brain metastasis; many histologies included; 132 patients; study showed no difference in survival for patients with radiosurgery *vs* those with observation after craniotomy; but study designed to evaluate local disease control, not difference in survival; local disease control much more likely in patients undergoing radiosurgery in addition to gross total resection of brain metastasis

Conclusions from data: craniotomy for single brain metastasis when disease elsewhere controlled likely prolongs survival; better local control by boosting resection cavity with radiosurgery; does not mean patients will live longer, but less likely metastases will recur at same site

Radiosurgery details: delivery of radiation in very precise way with steep falloff; radiation delivered only to tumor; very little spilled over to surrounding brain; by definition, must be done in one to five sessions; single fraction radiosurgery if one session; fractionated radiosurgery if two to five sessions; different techniques available; gamma knife most precise or conformal radiosurgery; involves dome made out of lead with several piercings, hundreds of holes; each hole has radioactive cobalt source on other end; each hole can be opened or closed with different diameters; dome has spherical shape; each beam very weak; all come together in geometrical center of sphere where radiation very high; head frame pinned it to patient's skull with four pins; obtain volumetric MRI of patient's brain to obtain Cartesian coordinates for tumor relationship to head frame; head frame and patient then secured to stretcher controlled by robot; can position head of patient precisely over geometrical center to radiate tumor; can measure how much radiation delivered to particular site while exposing area to geometrical center of sphere for X amount of time; can then change position of patient; other technologies for radiosurgery include linear accelerators such as cyber knife and other similar devices; linear accelerators have single beam constantly rotating around patient head; most of tumor always subject to radiation; surrounding brain receives little radiation

Case example two: 60-year-old man with history of esophageal carcinoma and esophagectomy; presented with left face and arm weakness; MRI revealed two lesions; right frontal lesion by area of face and primary motor strip on right side and left centrum semiovale, deep-seated, subcortical white matter lesion with little edema; right side lesion ≈3.5 cm; left side lesion 2cm

Considerations: physical limit for effective and safe radiosurgery believed ≈3cm in greater diameter or 14 cubic cm for single fractions; exceptions to rule; can target larger lesions if using fractionated regimen

Treatment of case example two: resected superficial right motor strip lesion; performed radiosurgery to resection cavity of lesion and left-sided, subcortical, smaller brain metastasis; superficial tumors may be adherent to sulci, area where blood vessels pass; important to preserve integrity of blood vessels when performing craniotomy for resection of tumor; damage could lead to cortical strokes and significant symptoms, particularly with tumor in motor strip; in this case, part of tumor adherent to sulcus of motor strip; intentionally left small residual; achieved symptomatic relief after taking ≈95% of symptomatic lesion; within 2 days patient was off steroids and regained strength; radiosurgery then performed as complement to resection to control residual; patient presented 2 months later with new brain metastasis; staged again; no other active disease in body; metastasis now on midbrain in middle of brainstem; patient developed poor balance; single new brain metastasis in area clearly not amenable to resection; made decision to proceed with radiosurgery; had to calculate spill of dose to brainstem

Dose constraints of radiation to brainstem: different parameters; volume receiving 10 grays (Gy), volume receiving 12 Gy, and point dose; depends on how many fractions given to patient; dose constraints change greatly

How many lesions can be treated with radiosurgery?: ≈90% chance of local control when delivering radiosurgery with adequate dosing; does not decrease chances of additional brain metastases; amount of radiation not limiting factor; could treat hundreds of small radiosurgery targets with amount of radiation used in whole-brain radiation; limitations to how many lesions can be treated include amount of time patient must spend in radiosurgery device and issue of futility; example — patient having 40 lesions with each new MRI showing additional lesions

Evidence: study published by Yamamoto et al. in *Lancet Oncology* in 2014 compared difference in survival or outcomes for radiosurgery for one brain metastasis *vs* radiosurgery for two to 10 brain metastases; prospective observational cohort study; inclusion criteria one to 10 brain metastases and 70 or greater Karnofsky performance score; 23 institutions participated; study designed to determine non-inferiority comparison for radiosurgery of one brain metastasis *vs* two to four *vs* five to 10 lesions; included 1194 patients; patients with single brain metastasis lived longer than those with two to four and five to 10 brain metastases; however, patients with two to four brain metastases had no difference in overall survival compared to those with five to 10; no difference in adverse effects for radiosurgery between groups; those willing to do radiosurgery for two brain metastases should be willing to do radiosurgery for up to 10 brain metastases; room for interpretation

Recurrence after radiosurgery: retreatment depends on whether patient has resectable superficial lesion, lesion

symptomatic, systemic treatments available, and if patient has good systemic control and functional status; radiosurgery not possible with deep recurrence of brain metastasis, but laser interstitial thermal therapy can be used if patient otherwise in high functional status; procedure involves implanting laser probe using stereotactic techniques in operating room through very small incision through scalp with navigation; laser probe directed at center of tumor; patient transferred to MRI suite for mapping temperature elevation produced by laser; turning temperature up induces focal damage and control of disease; no class one data showing efficacy; alternative for extreme cases of local recurrence after radiosurgery

Multidisciplinary approach: treating brain metastasis requires crosstalk between radiation oncologist, medical oncologist, neurooncologist, and neurosurgeon; patient systemic status and functional status, and molecular make-up of tumor and potential targeted therapies weighed with neuroanatomy, neurological condition of patient, surgical accessibility of tumor, and technology available at institution; must come together to deliver best medical care

Case example three: 55-year-old female with history of local melanoma excised 2 years prior; naïve to immunotherapy; presents with right-sided hemiparesis worsening over 2 days; CT revealed hematoma in pons; hematoma eccentric to left and comes to surface; mass effect related to hematoma; MRI reveals small brain metastasis and associated acute hematoma that comes superficial; patient initially admitted for observation; bleeding does not increase in size on serial scans, but swelling increases and does not respond to steroids; patient becomes plegic, develops difficulty swallowing, and must be intubated; remains alert but has deteriorated; BRAF mutation status unknown; patient has single symptomatic brain metastasis in brainstem; not place where brain tumors considered resectable; however, lesion came out to surface of brain and was mostly not tumor, but blood clot exerting mass effect; performed infratentorial craniotomy using intraoperative electrophysiology monitoring; able to evacuate hematoma; postoperatively patient regained strength; patient ambulatory and extubated at 2 weeks, though not completely at baseline; decided against standard-of-care radiosurgery to avoid irritation and morbidity to patient brainstem; patient received immunotherapy and initiated melanoma systemic treatment as standard of care

Latest trends: integrating chemotherapy penetrating brain; includes lapatinib and osimertinib; targeted therapy and immunotherapy should be integrated into standard of care; consider fractionated radiosurgery for larger lesions; recommend against whole-brain radiation therapy when possible with exceptions such as small cell lung cancer

Suggested Reading

Aizer AA, et al: Brain metastases. *Neurol Clin.* 2018 Aug;36(3):557-77; **Fidler IJ:** The biology of brain metastasis: challenges for therapy. *Cancer J.* 2015 Jul-Aug;21(4):284-93**; Weidle UH, et al:** The blood-brain barrier challenge for the treatment of brain cancer, secondary brain metastases, and neurological diseases. *Cancer Genomics Proteomics* 2015 Jul-Aug;12(4):167-77.

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End-of-Life Care

Russell Portenoy, MD, *Professor of Neurology and Family and Social Medicine, Albert Einstein College of Medicine, Executive Director of the MJHS Institute for Innovation in Palliative Care, and Chief Medical Officer of MJHS Hospice and Palliative Care, New York, NY*

End-of-life care: from clinical perspective, better to describe 2 broad areas, caring for patients with advanced illness and caring for patients imminently dying from advanced disease; in care of patients with advanced illness, key task, optimize concurrent care (*ie*, providing palliative care related to symptom control and other factors that undermine quality of life [QoL] for patient or family while managing patient's disease processes through antineoplastic therapies); in care of imminently dying, key task, to optimize palliative care (sometimes called comfort care to emphasize focus on symptom control and relief of other problems that undermine QoL or enhance suffering of patient and family)

Palliative care: multiple definitions of palliative care, supportive care, and hospice; terms sometimes used interchangeably, although, in United States (US), tend to have different meanings; *supportive care* — tends to be used mostly in oncology practice; focuses on management of problems related to antineoplastic therapies and other issues such as family support; *palliative care* — international movement that focuses on management of factors that contribute to illness burden of patients or families; may be viewed as broader construct within which supportive care more narrowly defined term; hospice and palliative care often used interchangeably (international perspective); *hospice* — in US, government-supported program to provide specialist palliative care to eligible patients with advance illness

Definition of palliative care: promoted by World Health Organization and American Society of Clinical Oncology (ASCO); best understood as multiprofessional therapeutic approach appropriate for all populations with serious, chronic illnesses, with overarching goal to prevent or manage suffering and illness burden of both patient and family from time of diagnosis onward; patient and family should be considered unit of care; any factor that contributes to burden of illness for patient or family may be considered for palliative care intervention to prevent or manage these sources of illness burden; begins at time of diagnosis and needs to intensify as sources of illness burden multiply; physicians, nurses, social workers, chaplains, pharmacists, psychologists, various therapists, all individuals whose profession includes management of sources of illness burden participate

Palliative care goals: work in the US during past 25 yrs moved from broad definition of palliative care to bedside practices that promote relief of suffering and illness burden, and that maintain or improve QoL of patients and families

Clinical objectives: reduce stress from physical, psychosocial, or spiritual sources; enhance patient and family self-efficacy, coping and adaptation, and family cohesion; ensure therapies offered only if medically appropriate, likely to yield benefits greater than adverse effects, and consistent with patient's or family's preferences and goals; support informed medical decision making, goal setting, and advanced care planning consistent with patient's capabilities, preferences, and culture; from practical perspective, palliative care coordinates work of professional caregivers to reduce care fragmentation and ease care transitions; provides needed services; supports effective communication within family and between family and professional caregivers; ensures culturally sensitive, ethical, and legal care; provides care that prepares for dying process, minimizes distress during active dying, and offers support during period after death, including longer-term support for bereaved, palliative care not same as end-of-life care; begins at time of diagnosis

Generalist vs specialist palliative care: *generalist palliative care* — those interventions provided by clinicians with no specific identity as palliative care providers or specialists, but professionals who have competencies in treatments that address some objectives; *specialist palliative care*– reflects those interventions by clinicians who have specialist-level competencies in treatments that address objectives of palliative care; they contribute to more comprehensive approach to illness burden associated with serious illness; in US, specialist-level certification available for physicians, nurses, nurse practitioners, social workers, and chaplains; in US, have been effective in implementing this construct of specialist palliative care that involves education and experience that supports professional's high-level competencies in addressing important issues in illness burden; all clinicians who address sources of illness burden throughout course of illness engage in generalist-level palliative care; generalist-level palliative care practiced by all clinicians who address needs of patients with serious illness; specialists in palliative care typically involve individual or team that addresses more complex problems and works together; specialists usually called upon to take care of patients with advanced illness and short prognosis; specialists in palliative care, including those who work in hospice agencies, care for dying patients, but construct of palliative care as care model needs to be understood as starting from time of diagnosis going forward

Importance of palliative care: addresses 2 major problems associated with serious illness, particularly when progressive and prognosis short

High burden of illness: can be related to medical factors, care fragmentation and disparities, misaligned incentives in health system, and numerous patient factors (*eg*, type of illness, tempo or progression of illness, family's ability family to cope and adapt to problems associated with illness)

High cost of care related to partly avoidable expenses: ~5% of patients in US account for ~50% of health care costs (~11% of that for care in last year of life); patients with advanced illness and high illness burden account for disproportionate share of health care spending; reduction in health care spend not specific objective of palliative care, but may be considered epiphenomenon; occurs in patients getting good palliative care because it focuses on iterative goal setting and serious illness discussions; *serious illness discussions* — allow patients to make decisions about care they receive consistent with values and preferences, and reflect informed, shared decision making; process needs to be done with oncologists because some patients will elect less-aggressive care or will not be offered highly aggressive care when clear that likelihood of benefit, in terms of value outcomes for individual patient, not possible; some patients who need very intensive palliative care high-cost patients; in aggregate, patients with serious illness who get good palliative care throughout course of illness tend to cost less than patients who do not; palliative care addresses both high burden of illness and high cost of care related to serious illness

Other factors: patients who have prognostic awareness, especially those who have completed advance directives >30 days before death, die less often in hospital and use hospice care more and for longer durations; these changes impact both quality and cost of care; patients who have end-of-life discussions also more likely to be satisfied; typically die at place of their choosing and relatives or caregivers less distressed after their death; those who had access to palliative care consultation services have less symptom and psychological distress, and caregivers generally less distressed; patients with access to specialist-level palliative care and hospice do not die earlier; studies suggest that good palliative care prolongs survival; those with access have shown lower or equal cost to those who do not receive it

American Society of Clinical Oncology (ASCO) guideline: supportive of need for palliative care services for patients with cancer; recognizes importance of generalist-level palliative care provided by oncology practice and specialist care provided by referral to palliative care team; for newly diagnosed patients, early palliative care involvement within 8 wks of diagnosis highly suggestive (based on intermediate quality of evidence; strength of recommendation moderate and mostly from informal consensus); recommendation viewed as evolving best practice that patients likely to have prolonged course (*eg*, metastatic disease) should have palliative care involvement; patients with advanced cancer should be referred, if possible, to interdisciplinary palliative care team that can provide in- or outpatient care, at any point during course of illness, alongside active cancer treatment (evidence for this recommendation intermediate in strength, but strength of recommendation strong); if you have patient with progressive illness and access to interdisciplinary palliative care consultation program, ASCO guideline recommends referral; do not wait until patient's prognosis poor, life expectancy considered to be days or weeks, or cancer treatment no longer option; refer early so concept of concurrent care can be executed

8 domains of palliative care: expert panel published in the National Consensus Project for Best Practices in Palliative care, revised and republished by National Coalition for Hospice and Palliative Care (www.nationalcoalitionhpc.org); domains reflect widely accepted set of best practices

Physical aspects of care, or interventions for physical well-being: includes assessment and management of pain, symptoms other than pain, and other physical disorders that may produce distress (*eg*, pressure ulcers or delirium); more specific focus on physical aspects of pain consists of assessment of pain and other symptoms or disorders that can undermine physical well-being; this practice reflects generalist-level palliative care approach

Psychological and psychiatric aspects of care: focuses on assessment and management of illness-related psychological reactions (*eg*, mood disturbance, impairment in coping or adaptation to disease, grief reactions); assessment and management of comorbid psychiatric disorder, including axis 1 (*eg*, anxiety disorder, bipolar disease, substance use disorders, psychotic disorders, personality disorders) and axis 2 diagnoses; may require referral to mental health professionals

Social aspects of care: includes assessment and management of social needs, including financial resources and maintenance of social networks; addresses family integrity, involving communication within family and between family and professionals, family coping, and role functioning within family; oncologists may make referrals to address processes that can undermine social well-being

Spiritual, religious, and existential aspects of care: often defined in terms of disturbances in meaning and purpose, disturbances in sense of connectedness patients may feel with others or with other groups, connection patient feels to his or her faith and religion, and potentially, type of connection patient may feel in trying to achieve some type of transcendence; meaning and purpose, interconnected faith and religion, and transcendence key constructs; oncologists may not be able to provide spiritual care patient may need; rely on patient's religious connections or make referral to health care chaplain; spiritual distress important source of illness burden, relatively common in patients with serious chronic illness, and assessment may indicate patient expressing sense of emptiness because meaning in life has become impaired by necessity of living with illness; raise concern that patient experiencing level of spiritual distress that can impact QoL, increase suffering of patient and family, and can potentially be addressed through intervention

Ethical and legal aspects of care: all practice must be ethical and comply with appropriate law; important ethical and legal implications with advanced illness; think about nature of consent for medical care when patient lacks ability for decisional capacity; issues related to withholding or withdrawing life-sustaining therapy

at end of life need understanding of ethical basis and potential legal implications; issues may be addressed by referral to ethics committee; some challenging practices within palliative care (*eg*, use of palliative sedation for refractory suffering at end of life); *palliative sedation* — use of sedative-hypnotic drug to induce sleep-like state in effort to reduce suffering; can potentially hasten death, and question of whether clinician can engage in therapy that has this known risk if intent to reduce suffering; ethical principles of proportionality and double effect can guide clinical practice and allow clinicians with skills in palliative sedation to use it; palliative sedation now widely accepted technique worldwide; organ donation after cardiac death has important legal and ethical implications

Care of patients at the end of life: includes ability to prognosticate imminently dying patient, to communicate about likelihood of death with family members and other care providers, and management of symptoms or signs associated with dying

Structures and processes of care: refers to variety of factors that may improve ability to provide palliative care to patients with serious illness; emphasizes interdisciplinary assessment, care planning, and coordination; emphasizes goal-setting discussions with advanced care planning and points to necessity of effective communication with patient and family in order to have serious illness discussions, which can be documented and help establish patient's goals and preferences as disease progresses

Best system of care: focuses on use of hospice

Specialist-level palliative care: in US, can be institution or community based; most US hospitals have palliative care consultation services; nursing home palliative care consultation services uncommon but slowly emerging; community-based palliative care takes place in patient's home, uncommon because of current financing of health care system; community-based palliative care implemented through health care system (*ie*, hospice) prevalent

Hospice: commonly misunderstood health care system in US; used commonly by those dying of advanced illness as well as their families; best understood as government-supported health care system created >35 years ago to provide specialist palliative care in home for those with advanced illness; in US, hospice should be viewed as entitlement program like Social Security, which must be elected by eligible patients and can be revoked at any time; in 1980s, hospice created by government as country's first managed care insurance benefit; by regulation, most patients under hospice care have to be at home; in addition to hospice being home care program, entitlement program, and managed care insurance benefit, it may be construed as philosophy of care that focuses on best type of care provided for imminently dying patients; view that hospice represents philosophy of "good death" appears in literature; (lecturer's bias not to designate hospice as philosophy but rather as benefit providing suite of services;) patients and families need help, particularly with patients with advanced disease living at home, and hospice can provide no-cost benefit that offers care and services to address unmet needs; if easier for them to accept this care by not discussing the fact that hospice philosophy of care that addresses potential for good death, one should respect that

Services: case management by interdisciplinary team, including physician, nurse, social worker, and chaplain, at minimum; patient and family must have access to volunteers and home health aid hours; must have access to other services (*eg*, speech and swallow therapy, physical and occupational therapy, and wound care); all tests and treatments, drugs, durable medical equipment, and supplies must be provided at no cost if related to terminal diagnosis; if patient has acute need and requires skilled support, hospice agency must provide access to inpatient bed; patient who develops acute needs that require higher level of support must be provided access to period of continuous home care; if family needs respite because of caregiving responsibilities, hospice agency must provide access to inpatient stay for ≤5 days for patient; after patient dies, hospice required to provide bereavement services for 13 mos; no time limit for hospice as long as patient remains eligible (documented every 2 to 3 mos through recertification by hospice physician); patient can revoke benefit at any time and return to prior system of care; prior system of care remains in effect for all medical problems unrelated to terminal illness; challenge in caring for patients receiving hospice services, distinguishing between problems related or unrelated to terminal illness because former problems, but not latter problems, must be case managed by hospice agency; services provided without deductible, no requirement for copay, and no requirement for coinsurance; any payer system for cost of services unrelated to terminal illness allowed

Patients served: >4000 hospice agencies certified by government (serving >1.7 million patients, ~50% of those people aged >65 yrs die each year); hospice agencies range from small volunteer organizations to national corporate chains; most agencies for-profit organizations and offer differences in care from typical not-for-profit company; length of care provided by hospice very short; median period of care <25 days because of late referral; this suite of services only accessed for period of just ≥ 3 wks by 50% of patients; hospices vary in competencies required of staff, and variation in services; proportion of hospices do not have capability of providing continuous home care (but actually regulatory requirement); many hospices provide very little in way of bereavement services; patients who live in area with multiple hospice agencies should determine which agencies require education and competency testing of staff, have access to all elements of hospice benefit (*eg*, continuous care and bereavement support), provide education for their partners, and provide high level of services

Access to hospice: oncologists have obligation to try to improve access to hospice, given potential ability to address needs of patients and families living through advanced illness; to improve access, physicians need clarity about key features; *comanagement* — oncologist does not hand patient off to hospice agency for ongoing management with no further involvement unless patient or attending oncologist wishes; oncologist can choose to be attending of record or can remain consulting physician; nurse practitioners or physician assistants can choose to be attending of record; oncologist seeing patient for treatment of disease can accompany that

patient and can potentially be central factor for both patient and family as they live through dying process; *reimbursement* — every clinician encounter with patient enrolled in hospice agency reimbursable, and physicians can be reimbursed for every encounter if billed appropriately; if physician attending of record, continue to bill government through part B Medicare; if physician consultant, must bill hospice agency; common misconception that physician care of patients enrolled in hospice pro bono; hospice agencies receive per diem payment from government based on level of care (4 levels) patient receiving; hospice agencies must provide all care stipulated by regulation for that single per diem payment; *important for hospice agency to truly case manage patients*– to be aware of what treatments patient receives, and what oncologist or other clinicians recommend so hospice agency can coordinate care and restrain costs in way that allows them to remain in business, receiving per diem payments for all care under the hospice benefit; palliative care saves payers and hospice saves Medicare money, depending on hospice length of stay

Eligibility review: understand who may be eligible for hospice benefit, how to develop process by which eligible patients have discussion about hospice, and how to do referral; *according to government regulation, eligibility for hospice has only 2 criteria* — 1. two licensed physicians (1 employed by hospice agency) must certify that patient's life expectancy ≤6 months if disease runs its expected course; fundamentally clinical judgment; if physician views patient's primary illness and comorbidities as together producing situation in which prognosis likely to be ≤6 months if disease runs its expected course, patient eligible; o 2. patient or surrogate must elect benefit; no requirement that patients give up anything when they enroll in hospice; hospice agencies will define what patients they can and cannot take as result of need to provide case management and incur care costs; hospice agencies typically unable to accommodate patients receiving infusional chemotherapy because costs and complexity too great; every hospice agency will determine for itself what it can and cannot cover based on risk pool, size of agency, mix between patients who have complex needs and those who do not, and skill set of their clinicians

Improving access to hospice: *2-question protocol* — 1. is patient medically eligible for hospice? 2. is patient appropriate for hospice, given planned treatments and known patient and family preferences?; medical eligibility based on total picture; consider using "surprise question" to develop understanding of prognosis; surprise question asks clinician if they would be surprised if patient were to die of this illness in next 6 mos to 1 yr; if no, patient may be eligible for hospice; if yes, high probability patient not eligible

In 2-question protocol, first question (is patient medically eligible for hospice?) nay be informed by asking yourself or having staff trigger you or other clinicians involved with case to answer surprise question; second question (is patient appropriate for hospice given planned treatments and patient and family preferences?) answered by having understanding of types of treatments that will be accepted by hospice, may require prior knowledge or prior work with individual hospice, and some idea about whether patient or family may be open to hospice referral; do not make broad assumptions about expectations regarding patient's or family's views

Prognosis related to medical eligibility: most clinicians recognize that performance status scales predictive of prognosis; ECOG scale, Karnofsky performance status scale, and palliative performance status scale work equally well; for ECOG, score of 3 to 4 typically associated with prognosis of mos, suggesting patient may be hospice eligible; studies suggest core group of symptoms that may be considered particularly important in determining prognosis, including presence of dyspnea, cognitive impairment, and group of gastrointestinal symptoms (*eg*, dysphagia, anorexia, weight loss, dry mouth); if those broad areas of symptoms and signs involved, patients have shorter life expectancy; tools have been developed to improve prognostication; palliative prognostic score, so-called PAP, uses Karnofsky performance status, anorexia, dyspnea, 2 tests available on complete blood count (white blood cell count and lymphocyte percentage), and clinical prediction of survival; score validated and not generally used in clinical practice, but gives sense that, in addition to performance status, other elements (*eg*, biomedical factors, symptoms) important in prognostication

Active dying: actively dying patient must be recognized as transitioning to this phase; then symptoms and signs need to be addressed; important elements related to communication, appropriate goal setting, and support of family should be activated

Signs that suggest patient transitioning to active dying: typically, declining response to voice and contact; changes in muscle activity, urinary function, breathing, skin color, and vital signs; most clinicians gain experience with recognizing these changes and can communicate shortness of time to family; requires careful assessment and management; must be addressed with cultural sensitivity

Management: management of more challenging elements may require working knowledge of clinical bioethics, and may be necessary to make referrals and bring in resources that can help patient and family, particularly if home death planned; for oncologist, first step often to reassess decision making if change has occurred in patient's decision or capacity, or if change in identified decision maker; patients transitioning to period of active dying often noncommunicative; at this point, advanced directives become critically important; hopefully, these advance directives have been kept updated and consistent with patient's and family's values and preferences; *may be important to reassess goals of care* — deprescribing common and often done by hospice physician upon enrollment in hospice program; if patient no longer benefiting from drug or if potential for harm exceeding benefit, drug should be stopped; also important to consider that other therapies, including some that may be labeled life sustaining, now have burdens greater than benefits and may be withdrawn; withdrawal of life-sustaining therapy on grounds of individual preferences or futility more challenging problem that often involves discussion with family, clear understanding of patient's prior expressed wishes, and may involve interactions with

ethics consultation service; *assessing place of death* — home death may be offered to patient and family if hospice in place, and it may be important to have conversation with patient or surrogate decision maker

Common conditions at end of life that may be addressed from medical perspective: agitated delirium; preterminal delirium common; delirious patients expected to die imminently have set of goals that typically do not include reversal of factors driving delirium, but rather aggressive treatment of symptoms of delirium to reduce distress; patients may have pain, anxiety, breathlessness; unconscious patients may have noisy respirations ("death rattle"), which can be distressing to families; may have need for mouth care or management of wounds and ulcers that need to be performed until patient dies; key treatment issue with imminent death, provide care that reduces suffering; routine interventions may not accomplish this goal

Palliative sedation: medical treatment by which patient believed to be near end of life given drug with goal of producing sedation sufficient to relieve suffering; widely accepted when physical symptoms refractory to conventional therapy near end of life; based on ethical practices predicated on constructs of proportionality and principle of double effect; more controversial when sources of suffering existential or spiritual; in most cases, palliative sedation performed because of agitated delirium that fails to respond to medical intervention; under these circumstances, can be highly effective in reducing patient's suffering and allowing patient to have safe and dignified end-of-life experience, and families to experience patient's death with minimum of their own suffering

Suggested Reading

Ferrell BR et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(1):96-112; **Garetto F et al:** Palliative sedation for the terminally ill patient. *CNS Drugs*. 2018;32(10):951-61; **Hui D et al:** Prognostication in advanced cancer: update and directions for future research. *Support Care Cancer*. 2019;27(6):1973-84; **Schlick CJR, Bentrem DJ:** Timing of palliative care: when to call for a palliative care consult. *J Surg Oncol*. 2019;120(1):30-4.

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Anti-Cancer Drugs I: Cell Cycle–Targeted Therapies

R. Donald Harvey, III, PharmD, *Professor, Departments of Hematology, Medical Oncology, and Pharmacology, Emory University School of Medicine, and Director, Phase I Clinical Trial Section, Winship Cancer Institute of Emory University, Atlanta, GA*

Cell cycle-targeted therapies: agents include antimetabolites, antifolates, taxanes, vinca alkaloids, topoisomerase inhibitors, alkylating agents, some differentiating agents; all-trans retinoic acid (ATRA), and histone deacetylase inhibitors (HDACi); when we think about the use of antineoplastics and conventional cytotoxic chemotherapy, we have to first address the goal of chemotherapy, ie, whether we are looking to cure patients or palliate them; then consider the mechanism of action of the drugs and how we might incorporate them into therapeutic regimens; with cell cycle pharmacology, we have to remember the 4 main phases of an actively differentiating cell; there is also the G0 phase, which is quiescence, when nothing works; when cells are not undergoing active alterations and division, it is difficult to target those cells with anything but surgery; within the cell cycle, the 4 main phases are G1, where cells prepare for DNA synthesis, the S phase where DNA synthesis occurs and antimetabolites most commonly work; in the G2 phase, cells prepare for mitosis, which then occurs in the M phase, which is where the taxanes and vinca alkaloids work; although cancer cells spend a short time within the M phase, this is where cells are very sensitive to inhibition with anti-cancer agents

I. **Antimetabolites:** the classic antimetabolite, 5-fluorouracil(5-FU), can be used as a backbone for treatment of advanced colorectal cancer among others; other fluoropyrimidines include capecitabine and TAS-102, a newer fluoropyrimidine; overall, antimetabolites are similar to the compounds needed for normal cell function, ie, the building blocks of DNA; 5-FU is similar to uracil, and it inserts within the DNA when it encodes, acting as a false base and preventing the growth of the cancer cell; DNA replication is disrupted, and the cancer cell is targeted for apoptotic death; antimetabolites work primarily in the S-phase, where DNA is actively being replicated; specifically, antimetabolites fall into a number of categories, the antifolates, eg, methotrexate and pemetrexed; the classics, 5-FU and capecitabine

Pyrimidine antagonists: eg, 5-FU, capecitabine, TAS-102; 5-FU can be given by a bolus or by a continuous IV infusion; 90% of 5-FU is degraded by dihydropyrimidine dehydrogenase(DPD); should a patient have pronounced cytopenias and stomatitis from 5-FU, it might be worthwhile to check their DPD status; it is rare that patients have full loss of DPD function, but when they do, think about it as having given a patient a 9-fold overdose; there are new drugs that can be used to degrade 5-FU should there be a suspicion of overdose; overall, 5-FU is well known to many oncologists and is a very commonly used drug

5-FU toxicities: when given by continuous infusion it has different dose-limiting toxicities than when given by bolus; the bolus tends to cause a lot of myelosuppression; continuous infusion tends to cause more GI toxicity, specifically stomatitis, mucositis in the upper GI tract, and diarrhea; 5-FU and many of the other agents within this class act on rapidly dividing cells, eg, the bone marrow; 5-FU is commonly used in combination with leucovorin; not the same as leucovorin use with methotrexate; leucovorin should be given before 5-FU to improve the activity of 5-FU on its target enzyme of inhibition; rarely, 5-FU can cause cardiovascular issues, specifically vasospasm, a condition that looks a lot like unstable angina on EKG at the time of that adverse event (AE); if patients are complaining of chest pain while taking the drug, then they should be treated as you would for an unstable angina event, with aspirin, nitrates, etc; it is probably best not to reintroduce 5-FU if patients have ST changes on EKG

Capecitabine and other pyrimidine antagonists: an oral fluorouracil prodrug, capecitabine has a different side-effect profile from 5-FU; dose-limiting toxicities include hand-foot syndrome; very useful drug in many patients; it is dosed on a mg/m^2 basis depending on the regimen; often given in combination with oxaliplatin; 5-FU also usually given in combinations; TAS-102 is mostly used in the refractory setting of colorectal cancer therapy

Purine antagonists: also act as false bases; drugs in this class include 6-mercaptopurine, 6-thioguanine, primarily used in the treatment of acute lymphocytic leukemia; the classic drug in adults is cytarabine (Ara-C)

Ara-C: mimics cytosine and inserts within DNA in its place; for induction therapy for acute myeloid leukemia, a 100 mg/m^2/day dose is given as a continuous infusion, typically in combination with an anthracycline or in other regimens; the total dose is 700 mg/m^2 and occasionally 200 mg/m^2/day for a total dose of 1400 mg/m^2; induction therapy has a very different AE profile than the Ara-C doses used in consolidation therapy

High dose Ara-C (HiDAC): dose is generally 3 g/m^2 given every 12 hours on days 1, 3, and 5; think about the drug very differently than when used for induction; with Ara-C for induction, the total dose is around 700 mg/m^2 compared with HiDAC where the total dose is ~18 grams/m^2, resulting in a very different

side-effect profile; Ara-C given in very high doses and shorter infusions gets into the CNS and into the ocular space, leading to cerebellar toxicity, which needs be monitored in patients getting consolidation therapy for acute leukemia; cerebellar toxicity is best assessed by finger-to-nose testing, gait observation; if patients have changes in their cerebellar function, it is best to stop the dose to stop progression and dose reduce next time from 3-2 g/m^2 or 1 g/m^2; HiDAC is cleared by the kidneys, low dose Ara-C is as well, but we do not dose adjust for renal insufficiency with Ara-C in that setting; for conjunctivitis, and concerns of Ara-C getting into the ocular space, give artificial tears or dexamethasone-containing corticosteroid eyedrops starting with the first dose and continuing until 48 h after the last dose

Gemcitabine: another classic purine antagonist, primarily used in solid tumors and GI malignancies as well as in lung and breast cancers and occasionally in some salvage lymphoma regimens; typically causes myelosuppression, specifically thrombocytopenia, as a side effect

Other purine antagonists: include cladribine, pentostatin, and fludarabine, all agents used primarily in lymphomas and chronic lymphocytic leukemias; another drug in this class, hydroxyurea, inhibits ribonucleotide reductase; it is used primarily for count suppression in patients with newly diagnosed hematologic cancers; 3-4 g/day dose of hydroxyurea at minimum; works quickly on more differentiated cells, and drops in white cell and platelet counts occur 48-72 h after initiation; a rapid increase occurs once terminated; hydroxyurea can be helpful in patients where rapid count reduction is desired

II. Antifolates:

Methotrexate (MTX): the classical antifolate; MTX has a huge dose range eg, in graft vs host disease prophylaxis and allogeneic stem cell transplantation, 10-15 mg/m^2 is given for 3 or 4 days; however, in the treatment of CNS lymphoma and osteosarcoma, doses are in grams — upwards of 10-12 g/m^2 total; that very large dose range means very different AE profiles and very different activities; the larger doses, ie, single doses above 100 mg/m^2, require rescue with leucovorin and more specifically alkalinization of the urine prior to initiation of treatment

Renal issues with MTX: MTX is renally cleared, and dose adjustment in patients whose renal function is compromised needs to be considered; urine alkalinization can be achieved by different pathways; the classic one is combining $NaHCO_3$ and IV fluids and dextrose 5% in water (D5W); the goal urine pH prior to initiation of MTX is ≥7 (optimally pH 8); since MTX is an acidic drug, a basic environment drags MTX across the glomerular filtration system into urine; it is more rapidly cleared and therefore does not crystallize in kidneys; acute renal failure from MTX can and will occur in patients who have acidic urine; the drug will crystallize, and crystalluria is seen on urinalysis; clinically there can be a rapid rise in creatinine, which can be challenging; if patients overdose with MTX, another rescue agent, glucarpidase, which directly cleaves MTX is used

Leucovorin: important to remember with the use of MTX; leucovorin rescues cells,(primarily normal cells); it has less of a differentiating rescue effect on cancer cells; some principles of leucovorin and high dose MTX use are that leucovorin should begin no sooner than 24 h after the completion of MTX; that is an important point, because you want to give MTX time to inhibit dihydrofolate reductase within the cancer cell; leucovorin can be given as late as 48 h after giving/completing MTX, typically, the 24-48 h range is used to initiate leucovorin dosing; often, an empirical dose of leucovorin is given; ideally, you should work with pharmacists and others to understand changes in leucovorin dose based on MTX concentrations; concentrations should be obtained at least daily to guide leucovorin rescue both in terms of dose and duration; leucovorin should be continued until MTX concentrations are 0.1 micromolar or lower; some centers will go to 0.05 micromoles and even 0.01 micromoles, but 0.1 micromoles is the highest level at which you can discontinue leucovorin safely in most patients; MTX also is sequestered within pleural effusions, so patients need to have any extra fluids drained before they begin using it

Pemetrexed: another antifolate; is also renally cleared and should not be used in patients with creatinine clearances <45

III. Microtubule targeting agents: includes taxanes and vinca alkaloids; these drugs work within the M phase; originally paclitaxel was given as a 96 h infusion; in reality, patients can get paclitaxel over a much shorter duration and still have good activity; these drugs work within a very short timeframe of the cell cycle and are very effective in combination regimens; both taxanes and vinca alkaloids cause cumulative neurotoxicity, the classic being the stocking-glove distribution with tingling in the hands and feet; a classic case would be an ovarian cancer patient getting carboplatin and paclitaxel who has difficulty picking up a key or buttoning a blouse after ~6 cycles; that is often the beginning of peripheral neurotoxicity; if unchecked, and drugs are continued, that tingling will lead to motor weakness and can eventually cause more devastating neurotoxicity; holding the drug is best way to prevent neurotoxicity in these patients

Taxanes: include classic agents paclitaxel and docetaxel, as well as liposomal nanoparticle paclitaxel (brand name Abraxane); paclitaxel should be given with premedications including dexamethasone, diphenhydramine, and H2 blockers such as ranitidine prior to infusion; it is derived from the pacific yew tree, a natural product, so it can cause infusion reactions; with optimal premedication, infusion reaction rates drop to ~3%; docetaxel can cause pleural effusions and patients should get 8 mg dexamethasone twice daily for 3 days, beginning the day before therapy; both of these agents are used across many different tumor types including lung, bladder, breast, and others; they are very useful compounds to consider in the treatment of solid tumors

Taxane pharmacology: taxanes bind β-tubulin; in the M phase of cell division the microtubule is either assembling or disassembling, depending on what phase of mitosis you are in and where cell separation is occurring; taxanes bind β-tubulins, promote the assembly of dimers, and stabilize the microtubules, so that the cancer cell cannot disassemble and create a daughter cell; they are very useful drugs and helpful in many ways, but have their AE profiles; myelosuppression is associated with taxanes and

the primary concern is neuropathy with prolonged treatment; rarely, AEs such as nail changes and hyperlacrimation are associated with docetaxel

Vinca alkaloids: target the M phase, and include vincristine, vinblastine, and vinorelbine; like taxanes, vinca alkaloids have cumulative neurotoxicity as important AE; classically the dose of vincristine in the CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin [vincristine], and prednisone or prednisolone) and R-CHOP (CHOP plus rituximab) regimens for treatment of lymphoma is 1.4 mg/m^2; clinicians have historically capped the dose at 2 mg/m^2; an argument can be made against that, since studies show that the dose intensity of vincristine is optimized when you dose on full body surface area; if patients experience neurotoxicity, dosage should be held until toxicity is resolved; vincristine and other neurotoxic drugs can also cause autonomic neuropathy; eg, a young patient with lymphoma who is getting vincristine as part of their therapy complains of constipation, a frequent problem with vincristine; patients should be advised to take prophylactic regimens for constipation prior to and after vincristine to prevent constipation and obstipation

Neurotoxicity and myelosuppression with vinca alkaloids: vincristine has little to no effect on the bone marrow compartment; myelosuppression is not associated with it unless it is used in hematologic and oncologic disorders such as ITP (idiopathic thrombocytopenia purpura) and other situations where one wants to give a drug to reduce the B-cell population but not cause myelosuppression; going along the spectrum of drugs from more neurotoxic to less neurotoxic (similarly less myelosuppressive to more myelosuppressive), vinblastine, almost in the middle, causes some neurotoxicity and some myelosuppression; used primarily in the treatment of testicular cancer; vinorelbine was initially used in breast cancer and lung cancer; it is a weekly regimen, tends to cause less neuropathy over time; however, myelosuppression is seen often and is a concern

Vinca alkaloids and cytochrome P450: these drugs are substrates of the cytochrome P450 3A4 (CYP3A4) system; interactions are rare, but in patients who are getting strong CYP3A4 inhibitors (some of the azoles and antifungals), concurrent use with vinca alkaloids should be avoided to prevent excessive exposure to the antineoplastic

IV. Topoisomerase inhibitors: topoisomerase is an enzyme responsible for relaxing DNA, and includes topoisomerase I (topo I) and topoisomerase II(topo II); both of these enzymes are important in cellular replication; we have drugs that inhibit either topo I or topo II; topo I inhibitors are the camptothecins (irinotecan and topotecan)

Topotecan: primarily used in small-cell lung cancer and ovarian cancer; myelosuppression can be seen with it and is dose limiting; can be a tough drug to tolerate for some patients, however it does have activity

Irinotecan: the other agent commonly used in this class; now there is also the newer formulation of liposomal irinotecan; irinotecan's dose-limiting toxicity is diarrhea; from a pharmacology perspective, it is a prodrug that is converted by CYP3A4 from the parent irinotecan into the drug SN-38; SN-38 is then cleared through the biliary system and is partially metabolized by the UGT (uridine 5′-diphospho-glucuronosyltransferase) system, specifically UGT1A1; there are patients who have UGT1A1 abnormalities and are unable to clear SN-38 as quickly as other patients; when this system is utilized to clear irinotecan it adds a glucuronide to the SN-38 molecule; that combination is then cleared through the biliary system, which carries it into the proximal small bowel; within the small bowel there may be bacteria that contain glucuronidases that may cleave the SN-38 glucuronide complex, leaving free SN-38 in the bowel leading to the (later) diarrhea; there are a number of ways to deal with this; early diarrhea seen with irinotecan is prevented with atropine; later diarrhea occurs typically around day 2 or later, and patients can be advised to take loperamide at the first sign of any diarrhea and really be aggressive with the dosing; eg, 4 mg every 4 h; if patients have life-threatening diarrhea, there are ways to prevent it in the next cycle; one is dose reduction; the other is to give a non-absorbable antibiotic such as neomycin ~1 w ahead of time; the doses of irinotecan have come down since its initial use in colorectal cancer; diarrhea is still a problem but can now be managed with newer interventions

Topo II inhibitors: work in late S and G2 phase, resulting in single-strand DNA breaks; the classic drug in this category is etoposide (also known as VP-16); etoposide is used across different hematologic and solid tumor cancers; it is formulated in a vehicle that can cause low blood-pressure when used in very high doses, eg, in the BEAM (BiCNU [carmustine], etoposide, ara-C [cytarabine],melphalan) regimen for autologous stem cell transplantation; etoposide is notorious for causing secondary DNA damage to normal DNA and secondary cancers; extensive exposure to etoposide in patients with hematologic or solid cancers, more commonly hematologic cancers, causes secondary myelodysplastic syndrome and secondary acute leukemias; it is associated with myelosuppression; it is a useful agent in many cancer types, eg, testicular cancer and refractory lymphomas

Anthracyclines: historically did not fall into the topoisomerase category, but probably should have; the classic is doxorubicin; other agents in the class are daunorubicin and idarubicin; originally thought to be intercalators of DNA, ie, to insert themselves into DNA, but they do inhibit topoisomerase; they all cause cumulative dose-dependent biventricular heart failure; patients receiving anthracyclines need to be monitored over time; doxorubicin is the classic anthracycline; all these drugs are brightly fluorescent based on their derivation; in doxorubicin, the standard cumulative lifetime dose of 450 mg/m^2 was associated with an increased risk of heart failure; in certain populations and certain instances, a lower lifetime dose may be targeted; in R-CHOP, used in lymphoma, the dose of doxorubicin is 50 mg/m^2; 8 cycles of that is 400 mg/m^2, fairly well below the lifetime cumulative dose; daunorubicin and idarubicin are used in acute leukemias at lower doses; epirubicin is in this category as well; mitoxantrone is an anthracenedione, but does have similar heart failure risks at cumulative doses; liposomal doxorubicin is used in certain instances; however, it has become a little more

challenging to obtain lately; all anthracyclines cause some degree of myelosuppression; doxorubicin may rarely be associated with bradycardia and other infusion-related events; doxorubicin is also a vesicant, and so should not be given peripherally, unless under very close supervision by nursing staff; optimally a central line should be placed in most patients receiving longer term treatment with doxorubicin

V. Alkylating agents: include some of the first anti-cancer drugs; the classic prototype is nitrogen mustard, first used as a gas in World War I; it was not effective as a war weapon, but was placed into solution and given to patients with lymphomas as part of the initial treatment of cancer in New York in the 1940s; the drug derived from it, mechlorethamine, is the M in the MOPP regimen for Hodgkin lymphoma (not much used any more); there are many alkylating agents within this class of nitrogen mustards; they are DNA binding agents that directly cross-link base pairs; they work throughout the cell cycle; other nitrogen mustards include chlorambucil, melphalan, and busulfan; the last 2 are commonly used in autologous stem cell transplant and allogeneic stem cell transplant; they have a steep dose-response curve and wipe out the marrow, but also have anti-cancer activity themselves; melphalan, a nitrogen mustard, is a very helpful active conditioning agent for myeloma patients undergoing autologous stem cell transplant

Other alkylating agents and nitrogen mustards: cyclophosphamide and ifosfamide, which are prodrugs, are converted by the liver to a number of active metabolites; all doses of ifosfamide need to be given with the compound mesna; mesna (a sulfur drug) binds acrolein, a toxic metabolite of ifosfamide that causes hemorrhagic cystitis; conventional doses of cyclophosphamide do not require mesna; higher doses, such as those used in stem cell transplants, may require it; another approach is hyperhydration to flush out acrolein metabolites; ifosfamide may cause encephalopathy due to a metabolite called chloroacetaldehyde (CAA); CAA is similar to chloral hydrate, and so sedation is seen initially with ifosfamide, typically in higher doses given over longer periods of time; rarely, the drug methylene blue may need to be used to treat patients who are having encephalopathy symptoms and signs after receiving ifosfamide; it is important to monitor CNS function; this can be challenging clinically if patients are also receiving other sedatives, such as lorazepam for nausea; try to minimize sedatives in patients receiving ifosfamide

Other alkylating and DNA binding agents: include the platinum compounds, cisplatin, carboplatin, and oxaliplatin; these form reactive species with DNA; all of these agents, much like the taxanes and vinca alkaloids, are neurotoxic with multiple cycles

Cisplatin: is the more common neurotoxic drug vs oxaliplatin and carboplatin; it is also nephrotoxic; it has a dose-dependent nephrotoxicity; previously, doses as high as 120 mg/m2 at a single dose were given; however, that is no longer necessary; split dose and lower dose cisplatin have become the norm in head and neck cancer and lung cancer (both small cell and non-small cell but more commonly small cell); it is nephrotoxic, and patients need to be hydrated well regardless of dose, with normal saline-containing fluids; patients may be given mannitol, which acts as an osmotic diuretic, to help promote the excretion of cisplatin through the urine; if patients develop nephrotoxicity, it is manifest as increased creatinine, which occurs from ~3-7 days after administration of a single dose; creatinine can go up, usually peak and then at some point either return to normal or stay where it is; nephrotoxicity can be reversed in most patients; patients at risk are those with low magnesium at initiation; the drug itself also causes magnesium wasting; monitoring magnesium in patients receiving cisplatin is important; cisplatin has a lower myelosuppression rate than carboplatin and oxaliplatin in the same class; however, most doses of cisplatin are highly emetogenic and giving multiple antiemetics is important

Carboplatin: is primarily renally cleared; as a single agent, carboplatin's dose-limiting toxicity is thrombocytopenia; a pharmacokinetic and pharmacodynamic model, created by Hilary Calvert and published in the 1989 *Journal of Clinical Oncology*, contained an equation in which exposure was directly linked in a linear fashion to thrombocytopenia; in the Calvert equation, the dose in absolute mg (not mg/m^2) = target AUC [area under the curve] (target mg x min/mL) x (the patient's estimated GFR [or creatinine clearance] + 25); typically our goal AUC for treatment is anywhere from 5-8 with 6 being common; the higher the AUC, the more the likelihood that single agent carboplatin will cause thrombocytopenia; it is renally cleared, but you use this formula regardless of renal function; it plugs in renal function, then allows you to calculate a specific dose for a patient based on their underlying renal function; you do not have to think about creatinine, you just have to know creatinine clearance; you do not have to empirically dose reduce because the formula does that for you; again, thrombocytopenia is the primary end point of this formula, so platelet counts are a concern when carboplatin is given with paclitaxel; carboplatin does not have as high a degree of thrombocytopenia when given with paclitaxel as when given as a single agent

Carboplatin hypersensitivity: carboplatin is associated over time, typically after ≥6 cycles, with an IgE-mediated hypersensitivity; as an example, an ovarian cancer patient who is on ongoing carboplatin-containing therapy may show up for cycle 7 and suddenly, on the first drop of carboplatin infusion, have an anaphylactic reaction, which is an immunologically based IgE-mediated mechanism; therefore, one may need to desensitize patient if further carboplatin therapy is needed

Oxaliplatin: is primarily used in luminal GI cancers, colon cancer being the classic, but also pancreatic cancer and others; it can cause nausea, vomiting; a classic peripheral neuropathy can be associated with it and can be seen from the first dose, specifically a cold-sensory and cold-exposure dysesthesia; patients may have sharp pain in their hands if they are outside in winter or if they drink a very cold beverage after receiving oxaliplatin; it can also be linked to the type of peripheral neuropathy spoken of earlier with cisplatin and is similar in distribution to that seen with

taxanes and vinca alkaloids; peripheral neuropathy with tingling in the hands and feet and occasional burning can occur; patients need to be monitored carefully, as this is often the dose-limiting toxicity for oxaliplatin; oxaliplatin also causes myelosuppression; if one is using the FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) regimen with bevacizumab, and the patient has myelosuppression, dropping the bolus of 5-FU and just giving continuous infusion, or potentially reducing the dose of oxaliplatin may be necessary

Methylating agents: also in alkylating agent class; are rarely used, but are seen sometimes in brain tumors and other areas; dacarbazine and procarbazine are also DNA binding agents in this class; procarbazine can have unusual AEs; the meat and cheese reaction, (ie the tyramine reaction) occurs with procarbazine use; therefore, patients should be advised to avoid aged meats and cheeses to prevent a hypertensive crisis

Differentiating agents: include all-trans retinoic acid (ATRA) used in acute promyelocytic leukemia, arsenic trioxide and HDACi

ATRA: primarily used in patients with M3 subtype of acute myeloid leukemia (AML-M3); it turns on a system that causes rapid differentiation of leukemic clones into normal cells; when patients with AML-M3 start ATRA, they need to be monitored carefully for a variety of reasons; one is that if you create a situation where a large increase in normal myeloid progenitors is being pushed through a system, you can have a rapid rise in white count; this may lead to differentiation syndrome, characterized by difficulty breathing, white cell infiltration into the lungs, and some degree of hemodynamic changes; in patients who start to experience these AEs, early and aggressive dexamethasone needs to be implemented to lyse these cells, and ATRA can be continued; should patients get into a very extreme situation needing more intensive therapy and monitoring, ATRA should be held

Arsenic trioxide: used in acute promyelocytic leukemia; can also have a differentiation syndrome associated with it when used early on or in a refractory setting; with arsenic it is important to follow cardiotoxicity parameters to prevent arrhythmias; specifically, patients undergoing therapy with arsenic need to have a QTc of less than 450 ms and need to have their electrolytes normalized prior to arsenic therapy, because it causes QT prolongation in and of itself

HDACi: classic drugs in this group are vorinostat, panobinostat, romidepsin, etc; these agents had initial promise in the treatment of both hematologic and solid tumor malignancies; however, they now are primarily useful for hematologic cancers, particularly T-cell lymphomas; HDACi work by repressing an inhibitory enzyme, which allows for cells to grow unchecked; the lymphomas, both T- and B-cell, are more commonly susceptible to this pathway; HDACi are typically associated with thrombocytopenia; the first HDACi, valproic acid, was discovered through patients receiving the drug for indications other than cancer having idiosyncratic reductions in their platelets; an investigation of valproic acid's mechanism on those cells led to the molecular biology discovery of histones and histone deacetylases in cancer; these drugs are both oral and IV; AEs include fatigue and thrombocytopenia

Summary: this lecture has covered classes of drugs that work on the cell cycle; some are cell-cycle specific, eg, antimetabolites, taxanes and vinca alkaloids, which work during the M phase; alkylating agents are cell-cycle independent and work in any cell-cycle phase as long as the cell itself is in a growth phase rather than a quiescent phase; radiation is technically an alkylating agent; however, it is focally delivered and is not necessarily going to work across different areas; within these drugs it is important to note that many cause myelosuppression (a dose-limiting toxicity), also many of these drugs are classically used in conditioning regimens for stem cell transplants because of their linear dose-response curve; drugs that cause renal changes based on creatinine clearance (Ara-C, MTX, capecitabine, cisplatin, melphalan, fludarabine, topotecan) need to be adjusted for renal function if patients have creatinine clearances ≤50, and each of them has a different side-effect profile based on their renal functions; remember, carboplatin takes creatinine clearance into account, so you do not have to empirically dose-reduce carboplatin while targeting the same AUC; some of these drugs may have hepatic alterations as well; with the exception of irinotecan, most are not hepatically cleared but they may have hepatoxicity associated with them; many people think MTX causes hepatic toxicity; however, the reality is that hepatotoxicity is most commonly seen when MTX is used in rheumatoid arthritis; this is chronic use, low-dose therapy given over an extended period of time; high dose busulfan can be associated with sinusoidal obstruction syndrome/veno-occlusive disease when given in transplant; acute hepatic issues occur with busulfan and rarely melphalan; busulfan therapeutic concentrations are often measured in patients undergoing transplant to prevent that specific AE

Suggested Reading

Todd A, Groundwater PW, Gill JH: *Anticancer therapeutics: from drug discovery to clinical applications*. Hoboken, NJ: Wiley-Blackwell; 2017; **Shah RR:** Safety and tolerability of histone deacetylase (HDAC) inhibitors in oncology. *Drug Saf.* 2019 Feb;42(2):235-45.

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Anti-Cancer Drugs II: Bleomycin

Alex Adjei, MD, PhD, *Professor of Oncology, Professor of Pharmacology, Consultant, Division of Medical Oncology, Mayo Clinic, Rochester, MN*

Bleomycin: compound comprised of two components; 70% bleomycin A2; 30% bleomycin B2; water soluble glycopeptide antibiotics isolated from cultures of *Streptomyces verticillus* bacteria

Mechanism of action: production of double-strand DNA breaks; cells more sensitive to drug in G2 phase of cell cycle

Administration: drug administered by multiple routes, subcutaneous, intravenous, or intramuscular; no difference in efficacy regardless of route of administration; safely administered into pleural or peritoneal space to control malignant effusions; method replaced by more efficient pleural catheters for malignant effusions

Excretion: mainly excreted in urine; 50% to 75% of administered dose excreted in first 24 hours; dose modification required in patients with compromised renal function

Uses: used in combination regimens to treat squamous cell carcinomas of skin, genitalia, and head and neck; activity against Hodgkin and non-Hodgkin lymphomas; commonly used for curative treatment of testicular carcinoma in combination; more recently, bleomycin use almost exclusively limited to treatment of testicular carcinoma; narrowly used in typical oncology practice; does not cause myelosuppression; readily allows for combinations with other chemotherapy agents

Pulmonary toxicity: most common and significant adverse event from bleomycin; two different syndromes

Interstitial pneumonitis: more typical syndrome; occurs in up to 10% of patients; patients present with dyspnea, tachypnea, and nonproductive cough; may hear rhonchi throughout lungs; chest x-ray and CT scans show patchy infiltrates and diffuse interstitial fibrosis; nodules may be present and can be confused with disease progression; appears somewhat dose dependent; relatively uncommon at low doses; incidence significantly increases above cumulative dose of 400 units of bleomycin; age >70, prior thoracic radiotherapy, renal insufficiency, and exposure to high oxygen tensions among other factors contributing to development of pulmonary toxicity; use caution when administering supplemental oxygen to patients on bleomycin

Hypersensitivity pneumonitis: second pulmonary syndrome; presents as cough, dyspnea, and rash; radiologic appearance can be similar to more common interstitial pneumonitis; unlike interstitial pneumonitis, hypersensitivity pneumonitis can occur at very low cumulative doses; also differentiated by peripheral eosinophilia on complete blood count and lung biopsy histology consistent with hypersensitivity reaction

Other toxicities: febrile reaction common with administration of drug; fever can be severe with patients developing hyperpyrexia syndrome characterized by high fever followed by excessive sweating, wheezing, mental confusion, and even hypotension; Raynaud's phenomenon can occur; dermatologic toxicity generally presents as erythema, induration, desquamation, and hyperpigmentation; pretreatment with acetaminophen and diphenhydramine can decrease incidence of hypersensitivity and febrile reaction

Trabectedin: also known as Yondelis® or ET-743; marine-derived compound initially isolated from Caribbean sea sponge; currently almost exclusively produced synthetically

Mechanism of action: complex; binds to minor groove of DNA; transcriptional interference by blocking DNA binding of transcriptional factors, which then promotes differentiation and reverses oncogenic phenotype; uniquely targeted; pathognomonic chromosomal translocation produces fusion oncoprotein in myxoid liposarcomas; trabectedin interferes with ability of fusion protein to bind to DNA promoter regions; results in broad antineoplastic effects; trabectedin can inhibit overexpression of multidrug-resistant gene MDR1 for P-glycoprotein, a major factor responsible for resistance to natural compounds used for anti-cancer therapy, including doxorubicin, daunorubicin, paclitaxel, and docetaxel

Use: FDA-approved as single agent for treatment of patients with soft tissue sarcomas, predominantly liposarcoma and leiomyosarcoma, previously treated with anthracycline-containing chemotherapy regimen or intolerant to anthracyclines; particularly effective in myxoid round cell liposarcoma; also approved by European Medicines Agency for patients with advanced soft tissue sarcoma experiencing disease progression after doxorubicin and ifosfamide

Toxicities: carries one in four risk of severe and fatal neutropenic sepsis, rhabdomyolysis, and hepatotoxicity; skin and soft tissue necrosis can occur following extravasation; heart failure also occurs; common side effects include fatigue, GI toxicity, headache, musculoskeletal pain, liver function abnormalities, and creatine phosphokinase elevations

Dosing: recommended starting dose of trabectedin 1.5 mg/m^2 administered intravenously over 24 hours on day one every 21 days through central venous line; dose adjustment recommended for moderate hepatic

impairment with recommended dose of 0.9 mg/m^2 in patients with bilirubin levels 1.5 to 3 times upper limit of normal and AST and ALT less than 8 times upper limit of normal; administration discouraged in severe hepatic impairment; pre-medication with dexamethasone shown to reduce hepatotoxicity risk

L-Asparaginase: enzyme with antileukemic activity; isolated from *E. coli* or *Erwinia carotovora* bacteria; first anti-cancer agent to interfere with tumor metabolism; FDA approved in 1978; two additional pegylated *E. coli*–derived products available

Mechanism of action: asparaginase hydrolyzes L-asparagine to L-aspartic acid and ammonia in leukemic cells; results in depletion of asparagine, inhibition of protein synthesis, cell cycle arrest in G1 phase, and apoptosis in susceptible leukemic cell populations; asparagine critical to protein synthesis in leukemic cells; many cells cannot synthesize asparagine de novo due to absence or deficiency of enzyme asparagine synthetase; L-asparaginase lethal in these cells

Adverse effects: patients can develop anti-asparaginase antibodies, leading to a significant decrease in the half-life of the drug; infusion reactions common; predominant toxicity of L-asparaginase; reactions range in severity from localized transient erythema and rash at injection site to life-threatening anaphylaxis; patients typically have pain, tenderness, swelling, and erythema at injection site, particularly when drug given intramuscularly; can also develop dyspnea, bronchospasm, pruritus, skin rash, and urticaria when administered intravenously; other symptoms include hypotension, laryngospasm, and angioedema in severe cases; most infusion reactions occur between second to fourth infusions within minutes of administration; can occur several hours or later after administration; delayed hypersensitivity reactions occurring hours or days after administration more common with pegylated, slow release forms with slow primary antigen exposure to body; infusion reactions more common with intravenous route of administration; more immunogenic non-pegylated forms frequently given subcutaneously or intramuscularly, while pegylated products often given intravenously to minimize painful medication administration

Half-life: can range from 5 to 17 days for pegylated products

Use: acute lymphoblastic leukemia, acute myelogenous leukemia, and non-Hodgkin lymphoma; currently utilized almost exclusively in acute lymphoblastic leukemia

Therapeutic drug monitoring: data suggests trough serum asparaginase levels >0.1 international units per mL therapeutic; patients treated with pegylated slow release formulations sometimes do not achieve target trough levels; moving to *Erwinia* bacteria preparation will typically result in improved outcomes

Mitotane: currently used only in palliative treatment of adrenocortical carcinoma; isomer of insecticide DDD, analog of DDT, produced in adrenal cortex in dogs; mitotane's chemical name is 1,1(Dichlorodiphenyl)-2,2-dichloroethane; cytotoxic agent; inhibits steroidogenesis but also has adrenal activity with long-acting use

Mechanism of action: unclear; known to act directly on adrenocortical cell mitochondria to inhibit 11 beta-hydroxylase and cholesterol side-chain cleavage enzyme; metabolized into acyl chloride binding to important micro[macro? Recording unclear]molecules in mitochondria; causes mitochondrial destruction and necrosis of adrenal cortical cells

Administration: orally; ≈40% bioavailable; like DDT, significant amount of drug stored in body fat; drug disappears slowly from serum over period of months once therapy discontinued; concern for toxicity

Toxicities: gastrointestinal with significant nausea and vomiting; central nervous system side effects including somnolence, lethargy, ataxia, and visual disturbances can occur; drug metabolized in liver; employ caution in patients with hepatic dysfunction; effects of mitotane can be nonspecific with effects on adrenocortical carcinoma cells and normal adrenals; prolonged administration can result in primary adrenal insufficiency; monitor urinary free cortisol levels; institute glucocorticoid replacement therapy when appropriate

Therapeutic drug monitoring: treatment usually initiated at 0.5 g twice daily; increased to 6 g daily over 4 to 12 weeks, based on tolerability; some patients unable to tolerate doses >2 g per day; most patients tolerate wide range; target serum concentrations of 14 to 20 mcg per mL; increase doses until toxicity seen when serum monitoring unavailable; doses then adjusted to tolerability; patients may tolerate 6 to 8 g per day in two divided doses

Anti-estrogens: comprise estrogen receptor antagonists and aromatase inhibitors

Estrogen receptor antagonists:

Tamoxifen: unique as mixed estrogen receptor agonist/antagonist; antagonist of estrogen effects in some organs such as breast and agonist in bone and endometrium; called selective estrogen receptor modulator (SERM)

Mechanism of action: tamoxifen inhibits signaling of estrogen receptor by competitively antagonizing effect; endocrine agent of choice for adjuvant treatment of premenopausal women at low to average risk; also indicated for postmenopausal women unable to receive aromatase inhibitors for any reason

Pharmacodynamics: originally used 10 mg twice daily; long half-life of 5 to 7 days caused switch to once daily dosing; currently almost universally used at 20 mg tablet once daily; considered prodrug because of metabolic conversion to primary metabolites 4-hydroxy-tamoxifen and endoxifen; ≈100 times more potent than parent tamoxifen at suppressing estradiol-stimulated breast cancer cell growth; endoxifen most abundant tamoxifen metabolite; produced after activation of parent tamoxifen by cytochrome P450 system isoenzyme 2D6 or CYP2D6; oxidizes tamoxifen to endoxifen; National Cancer Institute (NCI) synthesized endoxifen; studies at NCI, Mayo Clinic, and cooperative group settings evaluate endoxifen as agent in breast cancer; great interest in CYP2D6 enzyme activity in women taking tamoxifen and effects on efficacy due to genetic polymorphisms in CYP2D6; hot flashes side effect of tamoxifen; agents used to treat hot flashes include serotonin receptor inhibitors fluoxetine, paroxetine, venlafaxine, and others; all these agents

substrate for CYP2D6; concern that co-administration with tamoxifen might alter efficacy of tamoxifen by competing for conversion to more active endoxifen; studies show conflicting results; unclear whether CYP2D6 polymorphisms affect survival in women given tamoxifen; be careful with co-administration of CYP2D6 inhibitors, particularly ones used to treat hot flashes

Flare phenomenon: cases of initial flare-up on bone scan, suggesting significantly progressing disease, when starting tamoxifen in women with metastatic bone disease; patients may have bony symptoms of pain and stiffness; be careful not to prematurely stop tamoxifen; typical time course of bony complaints is 4 to 8 weeks; bone scans showing increasing activity may look like progressive disease, but once tamoxifen continued, women will have good responses; because of agonist effects of tamoxifen, improved bone health and cardioprotective effects shown with tamoxifen use

Side effects: endometrial hyperplasia and occasionally increased incidence of endometrial cancer due to agonistic effects of tamoxifen on endometrium; hot flashes common side effect; risk of thromboembolic disease; development of cataracts documented in small proportion of women on long-term tamoxifen; risk of cataracts seems to be low; thromboembolic disease more common; documented cases of deep vein thrombosis in extremities and pulmonary embolism

Advantages: consistently proven benefit of tamoxifen in preventing breast cancer in contralateral breast in women previously diagnosed with breast cancer; advantage over aromatase inhibitors; data suggesting tamoxifen can be chemopreventive agent in high-risk women, but is not much used for this purpose due to risk of toxicities

Fulvestrant: pure antiestrogen; antagonizes estrogen receptor; no agonistic effects; selective estrogen receptor degrader due to mechanism of action of binding to estrogen receptor; binding makes receptor more hydrophobic; leads to instability, misfolding, and degradation by ubiquitin/proteasome system; previously indicated for postmenopausal women with hormone receptor positive disease; 500 mg intramuscular injection; typically day one, 15, 29, and then monthly; use previously curtailed due to painful injection and restricted primarily to situations where patients had progressed on tamoxifen with no other options available; data suggests drug efficacious in patients progressing on tamoxifen; tamoxifen competitive inhibitor of receptor; upregulation of receptor or increased signaling as mechanism of resistance to tamoxifen; fulvestrant then degrades receptor; use in patients progressing on tamoxifen declined with widespread availability of aromatase inhibitors

Use: widespread acceptance when combined with CDK4/6 inhibitors palbociclib, abemaciclib, and ribociclib used in combination in patients with disease progressing on first-line hormonal therapy; when used in combination with cyclin-dependent kinase 4/6 inhibitors, treatment continued to progression or unacceptable toxicity; treatment combination alone in postmenopausal women; suggested pre- or perimenopausal women be treated with luteinizing hormone releasing hormone agonists such as goserelin or zoladex and leuprolide

Side effects: include nausea, injection site reactions, fatigue, and elevated transaminases; injection can be very painful; hypersensitivity reactions have occurred; anorexia, headache, and diarrhea can occur; as with tamoxifen, venous thromboembolism can occur; <1% incidence

Aromatase inhibitors: inhibit plasma estrogen levels by inhibiting aromatase enzyme responsible for peripheral conversion of androgens to estrogens; ovaries main source of estrogen in premenopausal women; estrogen produced in peripheral tissues when ovarian function declines at menopause; locally produced estrogen exerts effects locally in source organ; may be metabolized there; measurable amount escapes into circulation and can exert effects on distant organs including breast; primary effect of aromatase inhibitors on extragonadal aromatization of androgen to estrogens; aromatase inhibitors ineffective in premenopausal women with full ovarian function as most body estrogen produced in ovary; premenopausal women becoming amenorrhoeic after chemotherapy for breast cancer may not respond to aromatase inhibitors; must undertake ovarian ablation or suppression in all premenopausal women before utilizing aromatase inhibitors

Use: currently preferred adjuvant treatment of postmenopausal women with breast cancer; tamoxifen should only be used in women intolerant of aromatase inhibitors; three agents widely used; steroidal aromatase inhibitor exemestane — irreversible steroidal inhibitor; forms permanent bond with and deactivates aromatase enzyme; anastrozole and letrozole nonsteroidal aromatase inhibitors; compete reversibly with aromatase; inhibit estrogen synthesis; data from clinical trials suggests efficacy and tolerability between aromatase inhibitors seems equivalent; individual variation in toxicity; use agents based on tolerability; switch to alternative agent if one agent not tolerated

Side effects: can be severe; some women discontinue due to intolerance of side effects; unlike tamoxifen, which has been used >40 years with well characterized long-term effects, more long-term data needed for effects of aromatase inhibitors; worrisome effects include musculoskeletal pain and stiffness, hot flashes similar to tamoxifen, sexual dysfunction, and cognitive effects; in contrast to positive effects on bone and cardiovascular system seen with tamoxifen, aromatase inhibitors associated with higher risk of osteoporosis, fractures, cardiovascular disease, hypercholesterolemia, and diabetes; bone effects particularly troublesome when used in premenopausal women; lower risk of venous thrombosis and endometrial cancer compared to tamoxifen

Antiandrogens: older agents; three major agents; flutamide, bicalutamide, and nilutamide; block binding of androgens, primarily dihydrotestosterone, to androgen receptor; block functioning of receptor; may be used as initial treatment in patients with castration-resistant prostate cancer; primarily used to block flare reaction secondary to initial rise in testosterone when using gonadotropin releasing hormone (GNRH) agonists; total androgen blockade used to be predominant approach; goal of inhibiting testicular and adrenal androgens using GNRH agonists or orchiectomy with added antiandrogen such as bicalutamide to completely block testosterone; approach has fallen out of favor, since significant survival advantage not observed

Side effects: mechanism based; related to androgen withdrawal; occur across whole class; include hot flashes, gynecomastia, decreased libido, galactorrhea, impotence, and sometimes diarrhea

Use:

Antiandrogen rotation: antiandrogens previously rotated in patients with refractory progressive castration-resistant prostate cancer at time with few alternative agents; belief specific antiandrogens may interact with androgen receptor differently by binding different parts of receptor; rotating to obtain benefit rarely used now

First generation antiandrogens: seldom used in West; use of flutamide now out of favor due to frequent diarrhea, nausea, and vomiting in addition to anti-androgenic side effects; though uncommon, fatal hepatotoxicity has also occurred with flutamide; bicalutamide preferred agent when older antiandrogens used due to better toxicity profile; some evidence in large randomized trials bicalutamide more efficacious; nilutamide second agent of choice

Antiandrogen withdrawal: a decade ago, anti-androgens mainstay for patients with metastatic prostate cancer with progressive disease after prior orchiectomy or leuprolide; previous approach of adding antiandrogen like flutamide would usually lead to transient benefit; antiandrogen withdrawn after further disease progression; approach also used when patients treated with total androgen blockade with GNRH agonists and flutamide developed progressive disease; initial step was [anti- ? editor] androgen withdrawal; discontinuation of treatment with anti-androgen resulted in objective benefit with PSA responses and sometimes improvement in symptoms; these approaches may remain valid even with availability of newer agents; antiandrogen withdrawal not used as often now due to other agents to choose from, but approach worth keeping in mind

Androgen receptor antagonists: include enzalutamide, apalutamide, and darolutamide; agents all orally administered; act at multiple sites; interfere with androgen receptor signaling; documented mechanisms include inhibition of binding of androgen to receptor; agents documented to inhibit nuclear translocation of androgen receptor, a necessary step for signaling and biochemical effects; also able to inhibit association of androgen receptor with nuclear DNA; three sites of action; blocking interaction of androgen to receptor can inhibit receptor translocation into nucleus; can also inhibit interaction of receptor with nuclear DNA; enzalutamide first agent in androgen receptor antagonist class; has significant efficacy; penetrates blood-brain barrier; CNS effects and seizures occasionally documented; newer agents apalutamide and darolutamide have fewer CNS effects; preferred in certain situations; current data suggests seizure activity of enzalutamide related to penetration of blood-brain barrier and interaction with gamma-aminobutyric acid (GABA) type A receptors; incidence of seizures with enzalutamide can be as high as 2%

Use: approved for metastatic prostate cancer; significant efficacy; agents tend to have limited activity in case where patients have received abiraterone and docetaxel; use of agents in men with rapidly doubling PSA but no obvious evidence of metastatic disease under investigation

GNRH agonists: used for >40 years; currently five agents in class; leuprolide, goserelin, triptorelin, buserelin, and histrelin; leuprolide and goserelin oldest agents and most commonly used

Administration: all parenterally administered; goserelin can be administered intranasally; agents given by depot preparation; formulations have improved so agents can be given every 3 or 4 months; significant benefit for patient compliance

Mechanism of action: GNRH agonists more potent than natural hormone; bind to receptors in pituitary and cause initial increase in release of luteinizing hormone and follicle stimulating hormone; monotherapy with agents can be hazardous in presence of metastatic prostate cancer; transient large increase in testosterone dumped into circulation after activation of LH and FSH; hormones ordinarily cyclical with pulse releases and quiescence; once one activates receptors continuously, all stored testosterone dumped into circulation; leads to situation with minimal secretion

Negative effects: initial increase in serum testosterone levels can activate growth of prostate cancer cells; in presence of soft tissue disease around spinal cord, transient increase in swelling and cord compression can develop; cases of paralysis occasionally documented; patients may have significant pain and debility from these actions in cases of diffuse bony disease; now typically patients receive anti-androgen, blocking interaction of testosterone with androgen receptor, followed by agonists to prevent flare reaction and significantly reduce morbidity; with continued administration of GNRH agonists, receptors downregulated from continuous stimulation; leads to decline in pituitary production of luteinizing hormone and follicle stimulating hormone; decreased levels lead to decrease in testosterone levels to castrate levels in ≈4 to 6 weeks; when used with anti-estrogens [?] for purposes of reducing flare, anti-estrogens can be stopped after 4 weeks; castrate level of testosterone = serum level <50 ng/dL; cutoff represents that observed with orchiectomy; this is considered adequate castration testosterone levels after use of these agonists; in certain instances testosterone levels can rebound somewhat when GNRH agonists discontinued; contrast with orchiectomy, which is irreversible; GNRH agonists also used due to psychological impact of orchiectomy on patients

Therapeutic drug monitoring: not routine in management of prostate cancer; target level of testosterone used instead; give consideration to alternate or adjunctive methods of androgen blockade when using GNRH agent alone and testosterone levels consistently >50 ng/dL; might then add anti-androgen

GNRH antagonists: prostate cancer growth promoted by testosterone; reducing circulating testosterone to castrate levels goal of hormonal therapy for prostate cancer; GNRH agonists cause transient release of testosterone after use; can lead to significant complications; cases of urinary retention also seen; start agents together with anti-androgens; GNRH antagonists introduced to overcome these issues; antagonists block GNRH receptor; advantage

over agonists; rapid decrease in circulating testosterone due to direct receptor inhibition; flare effect and associated complications do not occur; do not need to be used with anti-androgens; agents found useful particularly in patients with prostate cancer bulky disease where fast control of disease needed; some agents peptide molecules; include degarelix approved in US and ganirelix and cetrorelix; abarelix previously approved but withdrawn from US market; small molecule drugs elagolix and relugolix can be administered orally; others administered subcutaneously or by intramuscular injection; use continues to evolve; relatively new; more information needed on long-term toxicity and safety

Inhibitors of androgen synthesis: androgens produced primarily in testes and adrenals in males; in cases of prostate cancer, some androgens produced by tumor cells themselves; leads to autocrine-paracrine loop where tumor secretes some androgens stimulating growth; testes removed as source of androgens in cases of orchiectomy; prostate cancer cells continue to grow in castrate-resistant prostate cancer even in absence of significant testosterone produced by testes; agents inhibiting synthesis of androgen useful; previously studied; aminoglutethimide and ketoconazole two older agents typically used in end-stage prostate cancer; not used frequently due to high toxicity and transient efficacy

Abiraterone: potent inhibitor of androgen synthesis; introduced for treatment of castrate-resistant prostate cancer; inhibits CYP17; by so doing blocks synthesis of androgens systemically; can block synthesis in testes, adrenal glands, and skin

Administration: standard dose 1 g taken once daily by mouth on empty stomach; patients can take agent 1 hour or more before food or 2 hours or more after food; due to CYP17 blocking, inhibition of enzymes not limited to single enzyme; can inhibit 17-20- lyase and 17 alpha-hydroxylase; 17 alpha-hydroxylase inhibition leads to decrease in serum cortisol; compensatory rise in adrenocorticotrophic hormone; results from hypothalamic response to partial adrenal inhibition by abiraterone; always given with concomitant glucocorticoids, typically prednisone, for this reason; prevents clinical adrenal insufficiency since cortisol production preserved; complex adrenal hormone interactions have led to hypertension and hypokalemia in some patients; for effective use, patients on abiraterone should have had orchiectomy or be on GNRH receptor agonist or antagonist; agent currently indicated in combination with prednisone for metastatic castrate-resistant prostate cancer; recent data suggest drug will also have activity in castration-sensitive prostate cancer patients with metastatic disease at high risk

Side effects: most commonly include fatigue, myalgias, headache, some nausea, vomiting, diarrhea, and peripheral edema; hypertension and hypokalemia can occur; hepatotoxicity and adrenal insufficiency unusual but severe side effects

Suggested Reading

Della Latta V, et al: Bleomycin in the setting of lung fibrosis induction: from biological mechanisms to counteractions. *Pharmacol Res.* 2015 Jul;97:122-30; **Gucalp A, et al:** The androgen receptor: is it a promising target? *Ann Surg Oncol.* 2017 Oct;24(10):2876-80; **Megerle F, et al:** Mitotane monotherapy in patients with advanced adrenocortical carcinoma. *J Clin Endocrinol Metab.* 2018 Apr;103(4):1686-95; **Shagufta, et al:** Tamoxifen a pioneering drug: an update on the therapeutic potential of tamoxifen derivatives. *Eur J Med Chem.* 2018 Jan;143:515-31.

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Anti-Cancer Drugs III: Targeted Therapies and Monoclonal Antibodies

R. Donald Harvey, III, PharmD, *Professor, Departments of Hematology, Medical Oncology, and Pharmacology, Emory University School of Medicine, and Director, Phase I Clinical Trial Section, Winship Cancer Institute of Emory University, Atlanta, GA*

Introduction: targeted therapies and monoclonal antibodies are two classes of drugs that have altered how clinicians think about cancer; monoclonal antibodies are some of the most targeted therapies used to treat cancer and are often added to backbones of chemotherapy or small molecule inhibitors with a number of specific targets in the monoclonal antibody space; lecture will cover VEGF (vascular endothelial growth factor), EGFR (endothelial growth factor receptor), HER2 (human epithelial growth factor 2), many of the CD markers including CD20, CD30, CD38; next, discussion will focus on some of the targeted therapies and small molecule inhibitors including PARP (poly (ADP-ribose) polymerase) inhibitors, proteasome inhibitors, other kinase inhibitors, and some of the other areas of therapy within cancer that are monoclonal-antibody driven

Monoclonal Antibodies

Monoclonal antibodies — two types: can be developed either as so-called naked antibodies, which is the antibody alone, which would be expected to bind to a specific ligand or receptor and then cause a therapeutic effect; other group of drugs in this class are antibody-drug conjugates, which are the antibodies themselves, a linker, and what is referred to as a payload; payload is classically something like a maytansinoid; maytansinoids are tubulin-active agents, so it is similar to giving combined monoclonal antibody with chemotherapy in a Trojan-horse-like approach; adverse event profiles from those drugs can be different

Anti-VEGF compounds:

Bevacizumab**:** First drug in class; approved and used in many different cancers; colorectal cancer and lung cancer are primary areas; inhibition of VEGF leads to inability of cancer cell to gather cellular and blood vessel nutrients; thus, inhibiting VEGF may have some off-target effects; bevacizumab inhibits the VEGF ligand; binds to the ligand and not the receptor; important, because there still may be activity of bevacizumab and off-target effects; VEGF has multiple paths and different responsibilities within the human system; proteinuria and hypertension may be seen with bevacizumab therapy; these are off-target effects of VEGF inhibition; all monoclonal antibodies, independent of target, tend to have a similar approach to dosing strategy and half-life; all are IgG1 or IgG4 molecules; they circulate in blood with a half-life of 10 to 14 days; some are outside that window, some are below that window, but overall, bevacizumab exhibits pharmacokinetic parameters similar to other monoclonal antibodies

Ramucirumab: another monoclonal antibody, directed specifically against VEGF receptor 2; both ramucirumab and bevacizumab can cause hypertension and proteinuria; can also cause bleeding and thrombotic risks due to on-target effects of VEGF inhibition; gastric cancer, lung cancer, colorectal cancer, renal cell carcinoma, and others have all been shown to be susceptible to VEGF inhibition, either via a monoclonal-antibody-directed therapy or small molecule inhibitors, so VEGF is an important target in the monoclonal antibody space

EGFR (epidermal growth factor receptor) inhibitors: class of monoclonal antibodies referred to as the first of the series of HER (human epidermal growth factor receptor) inhibitors; EGFR can be targeted either by a monoclonal antibody on the external cell surface or by a small molecule targeting the tyrosine kinase end of the receptor intracellularly

Cetuximab**:** 1st EGFR antibody was cetuximab, a chimeric antibody; that is what the U-X-I in the middle means; there are chimeric antibodies, which are partially murine and partially human; there are humanized or fully human antibodies as well; the fact that cetuximab is a chimeric antibody is important, because it means that there may be higher risk of infusion reactions; cetuximab's primary use is in head and neck cancer; also used in other cancers, such as colorectal, in specific populations; with cetuximab, infusion reactions can be seen with the 1st dose or 1st drop of drug; some patients, particularly those in the Southeast, have an endogenous response to cetuximab — an IgE-mediated adverse event; immune reaction can be severe; patients are premedicated with diphenhydramine prior to each infusion to prevent this, but doesn't prevent it in all patients; can be life-threatening; patients should be monitored carefully during their first infusion of cetuximab

Panitumumab: another drug in this class; is humanized, or more human than cetuximab, and has also been looked at in colorectal cancer

Rash: anti-EGFR compounds, whether antibodies or small molecules, but particularly the antibodies, can cause acneiform rashes; patients should be followed and counseled that they may have such rashes when receiving cetuximab; this drug has a long half-life, 14 to 21-days; is given intermittently across different therapies and different regimens, depending on combinations; may be seen with radiation in head and neck cancer as well as others; important backbone of therapy; when acneiform

rash is seen, may be treated with typical acne-type medicines; some clinicians may resort to oral antibiotics or topical therapies to try to prevent it

HER2 monoclonal antibodies: classic HER2 monoclonal antibody is trastuzumab; patients receiving therapy with HER2-directed monoclonal antibodies, unlike other monoclonal antibodies in this space, must be shown to have expression of HER2 in tumor tissue; classically has been breast cancer, but gastric cancer is also part of this group; ~20% of breast cancers overexpress HER2; similar and in same class of enzymes as EGFR, HER2 is a transmembrane protein, so can be targeted either by a monoclonal antibody or a small molecule inhibitor such as lapatinib or neratinib

Available HER2-directed agents: four are available for potential treatment of HER2-positive breast cancer, as well as the small molecules lapatinib and neratinib; others are trastuzumab, an antibody that binds the extracellular domain; pertuzumab, which binds the extracellular dimerization domain of HER2 and prevents it from self-dimerization, required in HER2-directed signaling for cell growth; pertuzumab also prevents binding to other members of EGFR family, the EGFR receptor, HER3, and others; there is also an antibody-drug conjugate in this class of agents, ado-trastuzumab emtansine; has trastuzumab as a primary antibody, a linker, and an anti-microtubule agent, DM1; may be referred to as T-DM1

Trastuzumab toxicities: with all of these agents, HER2 is expressed in cancer itself, but is also expressed in other tissues, for example, cardiac myocytes; patients undergoing treatment with HER2 inhibitors should be monitored for cardiovascular function; typically, patients receiving trastuzumab for breast cancer therapy in the adjuvant setting should have baseline echocardiograms and intermittent interval measurement of ventricular capacity in the metastatic setting; one clinical approach is to get a baseline echo, monitor over time, and get another echo at the completion of therapy, or when patients have symptoms; somewhat dependent on investigator and clinician preference; in adjuvant trials of trastuzumab, patients have been monitored closely every ~3 months with echocardiographic measurement of their function; other toxicities tend to be mild

Determining HER2 overexpression: for breast, IHC (immunohistochemistry)or by FISH (fluorescence in situ hybridization); by IHC, it is classically a 3+ staining; by FISH it is a ratio of ≥2 or a HER2 copy number of 6; strongly predict sensitivity to this targeted therapy; use of HER2-directed therapy in breast cancer has changed the way clinicians think about the drug, typically in combination with other treatments

Pertuzumab: is given in combination with trastuzumab in patients who are able to tolerate it; typically given along with either a taxane, such as docetaxel, or an anthracycline-containing regimen; used in patients who are HER2 positive and show a benefit above and beyond only trastuzumab in combination with backbone chemotherapy; important addition in patients who can tolerate it; adverse events associated with pertuzumab are those caused by combination with trastuzumab and docetaxel; in the regimen, docetaxel can cause cytopenias; cardiovascular dysfunction can also be seen; so far, appears that addition of pertuzumab to trastuzumab does not increase the rate of heart failure, but decreased ejection fraction can be seen in ~10 to 15% of patients getting a 3-drug regimen including docetaxel and trastuzumab; would be higher in patients getting an anthracycline, so heart function should be monitored closely with those 3 drugs

Ado-trastuzumab emtansine: antibody-drug conjugate typically utilized in second-line treatment of patients with HER2+ breast cancer; associated with improved progression-free survival in those patients; is a different drug in that it is not only the antibody trastuzumab, it is also the emtansine moiety; neurotoxicity is seen with the microtubule inhibitor; cytopenias can also be seen with T-DM1; thinking carefully about its use in certain patients is important; neutropenia, neuropathy, and peripheral edema can all be seen, typically less common than with taxane-based therapy alone; counts and neurologic function should be monitored in patients receiving therapy; along with the antibody-drug conjugate, a subcutaneous (SQ) formulation of trastuzumab is now available and is given with hyaluronidase; can be administered on an outpatient basis; biosimilars of trastuzumab have been FDA approved and are awaiting release to the market

Anti-CD20 monoclonal antibodies:

Rituximab: first in class; is, like cetuximab, a chimeric IgG1 specific antibody to CD20; has been used across many different cancers; got its start in lymphomas, both diffuse large B-cell and follicular lymphoma; rituximab can cause a cell-dependent lysis when given, so early on, for example, in patients with CLL (chronic lymphocytic leukemia), clinicians need to ramp up the dose gradually, rather than give a full dose of 375mg/m2 from outset; in CLL, dose is increased over time to prevent this lysis, because drug lyses all CD20 positive cells in circulation or in lymph nodes, and in CLL, there are a lot of circulating cells; can be used in skin diseases, rheumatoid arthritis and other areas; rituximab, like trastuzumab, has a SQ formulation which can be helpful; development of biosimilars to rituximab is ongoing; patients receiving rituximab need to be premedicated against both the infusion reaction due to the drug and the lysis of the CD20 cells; need corticosteroids and diphenhydramine prior to rituximab therapy to prevent infusion reactions; rituximab and other drugs in this class, such as ofatumumab and others, all target CD20; all can be used and have activity and indications for lymphomas; patients need to be screened for hepatitis prior to starting rituximab therapy, because it can reactivate hepatitis in patients who have been previously infected; is a B-cell-targeted agent and targets every CD20 positive B cell; a reduction in B cells and subsequent secondary immunodeficiency may be seen following these anti-CD20 therapies; when added to the backbone of CHOP (cyclophosphamide, doxorubicin, vincristine/oncovin, prednisone/prednisolone) chemotherapy in lymphoma, rituximab substantially improves activity and has become, with other agents in the class, an important backbone of combination therapies in lymphoma

Related agents: along with rituximab in this class, ofatumumab and obinutuzumab are also available; other anti-CD20 agents are in development; there were two antibody-radioimmunoconjugates with rituximab linked

to radionuclides; these are off the market now, but were approved for lymphoma therapy

Brentuximab vedotin: there is one anti-CD30 monoclonal antibody available, an antibody-drug conjugate — brentuximab vedotin; indicated for treatment of Hodgkin lymphoma refractory to prior therapy; also added to chemotherapy in some trials for initial treatment of Hodgkin lymphoma; dosed every 3 weeks and, much like other drugs in this class, has neuropathy as a dose-limiting event; is for patients expressing CD30 in certain diseases like peripheral T-cell lymphoma; otherwise, specific testing for CD30 is not necessary in Hodgkin lymphoma; associated with substantial neuropathy; patients need to be monitored carefully; may need dose reductions or holds due to this adverse event; have also been elevated transaminases; rarely but occasionally causes the same adverse event associated with busulfan, a high-dose sinusoidal obstruction syndrome; these are rare, but patients do need to have monitoring for liver function, myelosuppression (related to the maytansinoid component), and neurotoxicity; specific guidelines exist for how to handle each of these adverse events; grade 2 neuropathy patients can have dose reductions of about 30%; grade 3 and 4 patients need to either have the drug withheld or discontinued, depending on severity of the adverse event; should be avoided in patients with moderate to severe hepatic impairment and in those with a creatinine clearance below 30

Anti-CD38 compounds: leader in class and only drug available currently is daratumumab; indicated across various uses in multiple myeloma; CD38 is expressed on plasma cells, but also on other cells; does not need to have CD38 staining, like rituximab for lymphoma, prior to its use; when infused, has adverse event profile that can be seen in patients getting the drug either alone or in combination; adverse event profile is reflective of its target; when infused, CD38 cells lyse; some CD38 positive cells are basophils; basophils within the lungs can be lysed and cause dyspnea and breathing disorder; therefore, premedications for daratumumab are extensive and include corticosteroids, diphenhydramine, and occasionally H2 antagonists; also include montelukast, a leukotriene inhibitor that allows patients to be given daratumumab while reducing the frequency and severity of dyspnea; acetaminophen is an important premedication; has a clearance that is target-mediated; the drug is given early, than more frequently, because there is more CD38 around; as it lyses the CD38 cells and the myeloma cellular volume diminishes, the same dose can then be used and clinicians can extend the interval of therapy; a SQ formulation is being developed and has been filed for approval; has taken many different paths within myeloma therapy and in different combinations, for example, with immunomodulatory agents, proteasome inhibitors, melphalan, and other compounds; other CD38 antibodies are in development, both naked and conjugated to other therapies

Anti-CD52 compounds: alemtuzumab is an anti-CD52 monoclonal antibody that historically was used for patients with CLL; still available, although use has declined over time; CD52 is expressed on a number of immunologic cells; complete eradication of CD52, which alemtuzumab produces, leads to significant increase in risk of infectious complications, for example, CMV, adenovirus, and other, rarer infections seen in lympho-depleted and immunodeficient populations; given SQ or IV, generally IV, because in patients with CLL, more antidrug antibodies were created when drug was given SQ; dose escalation is required, and usually clinicians want to get to single doses of 30mg titrated up from 10mg every 3 days or so; indications besides CLL have been investigated, such as refractory chronic graft-versus-host disease following allogeneic stem cell transplantation and solid organ transplantation; has been rebranded and used in multiple sclerosis; infections, including bacterial, viral, fungal, and protozoan, can happen in patients receiving alemtuzumab; prophylaxis against PCP (*Pneumocystis carinii* [now *Pneumocystis jirovecii*] pneumonia) and herpes virus is required if used in refractory CLL patients

Targeted Therapies

PARP [Poly (ADP-ribose polymerase)] inhibitors: have been evaluated in platinum-sensitive and platinum-refractory ovarian cancer; mechanism of PARP inhibition is such that it tends to be more effective in patients with ovarian cancer and other cancers with BRCA mutations; due to the BRCA mutation, cancer cell has inability to repair itself through normal means, and inhibiting PARP takes out another mechanism for repair; almost synergistic to have BRCA mutations along with PARP inhibition; a number are FDA approved; an interesting pathway that will continue to grow in patients with other types of DNA repair abnormalities, like homologous recombination deficiency (HRD); PARP inhibitors are oral; have a classic side effect profile — cytopenias, myelosuppression, with a greater propensity for thrombocytopenia with standard doses; can also see anemia; neutrophil line is somewhat well-preserved compared to other cell lines; is continuous therapy; is selected in certain patients with ovarian cancer that either have BRCA mutation or HRD; some PARP inhibitors are FDA approved independent of BRCA mutation status; some PARP inhibitors, for example olaparib, are substrates of the cytochrome P453A system; considering what other drugs patients are receiving and changing the exposure of olaparib specifically is important; similarly, for any drug that is a CYP3A4 substrate, patients should be counseled to avoid grapefruit juice, which directly inhibits CYP3A through quinone and quinolone-based mechanisms

Proteasome inhibitors: multiple proteasome inhibitors are available; primarily used in multiple myeloma therapy; bortezomib was first proteasome inhibitor; inhibits 20S unit of proteasome; proteasome is the garbage can of the cancer cell; inability to empty trash created by cancer cell leads to its being targeted for apoptotic death; bortezomib given either IV or SQ; SQ is preferred due to reduction in frequency and severity of neurotoxicity; bortezomib is different from carfilzomib and the other oral agent, ixazomib; all cause cytopenias; with proteasome inhibition and specifically thrombocytopenia; a very elastic thrombocytopenia can be seen — if drug is given, and the next day platelet count reduces by 10,000 to 20,000, it will rebound fairly quickly, because these drugs affect the late stages of megakaryocytic maturation; often possible to treat through thrombocytopenia seen with these drugs; carfilzomib is another IV proteasome inhibitor used

across different indications; patients who have received bortezomib in the past still respond to carfilzomib; is an important drug to consider; bortezomib causes a sensory neuropathy over time; reduced with SQ route due to reduced peak concentrations after administration; carfilzomib has different side effect profile; concerns with carfilzomib are mainly with heart failure; should avoid carfilzomib or it should be used very carefully; patients need to have dexamethasone as a pre-medication; extending the infusion reduces the frequency of fever

Ixazomib: only available oral proteasome inhibitor; given in second-line setting or later, typically in combination with other therapies; ixazomib can cause a rash, which is different from the other proteasome inhibitors; generally a maculopapular rash which can start on the trunk and move forward; drug given weekly in a combination regimen; all proteasome inhibitors as a class can cause a reduction in the ability to fight off viral infection, specifically herpes virus infections; patients getting any proteasome inhibitor need to have prophylaxis with acyclovir at 400 milligrams twice a day orally while continually on therapy, as immune function status can be reduced

Small molecule inhibitors:

Drugs used in CML (chronic myelocytic leukemia): inhibitors of BCR-ABL [a fusion gene] tyrosine kinase; each of these agents has R-tyrosine kinase inhibitors; kinases are enzymes on the intracellular side of some extracellular and some not-extracellular receptors; easier to inhibit if tyrosine kinase is based on an ATP platform, so these small molecules get into the cell and inhibit the machinery that tells the cell to grow and proliferate; within CML, the tyrosine kinase is the BCR-ABL tyrosine kinase; drugs in this class include imatinib, dasatinib, and nilotinib, among a few others; prototype of imatinib is approved and has changed the landscape of CML; patients on imatinib chronically or other tyrosine kinases in this area can have long-lasting disease reductions; some patients may even be able to go off of these therapies over time; imatinib specifically, the most common drug used in the category, is a CYP3A4 substrate and thus has some hepatic issues; bioavailability is pretty good with imatinib and overall doses of 400 mg/day are generally well-tolerated; some nausea is associated with it; can also cause peripheral edema, fluid accumulations in different areas, around the eyes, for example, and some more idiosyncratic places; overall imatinib has longest track record in this class; other agents include dasatinib and nilotinib; all 3 are approved for frontline therapy of CML; dasatinib can cause pleural effusions, more commonly than imatinib; nilotinib has QT prolongation as a potential adverse event and its absorption is significantly increased by fatty foods and fat-containing meals; patients should be counseled not to take nilotinib with high fat-containing foods

EGFR-mutated lung cancer: drugs in this group are erlotinib, gefitinib and osimertinib, among a couple of others that are FDA approved like dacomitinib; EGFR agents are much like the monoclonal antibodies in that they can cause on-target adverse events of rash; less common with osimertinib, which is a more potent agent; osimertinib was originally approved for the patient population of T790M-mutated EGFR lung cancer; has been advanced forward to frontline therapy of patients with the disease; many patients are beginning therapy on osimertinib currently; osimertinib is better tolerated than erlotinib and some of the other drugs in the class; dosing for osimertinib is more straightforward; nausea, vomiting, and diarrhea are associated; diarrhea is a class effect of these drugs; in patients getting gefitinib or erlotinib, diarrhea was a classic adverse event along with the acneiform rash; rash is less common with osimertinib compared to the other drugs; osimertinib is a CYP3A4 substrate; erlotinib is a CYP1A2 substrate; for the rare patient who is smoking and taking erlotinib, exposure to erlotinib can decrease with smoking; erlotinib's absorption is reduced in the presence of acid-reducing therapies; patients should be told not to take proton pump inhibitors or H2 antagonists while on erlotinib if they can avoid them

Immunomodulatory drugs for treatment of myeloma: include thalidomide, lenalidomide, and pomalidomide; all are different; thalidomide is not used as often currently; lenalidomide is more commonly employed in the upfront setting of patients who are treated for symptomatic myeloma; lenalidomide is renally cleared, so doses must be altered in patients who have creatinine clearances below 50ml/min, and the starting dose of 25mg is subsequently reduced over time; lenalidomide causes myelosuppression and rarely a rash; generally dosed daily on an intermittent schedule; approved for maintenance treatment following autologous stem cell transplant with melphalan; pomalidomide is hepatically cleared, has lower dosing, and is a more potent agent; tends to be used in the more refractory patient population alone or in combination; renal function matters less with pomalidomide, because it is hepatically cleared; each of these drugs has a special place in the treatment of myeloma; all can cause myelosuppression; less common with thalidomide which tends to cause more sedation and neurotoxicity

Multikinase targeted therapies: often used in renal cell carcinoma; many drugs approved in this space; examples are axitinib, sunitinib, and cabozantinib, among others; these are multi-targeted tyrosine kinase inhibitors that need to be looked at carefully for their metabolic profile; many are CYP3A4 substrates; drugs like sunitinib can cause cytopenias; can also cause hand-foot syndrome and fatigue; cabozantinib can be challenging to tolerate at higher doses; lower doses are better tolerated, and not much activity tends to be lost with dose reduction over time; drugs like lenvatinib are in this category as well; generally these do not cause as many cytopenias as some of the other drugs in the class, but they can; these drugs inhibit enzymes like RET, VEGF, and others in the pathway, whether being used within renal cell carcinoma or others; many are VEGF-directed therapies; pazopanib is another multi-targeted tyrosine kinase inhibitor within this class; can cause liver function elevations; can cause an idiosyncratic effect of a patient's hair turning white; overall pazopanib is better tolerated than other drugs, for example everolimus, in the renal cell carcinoma space

Drugs for the treatment of ALK-rearranged lung cancer: include crizotinib and lorlatinib; these are agents used for ALK-mutated disease as well as some others that are available; generally CYP3A4 substrates and need to be thought of carefully in that space; can cause transaminase

elevations; have been helpful in the treatment of patients with advanced rearranged lung cancer

BRAF inhibitors: approved since ~2011; first on the market was vemurafenib; can be helpful in patients with V600E-mutated melanoma, generally in combination with a MEK inhibitor; agents in this class include vemurafenib, encorafenib, binimetinib and others; used in combination to try to reduce the clone in V600E-mutated patients; MEK inhibitors are also used to reduce adverse events of the BRAF inhibitor, like development of secondary squamous cell carcinomas, fever, and others; used in combination for tolerability and persistence on therapy; effective in patients with V600E-mutated disease

CDK4/6 inhibitors: primarily used in breast cancer; palbociclib was first in the class; others include abemaciclib and ribociclib; inhibitors of specific cyclin-dependent kinases in the cell cycle; CDK4 and CDK6 are 2 of the cyclin-dependent kinases that are important in cell cycle maturation; on-target effects are seen that may be seen with other cell cycle-specific drugs including myelosuppression, specifically, anemia, thrombocytopenia, and neutropenia; can be seen with each of these compounds; otherwise, generally well tolerated; used in combination with hormonal therapy in many instances; combinations with other drugs are currently being evaluated for treatment across different cancers

Abiraterone: selectively and irreversibly inhibits CYP17, which is required for androgen biosynthesis in men with prostate cancer; recommended dose is 1,000 mg fasted in combination with prednisone 5 mg twice daily; a recent study showed that if 250 mg is given with a small meal, bioavailability is equivalent to 1,000 mg dose given on an empty stomach; can cause cardiovascular abnormalities, including hypertension; edema can be seen; rarely arrhythmias and heart failure; can cause fatigue and hyperglycemia; patients should be monitored with complete metabolic profiles; careful consideration of therapy in those who have preexisting hypertension and may have treatment-emergent hypertension; increased transaminases can be seen; ALT is increased in ~1 out of 10 to 1 out of 2 patients; similar rate with AST and bilirubin; hepatic abnormalities can be seen in men who are candidates for abiraterone therapy

mTOR inhibitors: multiple available; reduced frequency of use; drugs like everolimus and temsirolimus, for example, have been approved for renal cell carcinoma and neuroendocrine cancer; everolimus is approved for breast cancer therapy in combination with hormonal treatment; mTOR is an enzyme that is important late in the cell cycle in the PI3-kinase/AKT/mTOR pathway; mTOR inhibitors can cause elevated triglycerides and hyperglycemia as an effect from GSK31 beta; patients should be monitored for hyperglycemia; may also cause stomatitis; use is generally declining across cancers; however, they have a significant role in certain areas in refractory patients and renal cell carcinoma

Single agents in classes used in hematologic cancers:

BCL2 inhibitor: venetoclax is a BCL2 inhibitor approved for AML (acute myelogenous leukemia) and CLL therapy; in CLL, can cause a tumor lysis syndrome; should be escalated carefully upward to target dose; also effective in patients with specific subsets of myeloma, although not an on-label use yet

BTK inhibitors: available for use in patients with hematologic cancer, specifically lymphomas; first drug in the BTK class was ibrutinib; approved for use in patients with CLL, SLL (small lymphocytic lymphoma) and mantle cell lymphoma at doses that range from 420 mg/day up to 560 mg/day; also approved in Waldenstrom macroglobulinemia

Ibrutinib use with azoles: ibrutinib is a CYP3A4 substrate; in CLL and other lymphohematopoietic cancers, patients may often need to receive antifungal prophylaxis with azoles like posaconazole or voriconazole; doses should be reduced in patients on moderate CYP3A inhibitors like fluconazole to 280 mg/day; in patients receiving voriconazole at lower dose or higher dose, posaconazole, or voriconazole, reduce ibrutinib doses to 140 mg/day with lower dose voriconazole versus 70 mg/day with higher dose voriconazole or posaconazole; consultation with drug information and the pharmacist are helpful in managing patients receiving ibrutinib therapy to manage those interactions

Other ibrutinib side effects: ibrutinib can cause cytopenias as an on-target effect; associated with increased risk of bleeding; patients should be counseled that they may bruise more often; in patients receiving concurrent anticoagulants, need to be counseled and managed carefully for possible increased bleeding events due to use of the 2 drugs in combination

Idelalisib: also within this group of medications; idelalisib is a potent inhibitor of the delta isoform of PI3-kinase or phosphatidylinositol 3-kinase, which is highly expressed in patients with malignant lymphoid B-cell abnormalities; inhibition of the pathway results in apoptosis of cell; can see cytopenias as on-target effect with this drug; indications for idelalisib include relapsed CLL, relapsed follicular non-Hodgkin lymphoma and small lymphocytic lymphoma; recommended dose is 150 mg twice a day; concerns exist around hepatic abnormalities that have been seen; black box warning with idelalisib; serious hepatotoxicity occurred in ~16% of patients who received the drug; important to watch liver function testing prior to and throughout therapy and alter doses as recommended in product information in patients who develop any degree of transaminitis or other changes in hepatic function; other potentially serious adverse events with idelalisib include severe diarrhea or colitis, which occurred in ~15% to 20% of patients; pneumonitis can occur, although much rarer, less than 5%; due to the way the drug works and its inhibition of T-cells, serious infections may occur in up to half of patients; hard to know if disease or drug-related; prophylaxis called for in individuals at risk for infection and perhaps all patients receiving idelalisib; rarely, can see intestinal perforation; important to remember idelalisib is a major CYP3A4 substrate; also an inhibitor of CYP3A4, so concomitant use of the azoles is challenging but can be done

FLT3 inhibitor: midostaurin; used in specific subtypes of AML and in FLT3-positive AML; patients who have been induced and are ongoing can receive midostaurin to prolong their CR (complete remission) intervals; other FLT3 antagonists are in development

IDH2 inhibitors: enasidenib; helpful for patients with IDH2-mutated AML

Suggested Reading

Cardones AR et al: VEGF inhibitors in cancer therapy. *Curr Pharm Des.* 2006;12(3):387-94; **Liu X et al:** Epidermal growth factor receptor (EGFR): A rising star in the era of precision medicine of lung cancer. *Oncotarget*. 2017 Jul 25;8-30; **Andrikou K et al:** Emerging antibodies for the treatment of pancreatic cancer. *Expert Opin Emerg Drugs*. 2017 Mar;22(1):39-51; **Atkins MB et al:** Emerging monoclonal antibodies for the treatment of renal cell carcinoma (RCC). *Expert Opin Emerg Drugs*. 2016 Sep;21(3):243-54; **Bauman JE et al:** Integrating novel therapeutic monoclonal antibodies into the management of head and neck cancer. *Cancer*. 2014 Mar 1;120(5):624-32; **del Rivero J et al:** PARP Inhibitors: The Cornerstone of DNA Repair-Targeted Therapies. *Oncology (Williston Park)*. 2017 Apr 15;31(4):265-73; **Tangutoori S et al:** PARP inhibitors: A new era of targeted therapy. *Maturitas*. 2015 May;81(1):5-9; **Manasanch EE et al:** Proteasome inhibitors in cancer therapy. *Nat Rev Clin Oncol.* 2017 Jul;14(7):417-33.

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Anti-Cancer Drugs IV: Immunotherapy

Christian M. Capitini, MD, *Associate Professor of Pediatrics, Division of Hematology, Oncology, and Bone Marrow Transplant, University of Wisconsin School of Medicine and Public Health, Madison, WI*

T cells: lymphocytes present within immune system; able to recognize virally infected and tumor cells; work through engagement of T cell receptor on T cell surface and major histocompatibility complex (MHC) molecules present on tumor cell surface; MHC molecules have peptides unique to tumor; allow T cell to recognize tumor as foreign; T cells also require engagement of co-stimulatory receptor

PD-1: co-stimulatory receptor; engages PD-L1 ligand on tumor; when PD-1 engaged, T cell undergoes exhaustion; will no longer proliferate in response to MHC and peptide complex; will cease attacking tumor cell; tumors often use PD-L1 expression to escape immune pressure

Checkpoint blockade: class of clinically available antibodies to PD-1 and PD-L1; shown in clinical trials to enhance anti-tumor responses to variety of hematologic malignancies and solid tumors; activate T cells

Anti-PD-1 antibodies: examples include nivolumab and pembrolizumab; nivolumab used with classical Hodgkin lymphoma relapsed or progressed after autologous hematopoietic stem cell transplantation; tumor expression of ligand for PD-1 not required to initiate therapy; in Hodgkin lymphoma, anti-PD-1 therapy has led to dramatic responses in patients previously refractory to chemotherapy, stem-cell transplantation, and anti-CD30 therapy with brentuximab; anti-PD-1 therapy now available for treatment of variety of solid tumors including melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin disease, head and neck cancers, urothelial cancers, and hepatocellular carcinoma; anti-PD-L1 therapies also available for bladder cancer, Merkel cell cancer, urothelial cancers, and non-small cell lung cancer; anti-PD-1 therapies also approved in tumor agnostic fashion; some tumors have mismatch repair deficiencies; result in absence of mismatch repair enzyme that prevents mistakes occurring during normal DNA replication; proteins with mutation-associated neoantigens produced in the presence of mismatch repair deficiencies; neoantigens recognized as foreign by T cells; expression of PD-L1 by tumor engages PD-1 on T cell, blocking T cell activation; providing anti-PD-1 therapy allows T cell to recognize mutation-associated neoantigen but not be inhibited by PD-1/PD-L1 interaction and can thus eliminate tumor; this has led to variety of responses in several solid tumors in adults associated with microsatellite instability or mismatch repair defects

Ipilimumab: CTLA-4 checkpoint inhibitor; first checkpoint inhibitor approved by FDA in 2000 for melanoma; used as alternative means of treating stage III patients with unresectable melanoma or stage IV patients with metastatic melanoma; patients with stage III melanoma usually undergo surgery to remove primary melanoma on skin and nearby lymph nodes; when ipilimumab given as adjuvant treatment after surgery, patients can experience longer relapse-free survival

Combination therapy: ipilimumab and nivolumab FDA approved; researchers have given anti-CTLA-4 and anti-PD-1 therapy in combination for patients with melanoma; results in higher remission rates and better progression-free survival than ipilimumab alone

Immune-related adverse events: toxicities from preventing inactivation of T cells emerging with growing usage of checkpoint inhibitors; immune-related adverse events can occur in almost every organ system; may be due to cytokine release from activated T cells; can become serious and life-threatening; require prompt recognition and treatment; in some cases, stopping checkpoint inhibitor therapy can reverse toxicity; in other cases, additional immune suppression such as corticosteroids may be needed; close monitoring needed for patients with underlying autoimmune diseases; concern checkpoint inhibitor will exacerbate underlying diseases often driven by T cells; in general, side effect profile for checkpoint inhibitors much more favorable than other classic chemotherapy agents and small-molecule inhibitors; clinical trial comparing nivolumab — anti-PD-1 inhibitor *vs* everolimus mTOR inhibitor in patients with advanced renal cell carcinoma; patients receiving nivolumab reported improved quality of life for duration of study; fatigue for nivolumab most common treatment-related adverse event reported; no grade three or four symptoms reported in that study; serious adverse events occurred in <20% of patients receiving nivolumab; <40% of patients receiving everolimus

Future exploration: determine if rare but serious toxicities or late toxicities will emerge; evaluate if certain toxicities make combination therapy with anti-CTLA-4 and anti PD-1 difficult; determine if history of autoimmunity limits application of drugs in these patients; each immune-related adverse event has different kinetic of onset; example — skin manifestations such as rash and pruritus often occur early after initiation of treatment; peak at ≈6 weeks after therapy and resolve; complications such as hypophysitis or other endocrinologic complications tend to occur ≥6 weeks after initiating treatment and can persist; further therapies needed; more evidence needed for combination of checkpoint inhibitors and traditional chemotherapeutic agents to better understand toxicity profile that can be tolerated without sacrificing efficacy

Weaponizing T Cells to Recognize and Kill Cancer

Chimeric antigen receptor (CAR): endows T cell with ability to recognize tumor cell with antibody-like properties while maintaining natural killing machinery; delivered to T cells using retroviruses or lentiviruses; delivers single-chain variable fragment that can recognize antigen on tumor cell surface; antigen CD19 targeted by FDA-approved products; when CD19 engaged on tumor by single-chain variable fragment on CAR, signal transmitted into T cell through costimulatory domain such as CD28 or 4-1BB; activates cytotoxicity signal mediated by CD3 zeta; has resulted in dramatic remissions for children with acute lymphoblastic leukemia and adults with non-Hodgkin's lymphoma

Procedure: leukapheresis isolates T cells from patients with relapsed or refractory disease; cells then shipped to central manufacturing facility, activated, and transduced with virus that delivers CAR; after expanding cells over weeks, cells undergo quality control and assurance testing before being sent back to referring site for infusion into patient; prior to CAR T infusion, patients typically receive lymphodepleting chemotherapy to eliminate endogenous T cells and increase production of homeostatic cytokines that can promote CAR T cell expansion; in adults with lymphoma, two products available; axicabtagene ciloleucel or tisagenlecleucel; axicabtagene approved for adult patients with relapsed or refractory large B-cell lymphoma who have progressed after two or more lines of systemic therapy; includes patients with diffuse large B-cell lymphoma, high grade B-cell lymphoma, or diffuse large B-cell arising from follicular lymphoma; tisagenlecleucel approved in adult patients with relapsed or refractory large B-cell lymphoma; includes diffuse large B-cell lymphoma, high grade B-cell lymphoma, and diffuse large B-cell arising from follicular lymphoma after two or more lines of systemic therapy

Response: overall survival for adults receiving axicabtagene ciloleucel in B-cell lymphoma ≈50%; responses observed in B-cell lymphoma can be durable; typically patients with complete response tend to have higher chance of having durable response >12 months; median overall survival for patients receiving tisagenlecleucel ≈50% at ≈22 months; seems to be cancer-specific; patients with follicular lymphoma have higher overall survival at 93% at median follow up of 28 months; children with B-cell acute lymphoblastic leukemia refractory or in second or later relapse see 82% response rate 3 months after receiving CAR T therapy; results in 73% event-free survival at 6 months and 90% overall survival at 6 months; median duration of remission not yet reached

Cytokine release syndrome (CRS): side effect after infusion of CAR T cells; level of inflammation induced by CAR T cells eliminating leukemia or lymphoma cells at high rate; in part due to reaction of host immune system; interleukin-6 (IL-6) cytokine implicated in CRS; tocilizumab — antibody to anti-IL-6 receptor; approved at same time CAR T cells approved; tocilizumab now used to help manage grades of CRS that have potential to become life-threatening; even after one dose of anti-IL-6 receptor therapy, patients can see resolution of CRS symptoms in rapid fashion; some patients require repeated dosing of tocilizumab to see optimal effects; corticosteroids can be used to reverse effects of CRS when tocilizumab insufficient; supportive care critical for patients; conditions such as fever, neutropenia, headache, hypotension, and hypoxia can often predominate; some patients require intensive care support for multiorgan failure

Neurotoxicity: developed by some patients after CAR infusion; can extend up to 60 days after infusion of cells; can manifest as variety of central nervous system complaints; range from encephalopathy, obtundation, seizures, and life-threatening cerebral edema; some can be managed with corticosteroids; supportive care given

Emerging studies: will explore using CAR T therapy in upfront setting for replacing and/or supplementing upfront chemotherapy in children with B-cell leukemia; in adults with lymphoma, CAR T cells will be compared to autologous hematopoietic stem cell transplant

Cytokines and Growth Factors

Interleukin-2 (IL-2): first FDA-approved interleukin; approved for renal cell carcinoma and malignant melanoma; normally activates NK and T cells and helps eliminate tumor cells; can also activate regulatory T cells, which help suppress immune responses; small proportion of patients can respond to IL-2 single agent-therapy; high degree of side effects include life-threatening capillary leak, which can result in hypotension; variety of IL-2 dosing regimens have been used; some used in outpatient setting; higher doses must be given inpatient for intensive care monitoring

Interferon alpha: typically produced by plasmacytoid dendritic cells; often increased during viral infections; approved for variety of cancers, including chronic myelogenous leukemia, hairy cell leukemia, some B- and T-cell lymphomas, and solid tumors such as melanoma, renal cell carcinoma, and Kaposi sarcoma; can be very toxic, leading to high fevers, capillary leak, and life-threatening hypotension

Growth factors: include granulocyte-monocyte colony-stimulating factor (GM-CSF); used to stimulate immune response against cancer cells; preclinical data shows leukemic blasts more susceptible to cytotoxic effects of chemotherapy when given before and during induction chemotherapy; GM-CSF currently used in combination with dinutuximab — anti-GD2 antibody that recognizes GD2 on childhood solid tumor neuroblastoma; combination of dinutuximab and GM-CSF along with IL-2 shown to improve event-free and overall survival in patients with high-risk neuroblastoma; now part of standard treatment; main side effects of GM-CSF include fevers, bone pain, and occasional splenomegaly

Cancer Vaccines

Sipuleucel-T: first approved vaccine for cancer; composed of autologous antigen-presenting cells expressing prosthetic acid phosphatase and GM-CSF; vaccine given to patients with asymptomatic metastatic hormone-refractory prostate cancer; trials showed 33% reduction in risk of death for [or?] progression; extended survival 4.1 months

Limitations of immunotherapy: tumor microenvironment hostile for T cells and other immune effector cells to mediate their effects; cells like M1 and M2 macrophages present within body; M2 macrophages — tumor-associated macrophages localizing into hypoxic regions of tumors and secreting various immunosuppressive cytokines; promote tumor progression by facilitating angiogenesis and

invasion; myeloid-derived suppressor cells (MDSCs) — collection of immunosuppressive granulocytic and monocytic granulocyte precursors; number of MDSCs expands as tumor grows; causes reduction in arginine levels; leads to subsequent increase in nitric oxide in tumors; results in inhibition of T-cell activation and antigen-specific responses; regulatory T cells subset of CD4+ T cells expressing high affinity IL-2 receptor CD25 and transcription factor FOXP3; regulatory T cells can produce immunosuppressive cytokines like Interleukin-10 and TGF-beta, which can suppress immune response; in addition to these cells, as well as the previously described checkpoint molecules like PD-1 and CTLA-4, there are a variety of molecules and cells tumors can use to avoid elimination by immune system; there are also a variety of enzymes and other small molecules produced by tumor cells to recruit other immune suppressive cells from immune system or inactivate immune effector cells present in immune microenvironment; lack sufficient therapies beyond checkpoint inhibitors to address these anti-inflammatory pathways; exploration of drugs combined with immunotherapy needed to overcome hostile tumor microenvironment

Suggested Reading

Abdel-Wahab N, et al: Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med.* 2018 Jan;168(2):121-30; **Handy CE, et al:** Sipuleucel-T for the treatment of prostate cancer: novel insights and future directions. *Future Oncol.* 2018 Apr;14(10):907-17; **Salter AI, et al:** Chimeric antigen receptor–modified T cells: CD19 and the road beyond. *Blood.* 2018 Jun;131(24):2621-9.

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Clinical Trials and FDA Drug Approval Process

Brad Monk, MD, *Professor of Gynecologic Oncology, University of Arizona College of Medicine—Phoenix, and Director and Professor of Gynecologic Oncology, Creighton University School of Medicine at St. Joseph's Hospital Medical Center, Phoenix, AZ*

Basic statistical considerations in clinical trial design: clinical trials use mathematical modeling

Null hypothesis: assumes no differences in two treatment groups; sometimes designated H_0

Alternative hypothesis: sometimes abbreviated H_1 or H_A; there is difference between two groups influenced by non-random factor, such as surgery, radiation, or chemotherapy interventions in oncology

Type I errors: falsely positive; wrongly rejecting true null hypothesis of no difference; wrongly accepting alternative hypothesis of difference occurring; statistical significance or alpha — probability of making type I error

Confidence intervals: create confidence boundary around point estimate, generally 95%; alpha would be 0.05; 95% minus 100%; 5% chance of type I error

Type II error: false negative result; failing to reject false null hypothesis; probability is beta; chance of type II error influenced by beta or sample size; might reach false negative conclusion in small studies without enough enrolled patients

Parametric statistics: assume data normally distributed, follow bell-shaped curve

Determinants of statistical power: statistical power — probability of impactful result; four factors contribute; 1) effect size — more patients required to find small effect size; 2) alpha — more patients required with smaller p-value; 3) statistical power, ie, probability of impactful result. 4) sample size

Randomization: process by which each subject has same chance of being assigned to intervention arm *vs* control arm; goals of randomization include producing groups comparable with respect to unknown risk factors, removing bias, guaranteeing validity of statistical tests, and balancing treatment groups; accomplished by stratification factors; generally randomize after determining eligibility and as close to treatment time as possible; randomization must be formal, secure, reproducible, and unpredictable to truly allocate patients randomly; accomplished in different ways; most randomizations balanced based on stratified permutational blocks; determine permutations in advance

Blinding: way to reduce bias; placebo easy to use, but randomized, placebo-blinded study may not truly be blinded, because intervention may create toxicity; blinding assessment is another approach; example — blinded independent radiology review in solid tumor oncology trials; creates challenges because investigator wants to stop treatment based on local radiologic review; many use placebos or blinded independent radiology review; FDA has guidelines on placebos, because placebo patient not receiving effective treatment; FDA requirements increase study cost and operational complexity

Sample size: large trials preferred though more expensive; sample size helps determine effect size, significance, and statistical power

Intent-to-treat analysis: all randomized subjects included in primary analysis; ensures no systematic differences between two treatment groups being studied; in contrast, can perform per-protocol analysis in which only those patients who completed assigned treatment are included in analysis

Kaplan-Meier curve: event-driven analysis; censoring — individual patient may not contribute to entire curve; survival function whereby estimation of survival and standard error plotted; curves then calculated and graphed; individual curves presented with confidence intervals; compared using non-parametric tests; parametric tests assume normal distribution; survival curves not normally distributed; log-rank test classic non-parametric comparison of survival curves; this is a proportional test — all parts of curve contribute to same level; a non-proportional survival curve comparison weights different portions of curve differently; most researchers want to evaluate entire curve, weighting it uniformly; this is accomplished with log-rank test

Cox proportional-hazard modeling: frequently used to evaluate survival data in exploratory analysis across various prognostic factors; also called forest plot

Consolidated Standards of Reporting Trials (CONSORT) statement: 25-item checklist including flow diagram on how clinical trials should be reported; includes title, abstract, introductions, methods; methods section very specific about trial design, participants, study settings, intervention, amendments (changes trial outcomes), how sample size determined, interim analysis, stopping rules, randomization, intervention, and flow diagrams; goes through exclusions, baseline demographics, intent-to-treat; results section to give primary endpoint first, then secondary endpoints; reports adverse events; discussion section outlines limitations of clinical trial, generalizability, and interpretation; include registration number; provide redacted protocol and funding source; guidelines to how clinical trials reported; be transparent in every way; clinical trials generate data; data not helpful unless statistics are pristine

FDA changes: transformational event occurred May 23, 2017; cancer and its treatment previously defined by original anatomic location of cancer; in May 2017, FDA changed paradigm with first-time approval of cancer

treatment based on biomarker without regard to tumor site; granted accelerated approval to pembrolizumab for patients with solid tumors that are microsatellite instability high or are mismatch repair-deficient; showed convincingly important clinically relevant response rate in endometrial cancer; has changed treatment of second-line endometrial cancer; in January of 2017, FDA established Oncology Center of Excellence (OCE) to streamline development of cancer therapies; uses experts from FDA Product Centers to conduct expedited review of drugs, biologics, and devices; more interactive, includes patient view and key stakeholder engagement, promotes novel clinical trial designs, reducing time and cost; offshoot of Cancer Moonshot program, helpful federal law

Novel FDA opportunities: Fast Track, Breakthrough Therapy, (BTD), Accelerated Approval, and Priority Review designations allow applicants to create new treatment options in streamlined way; focus on high-end medical needs, hopefully providing greater benefit for Americans

Fast Track designation: can be attained if drug intended for treatment of serious or life-threatening disease or condition and demonstrates potential to address an unmet medical need; preclinical and clinical data can be used; investigators may meet frequently with FDA team prior to filing investigational new drug (IND) application; can also meet at end of phase I and phase II to discuss study design and other issues that could affect safety and efficacy required to support approval

Breakthrough designation: program established through FDA Safety and Innovation Act of 2012; available for drugs intended to treat serious conditions and where preliminary clinical evidence indicates drug may demonstrate substantial improvement in clinically significant endpoint over available therapies; key components of this designation include high-end unmet medical need and demonstrating substantial improvement of clinically significant endpoint over existing medicines, generally overall response rate; designation provides for commitment of FDA senior management, experienced reviewers, and regulatory health project management staff to interact with sponsor; cross-disciplinary team leads program and serves as scientific liaison to members of review team when appropriate; OCE offers applicants opportunity to present case for breakthrough designation to OCE on continuing basis; examples — Breakthrough designation with rucaparib, PARP inhibitor in BRCA mutated ovarian cancer, based on phase II trial with 106 patients; Breakthrough designation of pembrolizumab and lenvatinib in non-microsatellite high endometrial cancers

Accelerated Approval: patients have access to FDA-approved therapy as result of on single-arm trial based on surrogate endpoint reasonably likely to predict clinical benefit; through OCE; can be other surrogate than overall response rate, such as duration of response; generally, oncology tumor shrinkage best way to accelerate approval; number of complete responses weighed against toxicity profile in setting of high-end unmet medical need; example — no Accelerated Approval for medications in second-line ovarian cancer because need met by bevacizumab in platinum-resistant and platinum-sensitive disease; temporary approval

Priority Review: approval in 6 months; faster than 10- to 12-month standard review; submit application; receive filing letter according to Prescription Drug User Fee Act (PDUFA) in 60 days; PDUFA date generally 6 months from filing of Priority Review application; external advisory committee — Oncology Drug Advisory Committee (ODAC) — may or may not meet to vet controversial submissions; FDA generally follows ODAC recommendations

OCE: coordinates expedited reviews; engages patients, researchers, advocacy groups, and academia; committed to advancing oncology regulatory science and policy and better incorporating stakeholder engagement; project is to reevaluate eligibility criteria; working with American Society of Clinical Oncology (ASCO) and other organizations to increase patient types enrolled in clinical trials, eg, recent recommendation to include men in breast cancer studies; interested in pragmatic trials to reduce time and cost of generating knowledge for medical decision-making and product development; randomized trials integrated into routine clinical care, reducing cost, allowing collection of data from electronic health records; large sample size could potentially provide high-level of power to reliably estimate therapy risk-benefit; interested in novel endpoints; have consensus conferences based on tumor types; generally co-authored by FDA members to provide additional information; data initiative actively exploring use of real-world data for generation of clinical evidence that may support or provide better understanding of chronic safety and long-term efficacy of cancer drugs; initiatives such as FDA Information Exchange and Data Transformation Initiative and collaborations with enterprises such as DataSphere, Flatiron, CancerLinQ, and US Oncology are building technical and organizational infrastructures for big data analytics; interested in patient-focused drug development; foster measurements of patient experience to assist in generating science-based recommendations for regulatory policy based on these discoveries; includes vulnerable populations such as pediatric and elderly

Phases of Clinical Trials:

Phase I clinical trials: first-in-human clinical trials; transform basic science discoveries into therapeutic applications; advance drug candidate from pre-clinical studies to initial human testing; serve as link to advance new promising drug candidates; conducted primarily to determine safe dose range and facilitate further clinical development; two primary endpoints — dose limiting toxicities (DLT) and maximum tolerated dose; problem with phase I studies is that there is very little discovery of target engagement; thus phase 0 studies have been developed, in which drugs dosed to effect rather than toxicity; emphasizes value of multiple tumor biopsies allowing rational dose determination

Considerations**:** starting dose selection, study size, and population; most phase I studies conducted on heavily pretreated patients; determine dose escalation once population defined; opportunities exist with adaptive designs; European Medicine Agencies (EMA) recently published guide on how to do first-in-human studies; multidisciplinary approach at most basic level; formulation scientist — involved with chemistry, manufacturing, and controls (CMC) — quality of intellectual product; complete response — negative FDA response; at least half of complete responses or

regulatory holds on IND applications related to CMC quality of development of agent; clinical development scientists — opportunity for oncologists to develop career in drug development; clinical pharmacologists allow pharmacokinetic and pharmacodynamic evaluation; toxicologists aid understanding of adverse events; clinical operation specialists, generally in form of clinical research organization (CRO), help manage site selection; Institutional Review Board (IRB) works closely with regulatory affairs group handling IND application

Phase II studies: probably most common types of clinical trials; phase I studies for an agent generally done once; phase II trials can be countless because they will be studied in number of various cohorts; single-arm or multi-arm; single-arm studies almost always have overall response rate as primary endpoint; single-arm phase II with surrogate endpoint leading to Breakthrough designation and Accelerated Approval can be efficient and cost-effective opportunity to bring drug to market; opportunities for randomized phase IIs with event-traced endpoints such as progression-free survival; important in evaluating biomarkers

Biomarkers: prognostic and predictive factors; single-arm phase II can find prognostic biomarker identifying group of patients with more favorable prognosis; may not be predictive of therapeutic benefit; must determine both prognostic and predictive significance; can use in prospective trial once biomarker validated and understood; cutoff and how biomarker measured further complications; genetic alterations probably more easily measured than immunohistochemical (IHC) markers; IHC open to subjective interpretation

Basket trials: biomarker or organ-site driven; approaches study of multiple tumor types based on biomarkers; opportunity to screen multiple tumor types; examples — vemurafenib in BRAF patients; ALK (anaplastic lymphoma kinase) fusion another opportunity

IRB requirements: establish regulations to protect patient rights and welfare; requirements critical to drug development; identify, mitigate, and manage conflicts of interest; most human research requires IRB approval; federal regulations define how, when, and why IRB approval necessary; Department of Health and Human Services regulations define human as living individual about whom investigator conducts research; Division of Cancer Prevention (DCP) involvement; only conduct clinical trials in setting of consent and IRB approval

IRB composition and functions**:** IRB should have at least five members of both sexes from varied professions; at least one member with primary concerns in non-scientific areas, one member with primary concern in scientific area, and one member not otherwise affiliated with institution; evaluate risks and anticipated benefits and create informed consent or assent using diverse backgrounds and sensitivity to patients, community attitudes, and vulnerable populations; define selection of subjects, safeguards, and how data collected, stored, and analyzed

Principal investigator responsibilities: to protect rights and welfare of human subjects, understand ethical standards and regulatory requirements, inform and educate staff on ongoing basis, inform and consent patients, and follow good clinical practice; these responsibilities audited by IRB; important to identify and report adverse events; may be serious or non-serious; serious adverse events must be reported within 24 hours of coming to attention of investigator; are unique requirements for genetics research

Types of IRB reviews: Full Review — required in setting of clinical trials; Expedited Review — setting with minimal risk; nine types of categories qualify for Expedited Review; can include devices or blood sticks and data or documents already collected in HIPAA-compliant way; Review for Exemption Status — research exempt in educational settings; involve surveys, procedures, and interviews with virtually no risk to patients

Post-marketing trials:: when drugs brought to market with Accelerated Approval, approval is temporary and investigators must negotiate with FDA to perform post-marketing trial to verify clinical benefit; as earlier trials may have been in heavily pretreated patients, post-marketing trial may be in patients at an earlier point in therapy; if these trials fail, FDA may withdraw approval; example is bevacizumab and breast cancer

Opportunities for research following drug approval: developing novel treatment combinations and investigating possible efficacy in other tumor types than that initially studied; seen with PARP inhibitors in gynecology; received Accelerated Approval with olaparib, rucaparib, and niraparib; investigated BRCA-mutated cohorts; moved to earlier line of therapy — second-line maintenance therapy; then moved use to front line; combinations and other tumor types being investigated; PARP inhibitors now approved in breast cancer; upcoming FDA approval in pancreatic and prostate cancer; drug development dynamic space; creates opportunities for oncologist and patients to compete in marketplace; opportunity to leverage clinical trial expertise to provide new opportunities to community in saturated market; patients see value in clinical trials; almost always in randomized clinical trials, intervention not worse than comparison treatment, though not always better; occasionally investigation arm more toxic; clinical trials create additional revenue for practice; expensive, but return on investment

National Comprehensive Cancer Network (NCCN): evidence-based algorithm of how to treat tumors; recommends clinical trials to bring new medicines to patients; clinical trial best option in setting of recurrent cancer with high mortality

Suggested Reading

Mahmud A, et al: Barriers to participation in clinical trials: a physician survey. *Curr Oncol.* 2018 Apr;25(2):119-25; **Nass SJ, et al:** Accelerating anticancer drug development — opportunities and trade-offs. *Nat Rev Clin Oncol.* 2018 Dec;15(12):777-86; **Umscheid CA, et al:** Key concepts of clinical trials: a narrative review. *Postgrad Med.* 2011 Sep;123(5):194-204.

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Ethical Issues in Oncology

Eric Kodish, MD, PhD, *Professor of Pediatrics, Lerner College of Medicine, Case Western Reserve University, Cleveland Clinic*

Adult oncology issues: significant differences from ethics in pediatrics

Ethics: defined practically, "do the right thing;" how do we know?

Categories of philosophy: 2 categories in Western philosophy, morality, and ethics; 1, deontological school of thought; 2, teleological approach; deontologists more concerned with "right" than "good;" teleological thinkers more focused on "good" and outcomes; many in oncology tend to be teleological, eg, evaluate Kaplan-Meier curves, think about best outcomes for patients, more utilitarian (which is likely justifiable); deontological thinking brings value in ethics; important to ask what the right thing to do is, not just what the best outcome will be, because sometimes ends do not justify means; clinical ethics involves application of ethical principles and ways of thinking; patients with cancer extraordinarily complicated; cancer extremely common disease, many types of ethical dilemmas in oncology medicine; *The Emperor of All Maladies: A Biography of Cancer* by Siddhartha Mukherjee is good book for practicing oncologists about history of cancer

Ethics and end-of-life care: prognosis for many patients with cancer now good for diseases that were once considered uniformly lethal; unfortunately, many patients with cancer still die; oncologists need to understand important aspects of end-of-life care and associated ethical dilemmas; good end-of-life care involves everything from code status, do not resuscitate (DNR) orders, and cardiopulmonary resuscitation (CPR) to understanding family dynamics, patient values and preferences, and often spiritual or faith-based beliefs of patients and families that may influence perspectives on end-of-life care; oncologists do not need to be experts in spiritual care; there are well-trained chaplains for this; important for oncologists to know when to make a referral to spiritual care expert; important to realize end-of-life care best provided as a team; solo oncologists may be destined for burnout or failure to provide quality care; nursing, nurse practitioners, social workers, art therapists, chaplains, respiratory therapists, nutritional support, and mental health experts among others are important members of teams that care for dying cancer patients as well as providing support to one another

Transitioning from curative intent to palliative care: most common set of questions around end-of-life care for cancer patients relates to transition from therapy with curative intent to palliative care and hospice care; curative intent is delivery of therapy with the hope and intention of patient entering remission, achieving long-term remission, and hopefully being cured; ethical questions arise when curative intent becomes a statistical outcome so diminishingly small that it ought not be called curative; eg, if patient has 5% chance of being cured with a particular therapy, should oncologist be able to say care is being provided with curative intent? curative intent is hope

Palliative care: when relapse occurs or disease is refractory to treatment, there is often a discussion of palliative care; some separate palliative care and hospice care, but the terms can be related; palliative care can start from the outset of cancer diagnosis, and is treatment designed to provide symptom relief; cancer patients experience a number of burdensome symptoms (eg, pruritus, constipation, dyspnea, pain); good palliative care can help to ameliorate these symptoms; oncologists may fear bringing up palliative care because patients may be worried oncologist is "giving up on them," thinking they no longer have curative intent; oncologists should be able to adequately explain to patients that palliative care can be administered concomitantly with curative therapy; palliative care begins at diagnosis so that abrupt transitions can be avoided

Hospice care: in contrast to curative intent and palliative care, patients with no further curative options entitled to hospice care; "entitled" used because Medicare allows hospice care for patients expected to live ≤6 months; many hospices require that patients forego therapy with curative intent; this is ethically problematic; may be changing, as hope is important to patients and families; however, providing false hope unethical; hospice care often more holistic than palliative; palliative care more a medical approach; hospice care can include more support from chaplains, mental health providers; bereavement care for families important part of hospice care; study by Temel *New England Journal of Medicine* [*NEJM*], 2019) showed evidence that patients with lung cancer referred to hospice or palliative care in randomized fashion had longer life expectancy and improved quality of life than those randomized to standard oncological care

Code status, DNR, CPR: performance of CPR is default standard of care for hospitalized patients who undergo cardiac arrest; however, prognosis for patients who receive CPR in the hospital is poor; some suggest DNR medical orders be changed to "do not attempt resuscitation" rather than "do not resuscitate;" patients with metastatic, advanced cancer are unlikely to benefit from CPR, yet many patients and families insist on "full code" resuscitation; ethically, oncologist caring for patient needs to be part of the resuscitation conversation; not uncommon for intensive care unit (ICU) doctors or emergency room physicians to have to negotiate code

status without aid of patient's oncologist; very important for oncologist to discuss issue with family and patient; oncologist should be available to colleagues who are doing intensive care medicine to have these conversations with patients; decision-making is ethically difficult when patient or family insists on resuscitation if oncologist's opinion is for DNR order; important difference between the patient himself or herself with decision-making capacity insisting on code status versus family member; in the best of circumstances, family members are expected to make substituted judgment decision (ie, decision the patient would make if he or she was capable); advanced care planning allows for this; if cancer patient has durable power of attorney for healthcare, allows them to designate somebody to make their decisions once he/she loses capacity; living will allows cancer patient to express their values and preferences on kind of care they want, rather than designating someone else to make the decision; lecturer (article with Bester in *Journal of Clinical Ethics*) argues that the doctrine of informed consent does not apply to CPR and DNR decisions; rule of rescue is underpinning philosophically for CPR; patients and families should not be able to insist on CPR against medical wishes; these situations warrant an ethics consult, getting help from other experienced clinicians, and when necessary, involving legal department; try to avoid letting it come to that

Physician-assisted suicide, physician aid-in-dying, and active euthanasia: extremely controversial area; in the practice of oncology, not unusual for a patient to ask doctor for help ending their life; they know they won't survive the cancer, they are suffering, they want to die with dignity; poignant ethical dilemma for an oncologist; one definition of an ethical dilemma from Rabbi Jonathan Sacks is, "It's a situation where there is no right answer or there is no wrong answer and there is going to be some amount of psychological or spiritual disturbance no matter which decision is made;" whether to give a terminal patient the means of committing suicide is a paradigm of an ethical dilemma; the oncologist sees the suffering but made a commitment as a doctor to avoid killing; in 1997, Oregon passed a law to allow physician-assisted suicide under strict oversight and regulation; since that time, there has been no "slippery slope," the law has not been abused, patients are not wanting to commit suicide in increasing numbers; also of importance, the regulatory regime is working; State Health Department in Oregon publishes annual statistics, which show that patients more likely to request prescription and not use it than actually use it to commit suicide; lecturer's interpretation of this is that patients want control, they want to be able to make the decision, but the fear of death is so profound for so many people that they don't end up using the prescription; author believes it is worth considering for this reason

Euthanasia: what in 1997 was called physician-assisted suicide (PAS) now called physician aid-in-dying; name change leads to ethical dilemma because name could encompass euthanasia; active euthanasia permitted in many European countries but illegal in United States; in lecturer's opinion, active euthanasia is wrong, and doctors should not kill their patients; there is a distinction between active euthanasia of patients and physician-assisted suicide; ethically different to write a prescription for a patient to choose to fill and use themselves compared to actively administering a patient's death; lecturer recommends paper by Siegler, "Doctors Must Not Kill"

Futility: term "futility" has fallen out of favor; Society for Critical Care Medicine has issued an excellent set of guidelines on patients in situations where "futility" might be invoked; now called "potentially inappropriate intervention;" calling something futile a "discussion ender," not a "discussion starter;" physiologic futility exists and makes for a clear-cut decision; eg, if a patient is on dialysis, but their blood pressure too low to dialyze, dialysis would be physiologically futile, ie, potentially lethal; consideration of "potentially inappropriate interventions" allows doctors, patients, and families to discuss risks and benefits of any particular treatment or test; important to engage in conversation with patients/family about what makes sense and what does not and to stand up for medical knowledge and beliefs rather than simply be a customer service person trying to keep the customer satisfied; to be a doctor sometimes means to do or not do things that patients and families desire in order to be left with integrity; oncologists often viewed as "messianic figures;" important to realize that comes with power and responsibility; extremely important difference between patient's right to insist on chemotherapy, dialysis, blood transfusion, resuscitation, etc. versus patient's right to decline an intervention; in ethics, negative rights are stronger than positive rights; eg, adult Jehovah's Witness has right to decline a blood transfusion; it would not be done against their wishes; patient has a negative right to say no to any medical intervention; on the other hand, a patient with a normal hemoglobin level who requests packed red blood cell transfusion could be denied the request

Cancer research ethics: goal of research to develop generalizable knowledge that will help patients in the future; goal of clinical care is relief of suffering, curing of disease, restoring of function for individual patients; physicians are doing research if any component of clinical effort is to develop generalizable knowledge, according to United States (US) regulations; Belmont Report, adopted in US, speaks to ethical values in research,; in Europe, Declaration of Helsinki has category for therapeutic research and makes distinction between non-therapeutic research and therapeutic research, which is closer conceptually to patient care description in US; in US, anything with any component of research is carefully regulated and overseen; lecturer will not discuss radiation therapy and surgery in this context, will focus on understanding ethical issues of drug development process and phases of research for antineoplastic drugs

Phase 1 research: classically, safety study; new agent used in humans for the first time; for phase 1 trial to be ethically sound, must have good preclinical evidence, including animal data in some cases, in vitro laboratory data, etc; patients in the trial are research subjects or research participants; informed consent for research more rigorous than informed consent for clinical care

Informed consent: 4 components necessary for informed consent to be ethically valid — disclosure, understanding, competency or decision-making capacity, and voluntariness; level of disclosure needed, degree of assessment for patient understanding, testing for decision-making capacity, how to avoid coercion not always well

defined with general informed consent; for informed consent for research, standards are higher because of potential inherent conflict of interest (ie, not pure patient care); investigator/doctor not only trying to help his or her patient, but also to help other patients in the future; pharmaceutical companies have their own sets of interests although many are ethically praiseworthy; drug companies trying to develop medications to help patients, but are also commercial entities, have shareholders to keep satisfied

Phase 1 study participants: for cancer research in general, eligible subjects are patients with no better proven options, must give appropriate informed consent, willing to try new medicine; phase 1 trials usually safety trials and study medicines starting at fairly low dose; in escalation trial design, 3 subjects treated at low dose; if found to be safe, modest increase in dose of medication for next 3 subjects, etc, until maximum tolerated dose determined and dose-limiting toxicities are assessed; goal of phase 1 study to determine best dose for phase 2 study; motivation to be a participant is important; lecturer researched phase 1 studies in children and found that motivation often personal benefit with decent understanding that altruistic component exists; one-third of parents understood the scientific design fairly well, one-third had modest understanding, one-third had very poor understanding of dose escalation, dose-limiting toxicity, maximum tolerated dose; ethically important to continue to research quality of informed consent for cancer research to ensure clarity of our patients'/subjects' understanding of these concepts; phase 1 trials offer hope and are a way to discourage resort to "quackery;" ill patients vulnerable to nonscientifically-based options; phase 1 trials ethically superior to this but in some cases can be ethically inferior to hospice care; depends on situation and patient preferences/values; avoid providing false hope

Phase 2 trials: uses most likely efficacious dose without undue toxicity, as determined in phase 1 trial,; often single-arm study with fairly limited number of patients for first assessment of efficacy; some efficacy assessment done in phase 1 studies, but not the primary goal; phase 2 trials carry some ethical issues associated with phase 1 as well as concerns about therapeutic misconception (also seen in phase 3 trials); once a drug has shown promise of efficacy in phase 2, will often be studied in randomized, controlled trial in which comparator arm is best proven treatment from previous studies; ethically, question of equipoise, are the 2 arms thought to be equally attractive options, equally effective, similar toxicity or some balance of increased toxicity with increased hope for efficacy; main issues in cancer research are efficacy and toxicity; as the field moves beyond cytotoxic therapy and therapy comes to involve molecular targets, checkpoint inhibitors, immune modulators, CAR-T (chimeric antigen receptor T-cell) therapy, some of the traditional statistical designs may need to be changed, and new ethical issues in cancer research may arise

Therapeutic misconception (TM): major concern for all types of research; TM is patient belief/misbelief that they are receiving treatment when in fact they are being studied; issue first noted in psychiatric patients but has been seen in many other groups of patients including cancer patients; clinical cancer research does provide excellent medical care in many situations; possible to have 2 intentions ethically; much of clinical cancer research approach allows patients to receive good care while gaining knowledge for future patients; the learning healthcare system can combine the big data in electronic medical records with genomic, proteomic data (and other data) to gain insight from every patient, a promising development for the future

Phase 3 trials: before these studies performed, must obtain Institutional Review Board (IRB) approval; IRB important safeguard to prevent patient exploitation in research; data safety monitoring board available to assess both arms and to stop study early if 1 arm is shown to be better based on prior-approved stopping rules; should provide patients and doctors with degree of comfort that they will not be harmed in the course of careful and vigilant clinical research; note that patients receiving treatment outside of clinical trials also have associated risks because there is less oversight; need to beware of "gizmo idolatry," the idea that the latest technology or treatment is always the best, also the title of article in *Journal of the American Medical Association* (*JAMA*) — about cardiology but which applies to cancer medicine

Genomic medicine and cancer: main issues to be aware of are the differences between a germline mutation and a somatic mutation; more ethical issues associated with germline mutations; germline mutations have implications for other family members; examples include BrCA genes, HNPCC (heritable nonpolyposis colon cancer), and p-53 gene/Li-Fraumeni syndrome; penetrance is an important issue to consider; age of onset extremely important as well; perhaps most importantly, avoid thinking in terms of genetic determinism — perform necessary testing, refer to cancer genetics expert when appropriate, remember that the patient still has privacy rights even if carrying a cancer gene; ethical framework to think through is whether the oncologist has a duty to warn family/children if a cancer patient possesses certain cancer genes and does not want to convey this knowledge to the family; ethically, does the oncologist have an independent responsibility to share that information with someone besides the patient against patient's wishes; in these cases, best to obtain an ethics consult; answer often depends on the situation; Tarasoff case provides guidelines about when physicians have a duty to warn others; interesting to assess whether this case might or might not apply in cancer genetics; patients with heritable cancer genes may have a sense of fatalism, but in some cases, their prognosis is actually better; interventions (eg, prophylactic mastectomy, oophorectomy) have been shown to provide benefits to patients

Burnout: being an ethically sensitive, conscientious, and thoughtful oncologist is not easy; important to embrace the ethical complexity in the work; sometimes there are no correct answers, but often are clearly wrong answers; physicians also have ethical obligation of self-care; rate of burnout and suicide among physicians is increasing dramatically; moral distress likely a factor; remember, career in oncology is a marathon, not a sprint; important to use resources of colleagues, family members, mentors, and students; remember to learn from the students

Suggested Reading

Allmark P et al: Ethical challenges in conducting clinical research in lung cancer. *Translational Lung Cancer Research* 2016 Jun;5(3):219-26; **Childers JW et al:** REMAP: A framework for goals of care conversations. *J Oncol Pract* 2017;13:e844-50; **Rotz S et al:** Ethical conundrums in pediatric genomics. *Hematology Am Soc Hematol Educ Program* 2018;2018:301-6.

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Basics in Cancer Genetics

Steven M. Lipkin, MD, PhD, *Professor of Genetic Medicine, Gladys and Roland Harriman Professor of Medicine, and Vice-Chair of Genetic Research, Weill Cornell Medical College, Cornell University, New York, NY*

I. Basic Concepts

DNA: composed of deoxyribose sugars, phosphate groups, and four nitrogen bases — adenine, thymine, cytosine, and guanine; cytosine and thymine are pyrimidines — single carbon nitrogen rings; adenine and guanine are purines — double carbon nitrogen rings; each DNA subunit consists of nucleoside — one base, one phosphate group, and one deoxyribose; millions of nucleosides in DNA strand; two nucleotide chains compose DNA double helix

Pairing: chains held together by hydrogen bonds between complementary base pairs; adenine pairs only with thymine and guanine only with cytosine; pairing causes double stranded DNA to twist clockwise giving appearance of circular staircase; bases form steps; sugar and phosphate groups form sides; two chains have opposite chemical polarities; one strand runs in 5′ to 3′direction; other in 3′ to 5′; complementary nucleotide chains basis for accurate storage, retrieval, and transfer of genetic information; due to base pairing, one strand of double helix delineates nucleotide sequence of opposite strand; complementary chains ensure instructions encoding base pairs are transmitted when DNA copied or read

Replication: breaking hydrogen bonds between bases unpairs each strand of DNA; replication bubbles along strands of DNA allow DNA replication at multiple points along strand; process increases speed of replication; DNA polymerase uses single strand as template and adds nucleotides to 3′ end of new DNA strand; proofreading mechanism of DNA polymerase increases accuracy of replication; once replication complete, there is new double-stranded DNA molecule identical to original

Ribonucleic acid (RNA): creating protein from gene involves transcription of DNA into messenger RNA (mRNA) and translation of mRNA into protein; unlike DNA, RNA sugar backbone made of ribose instead of deoxyribose; instead of thymine, in RNA homologous base uracil pairs with adenine; mRNA synthesized from 5′ to 3′

Transcription: RNA polymerase initiates transcription; copies one strand of DNA into RNA by binding to promoter, a segment of DNA at the beginning of the gene; makes complementary copy of all regions, exons — encoded genes — and introns — intervening sequences between exons; polymerase detaches from DNA molecule on reaching termination site (stop codon); 5′ cap and 3′ poly-A tail added for stability and processing; introns spliced out of newly synthesized RNA molecule; exons joined to form mature RNA transcript; only information in exon triplet code used to create amino acid sequence; alternative splice sites allow splicing of same transcript in different ways; makes different proteins from same gene

Translation: mRNA travels to ribosomes in cytoplasm; translated into protein; transfer RNA (tRNA) — cloverleaf base strand of RNA; converts nucleic acid code of mRNA into amino acid code of proteins; tRNAs have amino acid binding sites and three-nucleotide anticodon site, which lines up with complementary mRNA codon that codes for specific amino acid that tRNA is carrying; ribosome catalyzes transfer of amino acid from tRNA to growing polypeptide encoded by mRNA; translation continues until stop codon reached

Triplet code: virtually all living organisms use same 20 amino acids as building blocks for proteins; order of nucleotide templates in gene determines amino acid sequence of expressed protein; translation of nucleotide sequences from DNA to protein depends on triplet code; each nucleotide triplet is called a codon; codes single amino acid; 64 possible codons; encode 20 amino acids; genetic code redundant; some codons have special functions; AUG or ATG codes for methionine, which starts translation of every protein; rarely, leucine substitutes for methionine; UAA, UGA, and UAG are stop codons, which terminate protein translation; remaining 19 amino acids encoded by 60 codons; most amino acids coded by more than one codon; some DNA mutations do not change amino acid sequence of given protein; gene may have different forms or variations of DNA sequence; can be seen when comparing cancer cells to normal DNA

Genes: locus — location of gene on chromosome; alleles — variant forms of same gene; one copy of each homologous chromosome pair inherited from each parent; each parent has two alleles for same gene; sex chromosomes exception; XX in women; XY in men; during meiosis, chromosomes segregate; each sperm or egg carries only one allele; when two germ cells fuse, offspring have two copies of each allele; reflected in all body cells; heterozygotes carry one copy of given sequence variant; heterozygote called mutation carrier if allele associated with disease; most genes transcribed in specific tissues at specific times; small proportion of genes actively transcribed in most cells; each cell type makes different protein products; tumor cell chromosomes segregate during meiosis and often have aberrant segregation; causes aneuploidy — unequal and abnormal chromosome number; affects expression levels of oncogenes and tumor suppressor genes; chromosomes can also form independent units, sometimes called double minutes, which are amplified and carry extra copies of

important oncogene drivers; examples are MEK and KRAS oncogenes

Control: RNA transcription requires interaction of complex of ≈50 proteins, which include general transcription factors binding to RNA polymerase and specific DNA sequences in promoter region; example — TATA box initiating transcription; genes controlled by proteins binding to control regions near their promoter; activate or repress genes; enhancer sequences — enhance gene transcription; silencers — DNA sequences repressing transcription; both can be located hundreds or thousands of base pairs away from promoter; mutations in enhancer, silencer, or promoter sequences and genes encoding transcription factors can lead to faulty gene expression and cancers; increasing or decreasing stability of mRNA through inhibition or enhancement of degradation of RNA leads to alterations in corresponding protein expression

Splicing factors: regulate levels of transcripts, which can be alternatively spliced; source of tumor mutations that can affect specific driver oncogenes and tumor suppressor genes; non-coding RNAs also important to regulate expression of genes; sometimes called long non-coding RNAs (lncRNAs) and small RNAs (snoRNAs); most common of small RNAs called microRNAs — specific sequences transcribed and combined to express transcripts of indicated genes; microRNAs can regulate levels of RNA stability and expression and translation of protein resulting from binding sequences

II. Chromosome Analysis

Genome: complete set of DNA sequences and all chromosomes; normal human genome has 23 pairs of chromosomes, 22 pairs of autosomal chromosomes and one pair of sex chromosomes; normal human genomes are represented as 46, XY for male and 46, XX for female; homologous chromosomes — two chromosomes that make up each pair

Cytogenetic laboratory techniques: include special staining procedures; create banding patterns specific to each chromosome; allow identification of all human chromosomes; karyotype — display of stained chromosomes arranged in homologue pairs; harvested at metaphase stage of mitosis when the highly condensed chromosomes are easy to visualize

Centromere: region of chromosome that separates two arms; P arm — shorter region above centromere; Q arm — longer arm; each arm divided into regions and bands numbered differently for each chromosome; number of gene copies determined from gene sequencing panels; important in identifying oncogene amplification such as HER2/neu ERBB2 gene or loss of copies of tumor suppressors such as TP53

Chromosome microarrays: used to interrogate genome across all 46 chromosomes; detect alterations in copy numbers, such as deletions or insertions resulting from hundreds to thousands of DNA base pairs changed in tumors compared to normal germline

Noncoding genes: human genome made up of 2.9 billion DNA base pairs and ≈20,000 genes, which account for ≈30% of all DNA; most DNA does not code for proteins; exon coding region ≈1.5% of DNA; remaining parts include promoter regions, regulating expression of gene RNA levels, and introns; some extragenic sequences not involved in coding DNA still involved in regulation of gene expression as distal enhancers or silencers or are important for chromosome stability

Organization: completion of sequencing of human genome in early 2000s gave major insights into how humans are different from other species and how cancers can evolve in response to different therapies and be harder or easier to treat with targeted therapies; mammalian cells eukaryotic — genetic information stored in cell nucleus; organized into tightly packed units of DNA and structural proteins; each chromosome contains hundreds of thousands of genes; each gene contains information for protein synthesis; gene smallest functional unit of inherited information; subdivided into exons

Normal cellular growth: cell division or mitosis controlled by cell cycle regulators; include growth inhibitors such as tumor suppressor genes and growth factors, including oncogenes, growth factor receptors, and others; cancer cells acquire ability to bypass growth signaling

Mutation: change of normal base-pair sequence of DNA; single-base substitutions cause missense mutations; larger substitutions, of a few nucleotides, are called insertion-deletion — or "indel" — mutations; larger changes, called structural variants or copy-number variants, can cause large deletions or insertions, affecting up to thousands of base pairs of DNA; translocations are fusions of different sequences that are not typically linked; example is ECR-ABL, oncogene resulting from translocation of chromosomes 19 and 22 in BCR-enabled genes; now >500 genes in which somatic mutations have been causally implicated in cancer; the average solid tumor has 33 to 66 mutated genes; number and type of variations differ among different cancers, most comprehensively listed in Tumor Genome Atlas (TCGA); childhood tumors tend to have fewer mutations than adult-onset cancers

Mutation effects: silent if occurring in introns or DNA non-coding regions; some base-pair changes in coding region also silent; may not alter even one amino acid due to redundant genetic code; mutation at third point in codon often does not affect amino acid encoded; term "mutation" often refers to DNA sequence changes affecting protein function; disease-associated mutation is change in DNA sequence that alters or destroys function of a protein, causing predisposition to cancer or somatic changes driving cancer; many mutations do not have causal effect; driver mutations specifically change activity of a protein important in oncogenesis; mutations in non-coding regions of genes, such as promoters, enhancers, or negative regulatory regions can result in under- or overexpression or complete absence of protein

Polymorphism: benign genetic variance of DNA sequence; occurs with base substitution or change in coding region without specific change in amino acid or changes to amino acid sequence that do not change protein function; commonly occur in tumors in intronic and non-coding regions; used by geneticists to track inheritance patterns of certain familial cancers; associated with differences in drug metabolism; includes genes relevant to oncology; example — TPT gene and mercaptopurines used for leukemia; TPT polymorphisms alter levels of administered thiopurines

Silence sequence variants: changes in DNA base sequences that do not change redundancy of genetic code; do not result in cancer or other diseases; minor variations such

as those encoded in seemingly neutral sites rarely create cryptic mRNA splicing site or otherwise affect splicing; can change coding results in ways difficult to predict; role of exonic splicer sequences in cancer currently active source of study; variation occurs typically in final codon base; mutation in third base of codon often encodes for same amino acid, but can affect splicing

Point mutations: alter a single base, and have different effects on protein

Nonsense mutations: base-pair mutations that change amino acid codon to one of 3 stop codons; caused by single-base point mutation or frameshift mutation

In-frame mutations: deletion or insertion of base pairs in multiples of three; downstream reading sequence not altered; resulting protein may not be drastically altered; function depends on specific amino acid change

Frameshift mutation: insertion or loss of one or more nucleotides that alters triplet codons downstream; often changes amino acid sequence and often creates early stop codon

Missense mutations: base-pair mutations that change single amino acid in protein; have potential to create deleterious changes or activation of proteins; impact depends on specific amino acid changed; can have important functional effects on entire protein and its stability if it changes the folding of the protein in a functionally important region; often difficult to interpret in clinical practice; in vitro functional assays used if gene function unknown; uses TCGA and evolutionary biology to infer whether mutations in given positions drive cancer growth; mutations can also lead to changes in exon-intron boundaries; exonic splicing enhancers and silent elements prevalent in many alternatively spliced exons; conversion of cytosine to thymine (C<0x2192>T) is among most common types of missense mutations; accomplished by addition of methyl group to cytosine base to form 5-methylcytosine; subsequent loss of amino group — deamination — forms thymine resulting in cytosine to thymine substitution; affects specific amino acid encoded; results in change of protein function, alternative splicing, or other characteristics

Splice-site mutations: occur in non-coding regions adjacent to exons; may have profound effects on resulting protein; before RNA leaves the nucleus, it is processed to remove introns and remaining exons are joined by splicing; controlled by specific intronic sequences called splice donor and splice acceptor sequences that flank exons; proper splicing requires GT at 5′ donor splice site and AG at 3′ acceptor site; mutations in these sequences may lead to entire exons of RNA being spliced [erroneously]; typically results in nonfunctional protein

Deletions: typically occur during recombination in mitosis, when homologous chromosomes exchange genetic information; duplications or deletions of genes may lead to diseases if gene has dosage sensitivity; example — inherited Beckwith-Wiedemann is overgrowth syndrome with predisposition for Wilms tumor of kidney; caused by extra copies of IGF2 gene

Inversions: two breaks in chromosome followed by reinsertion of chromosome segment in reverse order

Nondisjunction: leads to trisomy or monoploidy of given chromosome; affects total number of chromosomes

Transposons: mobile elements able to replicate and insert themselves in other locations on chromosomes; insertion of transposon causing frame-shift mutation can lead to disease; example — neurofibromatosis, familial breast cancer, and familial colon cancer

Translocations: occur when segments of one chromosome break off and fuse to different chromosome; balanced translocation — no loss of genetic material; loss of genetic material or disruption by breakpoints may cause dysfunction; many involved in tumorogenesis; example — Philadelphia chromosome, resulting from translocation between chromosomes 9 and 22 and seen in almost all cases of chronic myelogenous leukemia; occurs between proto-oncogene ABL; receiving end of translocation is moved from its normal position on chromosome 9 to chromosome 22, altering its gene product and resulting in amplification of levels of protein ABL kinase; another example — Burkitt lymphoma; proto-oncogene MYC translocated from 8q to 14q near immunoglobulin heavy-chain loci; occurs in B-cell malignancies, which naturally have recombination of immune globulins as part of their native biology; DNA strand breaks with potential to be repaired by non-homologous recombination with other spontaneously occurring DNA strand breaks cause translocations; typically identified during precision medicine or liquid biopsy cell-free DNA tests; not all testing includes analysis for translocation; evaluate case by case for each ordered test

Imprinting: genes marked/imprinted differently in males and females; maternal or paternal inheritance important in some genes; genetic changes involving imprinting can lead to increased or decreased gene activity; imprinting caused by differential methylation of cytosine residues in parental genome; hypermethylated cytosine residues associated with transcriptionally inactive DNA; hypomethylation associated with transcriptionally active DNA; imprinting occurs during embryo formation; transmitted to different cells; tumor cells can have significant differences in imprinting and DNA methylation

Uniparental disomy: both copies of chromosome inherited from one parent; can affect cancer predisposition syndromes; some individuals with Beckwith-Wiedemann syndrome (predisposition to Wilms tumor and adrenocortical carcinoma) have paternal disomy of chromosome 11p; total number of chromosomes in karyotype or copy number array may reflect number of genes but not expression level; paternal allele of H19 normally repressed; paternal allele of nearby Igf2 locus normally expressed copy; complete loss of H19 in some Wilms tumors correlates with increased Igf2 expression, leading to activity of growth suppressing H19 RNA and consequently increased expression of Igf2 growth factor; NOEY2 — member of RAS superfamily; expressed only from one allele, inherited from father; loss of paternal allele preferentially occurs in 41% of breast and ovarian cancers; another example — bi-allelic expression of P73 gene expressed in maternal allele seen in some lung and renal cell carcinomas; mannose 6-phosphate or Igf2 receptor partially imprinted in some individuals increases risk of hepatocellular carcinoma

Phenotype: physical manifestation of trait; expression of genotype — genetic makeup; different mutations in same gene can result in different phenotypes; example — RET proto-oncogene; activating, gain-of-function germline mutations of RET lead to multiple endocrine neoplasia (MEN) type 2; can manifest in different

subtypes — MEN2a, MEN2b, or familial medullary thyroid cancer, depending on location of germline mutation; mutations in exons 10 and 11 expressed as familial medullary thyroid cancer; alternatively causes MEN 2A phenotype, characterized by medullary thyroid cancer, pheochromocytoma, and parathyroid adenomas; familial medullary thyroid cancer can also result from specific mutations in exons 13, 14, or 15; MEN 2B results from mutations in either exons 15 or 16; medullary thyroid cancer and pheochromocytoma present in MEN 2B without parathyroid adenomas or adenocarcinomas; in some families, gene causes loss of function rather than activating proto-oncogene within RET, leading to unrelated Hirschsprung's disease

III. Oncogenes

Regulation: genetic mutations that drive both cancer predisposition and the growth of cancer can be characterized as tumor suppressor genes, oncogenes, or DNA damage repair genes; tumor suppressor genes and oncogenes act in concert to regulate cell growth and division; protein products of tumor suppressor genes generally inhibit cell growth through a variety of mechanisms, such as halting cell division or promoting cell death; when both copies of a tumor suppressor gene are inactivated, a cell can divide unchecked, leading to tumor formation; oncogenes accelerate the growth and division of cells and are sometimes referred to as driver mutations; an activating mutation, one of the alleles of a oncogene, can lead to uncontrolled cell division in cancer; DNA response genes — subset of DNA caretaker tumor suppressors — are like repair mechanics for DNA; for example, may carry out DNA mismatch repair, detecting and repairing mismatches between nucleotide copy numbers; a mutation in one copy of a suppressor gene may not cause damage, but if both copies have mutations a clinically important phenotype is likely to result; defective DNA repair genes cause cancer indirectly in the germline as well by causing the accumulation of mutations in driver oncogenes

Oncogenes: start out as proto-oncogenes — genes involved in regulation of normal cell growth; encode proteins functioning as growth factors, growth factor receptors, signal transducers relaying messages from cell surface receptor, and nuclear transcription factors relaying signals to cell nucleus; normal proto-oncogenes essential for growth of cells in normal homeostasis; mutated or overexpressed proto-oncogene can become oncogene resulting in unregulated cell growth or transformation; oncogene expression is typically dominant, ie, only a single mutation in one allele required; often called driver genes

Driver genes: examples — germline mutations in RET proto-oncogene lead to MEN2 (multiple endocrine neoplasia type 2); germline mutations in MET and CDK 4 proto-oncogenes lead to inherited cancer syndromes such as melanoma; MYC and RAS are common oncogene drivers; can be characterized as actionable and non-actionable or druggable and non-druggable drivers, ie, certain genes have specific targeted therapies, while others do not; examples of druggable oncogene drivers include HER2/neu and Herceptin and other blockers of HER2 gene, BRAF and dabrafenib and others, and BCL-2 drugs venetoclax and navitoclax; MYC is non-druggable oncogene

Tumor suppressor genes: normally suppress cell growth by various means, some still unknown; some encode transcription factors to regulate other genes; example — TP53 directly binds DNA, resulting in expression of genes inhibiting cell growth and promoting cell death; other tumor suppressor genes encode for active proteins controlling cell cycle; example — CDKN2A gene encodes p16 protein; p16 inhibits cells from entering S DNA synthesis phase of cell cycle; inhibitory effect lost if both alleles of CDKN2A mutated; allows DNA synthesis to progress unchecked and accumulate mutations; not usually druggable, except for deficiency relating to BRCA1 and 2 and DNA mismatch repair

Two-hit model: both copies of tumor suppressor gene must be lost or mutated to lead to cancer; loss of one copy predisposes cell to cancer; remaining copy adequate to suppress cell proliferation; individuals carrying germline mutations in many tumor suppressor genes have only one functional copy in all cells; much greater risk of acquiring mutation in second copy of gene, leading to cancer; two-hit hypothesis proposed by Alfred Knudsen to explain early-onset and multifocal nature of tumors in hereditary retinoblastoma; inheriting altered cancer gene not sufficient for development of cancer; development of retinoblastoma requires inactivation of both copies of retinoblastoma gene; tumor supressor genes recessive at cellular level, while most cancer susceptibility predisposition syndromes are autosomal dominant; individuals inherit first hit in autosomal dominant fashion; acquire second hit in any cell, which then mutates and causes tumor development at accelerated rate

Loss of heterozygosity: loss of chromosomal material, leaving cell with only one intact allele of given gene, may lead to cancer if deleted region contains tumor suppressor gene; individuals carrying germline mutations typically heterozygous in hereditary cancer syndromes; each cell carries one normal and one mutated copy; individuals predisposed to cancer, because their cells already have sustained first hit; loss of heterozygosity may result if second hit causes loss of normal allele; variety of mechanisms can cause loss of heterozygosity; entire chromosome containing normal allele may be lost due to failure of chromosome copies to segregate properly during mitosis, sometimes because of nondisjunction; portion of normal chromosome may be deleted; unbalanced translocations can result in loss of portion of chromosome containing normal gene; reduplication of chromosome containing abnormal copy may result in two abnormal gene copies; gene may also be lost through mitotic recombination events when point mutation occurring in second allele inactivated because of recombination repair using first allele as template; second allele may be inactivated by DNA methylation in promoter region; occurs when methyl groups added to cytosine bases, particularly if adjacent to guanines or CpG dinucleotides; results in long-term gene silencing; once gene methylated, pattern of methylation can be maintained in replicated cells even after cell divides; mechanism of gene activation; examples include Von Hippel-Lindau gene in renal cell carcinoma, MLH1 gene in colorectal, gastric, and endometrial cancer, P16 in multiple carcinomas including melanomas, and E-cadherin gene in stomach and other cancers

DNA repair pathways: maintain genome integrity; replication of DNA during cell division surprisingly accurate given vast array of environmental exposures

acquired over lifetime; examples include cigarette smoke, ultraviolet light, byproducts of cellular metabolism, and high frequency of DNA replication over many years; DNA repair pathways used to repair DNA strand damage prior to replication; accumulation of mutations due to DNA damage or errors during replication can lead to cancer formation; cell cycle machinery can detect DNA damage and cause arrests at specific checkpoints in G1, S, and G2 phases to allow cell to proceed to mitosis to allow repair; cell may initiate apoptosis if damage too great to repair; no single DNA repair mechanism able to fix all types of DNA damage; seven known major DNA repair pathways, of which 4 are thought to be important in cancer predisposition — nucleotide excision repair, base excision repair, mismatch repair, and recombination repair; all known DNA repair pathways highly conserved across animal kingdom

Nucleotide excision repair: repairs damage caused by exogenous sources such as ultraviolet light; used for larger lesions, eg, pyrimidine dimers caused by UV exposure; these occur in single strand and cause distortion of helix and disruption in transcription, translation, and replication; process begins with repair and removal of region; proceeds by filling gap using intact complementary strand as template; inherited defects in nucleotide excision repair cause diseases such as xeroderma pigmentosa, melanoma, and other skin cancers; xeroderma pigmentosa — autosomal recessive disorder where affected individuals develop multiple skin tumors due to sensitivity to light

Base excision repair: prevents mutogenesis and small alterations of bases that may or may not impede transcription or replication, causing miscoding of specific codons and alterations in protein sequences; mainly concerned with damage due to effects of cellular metabolism; examples include oxygen radicals, methylation, deamination, and spontaneous mutations; mutations involve only one strand; repair mechanism excises errant base and replaces it using intact complementary strand as template

DNA mismatch repair: codes for proteins that recognize and repair mismatches in complementary bases in short repetitive sequences, such as single-base substitutions or short repeats; TGF beta type two (TGFBR2) tumor suppressor gene contains 10 adenines in row; repair can cause slippage causing frameshift mutation; inactivation of DNA mismatch repair causes accumulation of mutations that significantly increase spontaneous mutation rates and cancer risk for highly proliferative tissues such as lining of GI tract, including colorectal, gastric, pancreas, endometrial, and bladder cancers; hereditary nonpolyposis colon cancer (Lynch syndrome) associated with inherited germline mutations in MLH1 and MSH2 mismatch repair genes; two auxiliary genes, PMS2 and MSH6, have lower rates of cancer predisposition; mutation carrier losing normal gene copy with wild type allele results in two mutated copies; mutations accumulate significantly in individual cells; hallmark is microsatellite instability phenotype of unstable mononucleotide and dinucleotide repeats; slippage caused by replication of repetitive sequences during recombination; tumors with mismatch repair deficiency have extremely high mutation rates; susceptible to immunotherapies that enhance immune response against tumors with high levels of mutations

Recombination repair: double-stranded breaks are caused by X-rays, chemicals, and other insults during replication of single-strand breaks; after detection of a double-strand DNA break, a complex series of reactions initiates repair of double-strand break, halting the cell cycle and recruiting repair factors; one of the early initiators of repair pathway is ataxia-telangiectasia-mutated gene (ATM protein kinase), a DNA damage-response gene indicating active double-strand breaks; during mitosis, when intact chromosomes necessary for segregation, double-strand breaks may also cause variety of chromosomal anomalies, including deletions, duplications, translocations, and copy-number changes, causing gain or loss of entire chromosomes; homologous recombination preferred method after replication when second strand available; homologous recombination factors include RET51, BRCA, and BRCA2; after identification of identical sister chromatid sequence, intact double-stranded copy used as template to repair sequence; however, if cell in G phase 1 of cell cycle, it will only have homologous chromosome for recombination repair; may be difficult to locate homologue; in this situation, repair done by non-homologous recombination fusing ends of breaks together without any template; causes mutation

Cancer susceptibility predisposition syndromes: along with somatic tumor mutations, many syndromes are very genetically heterogeneous; different mutations expressed with same phenotype; allelic heterogeneity — located within same gene; locus heterogeneity — located in different genes; >300 known germline mutations in BRCA1 gene on chromosome 17; >200 on BRCA2 gene on chromosome 13; both mutations associated with hereditary breast and ovarian cancer predisposition; this heterogeneity has important implications for genetic testing; often not clear whether detected genetic change is mutation or merely polymorphism resulting from particular ethnic background or other characteristics of individual

Progression from normal cell to cancer: multi-step progression through series of mutations; cloner evolution — discrete stages in tumor formation associated with changes in genome of evolving tumor cell; example — loss of APC tumor suppressor gene is among first steps in formation of colorectal cancer; loss allows formation of hyperproliferative epithelium in early adenomas; in most cases, these are benign precursors that grow locally but do not gain ability to metastasize and migrate; in most colon cancers, both copies of APC gene lost via random somatic mutations; in some hereditary colorectal cancers, such as familial adenomatous polyposis, one copy of mutant APC gene is inherited, and only one somatic mutation required for loss of gene function and development of adenoma; adenoma may remain dormant for many years; however, if loss of APC gene followed by somatic mutation activating other changes such as KRAS oncogene, adenoma can progress to carcinoma; thus there are multiple pathways to cancer if one of copy of mutant APC gene inherited; these pathways can now be profiled at single-cell level

Cancer genomics and precision medicine: precision medicine defined as identifying specific mutations important clinically in treatment, diagnosis, or prognosis of individual patients at sites for which mutations are specifically not associated; site of tumor origin has

typically defined oncology therapy protocols; molecular biomarkers such as estrogen or progesterone receptor status have long been part of individualization of different breast cancer therapy regimens; number of molecular markers delineating therapy has greatly increased with cheap genome sequencing; precision medicine now part of mainstream oncology; specific therapeutic strategies targeted to individual mutations constitute >80% of oncology drugs in development in 2019; melanoma now recognized as BRAF positive or BRAF negative; BRAF or MEK have companion diagnostics and drugs specifically inhibiting those pathways; regardless of site of origin, tumor with deficient mismatch repair may be eligible for immune checkpoint inhibitor therapy to increase response against mutations occurring in tumor; number of patients currently benefiting from precision medicine therapies ≈10%; estimated to increase to >20%

Tumor mutation profiling: testing sample of tumor for presence of one or more molecular alterations that may be useful in guiding treatment decisions; liquid biopsy evaluates tumor DNA in plasma and in cells shed by tumors; alterations may include changes in level of DNA, RNA, and tumor DNA methylation; anticipated to extend to protein levels

RNA profiling of tumors: commonly used for certain tumors to dictate whether patients should receive adjuvant chemotherapies; example — several precision medicine tests available in US to delineate probability of cancer recurrence and advisability of adjuvant chemotherapy for node-negative breast adenocarcinoma; multianalyte algorithm-based assays predicated on simultaneous measurements of RNA levels of 10 to 30 different genes in tumor sample; used in combination with mainstream clinical pathological parameters such as tumor grade to provide recurrence risk score for each patient; if relevant chemotherapy has risk of significant adverse effects, risk score can be used to determine whether patient should be treated, or if watchful waiting with MRI or PET can be employed

Early-stage estrogen- and progesterone-receptor positive breast cancer patients: example of above — large scale trials (>10,000 women) using specific precision-medicine RNA-expression profiling and tumor signatures demonstrated that a reduced number of patients needed to receive cytotoxic therapy; divided patients into high, low, and intermediate risk categories

DNA mutation profiling: important and effective precision medicine test to delineate effective therapies, in many cases regardless of tumor site of origin; growth of FDA-approved targeted therapies to modulate specific activated cancer-driver genes or inactivated DNA repair pathways in tumor cells; not active in healthy tissue

Co-theragnostics: therapies co-developed with companion diagnostics; specific for given target alterations; EGF receptor (EGFR)-activating mutations in non-small cell lung cancer; EGFR important oncogene; point mutations in EGFR stimulate protein kinase activity as driver of lung cancer cell proliferation; ≈20% of non-small cell lung cancer tumors carry EGFR mutations specifically increasing kinase activity through either point mutation of L858R or deletion of regulatory exon 19; patients with these mutations particularly sensitive to treatment with multiple tyrosine kinase inhibitors; response rates >80% in some patients; newer therapies now targeted against specific mutated forms of L858R-carrying EGF receptor in non-small cell lung cancers that have progressed through the first stage of therapy

BRCA1 and 2: germline mutations carried by one in every 200 women; represent 5% to 10% of all breast cancers, >10% of ovarian cancers, and other cancers, including pancreatic; two major pathways for repair of double-stranded DNA breaks homologous and non-homologous end-joining repair; if one pathway is inactive, the other up-regulates to compensate; if both pathways inactivated, genome breaks apart and cancer cells die; patients with BRCA1- and 2-mutant tumors typically have homologous recombination pathway inactivated; poly (ADP-ribose) polymerase (PARP) inhibitors inhibit recombination repair non-homologous end joining; tumor cells of patients with BRCA1 or 2 treated with PARP inhibitors die from broken genomes; excellent therapeutic benefit; process called synthetic lethality — targeting cancer cell death from simultaneous inactivation of two pathways

DNA mismatch repair deficiency: occurs in approximately 2% of all solid tumors and 4% to 5% of all metastatic solid tumors; small mutations, particularly missense and small insertion-deletion mutations and short repeats, occur at high frequency; tumors with mismatch repair deficiency have extremely high mutation burden; further increasing the ability of the immune system to recognize these, mismatch deficiency has particularly high rate of insertion-deletion mutations; causes large number of frameshift proteins; can cause neoantigens — long stretches sometimes as long as 60 amino acids; tumors with mismatch repair deficiency particularly sensitive to immune checkpoint inhibitors that activate T-cells from adaptive immune system to recognize and kill mismatch repair-deficient cells while not affecting cells that have intact mismatch repair

HER2/neu oncogene: expressed via amplification in higher-than-normal levels in ≈20% of all breast cancers due to increase in copy numbers; called double minutes — extrachromosomal amplification of HER2/neu gene — causing increased signal activation of HER2/neu or ERBB2 pathway, resulting in breast cancer cell growth; there are multiple HER2/neu pathway-blocking monoclonal antibodies in small molecules that prevent receptor from activating pathways that promote proliferation and survival of breast cancer cells; HER2/neu expression levels and coding mutations are commonly included on precision medicine panels used today

BCR-ABL translocation/Philadelphia chromosome: results from reciprocal translocation between chromosomes 9 and 22; seen in 95% of cases of chronic myelogenous leukemia (CML); results in creation of oncogenic fusion protein BCR-ABL and extremely high active levels of ABL protein kinase; multiple targeted ABL-kinase inhibitors have been developed and specifically inhibit BCR-ABL fusions; ABL kinase inhibitors have increased median survival time for CML patients from 4 to 20 years and sometimes >25 years

Suggested Reading

Carrasco-Ramiro F, et al: Human genomics projects and precision medicine. *Gene Ther.* 2017 Sep;24(9):551-61; **Glaire MA, et al:** Cancer predisposition syndromes: lessons for truly precision medicine. *J Pathol.* 2017 Jan;241(2):226-35; **Pagliarini R, et al:** Oncogene addiction: pathways of therapeutic response, resistance, and road maps toward a cure. *EMBO Rep.* 2015 Mar;16(3):280-96.

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Basics in Cancer Biology

Steven M. Lipkin, MD, PhD, *Professor of Genetic Medicine, Gladys and Roland Harriman Professor of Medicine, and Vice-Chair of Genetic Research, Weill Cornell Medical College, Cornell University, New York, NY*

Tumorigenesis: process in which growth-regulated cells begin to divide in contexts where cell division not needed; arises largely from gene mutations; mutations largely stochastic — based on probability over large number of cell divisions in populations of different individuals; most accumulate over individual lifespan

- **Mutation:** any change in normal base-pair sequence of DNA, even changes that do not affect protein structure or function; however, term commonly used to refer to DNA sequence changes that do affect protein function; disease-associated mutation — change in DNA sequence that alters or destroys protein function causing disease predisposition; mutations may be silent, especially if occurring in introns or other noncoding regions of DNA; some base-pair changes in coding regions also silent; may not alter even single amino acid, due to redundant genetic code; mutations may be single base-pair point mutations or deletions, insertions, or translocations involving larger sections of DNA
- **Germline mutations:** occur in ova or sperm germ cells of parents; propagated throughout every cell in offspring; individuals carrying cancer predisposing germline mutations born with mutated allele in every cell; increased chance additional genetic damage in given cell will promote tumor growth; cancers occur at earlier age and at multiple sites in individuals carrying germline mutations in cancer predisposition genes; second hit hypothesis — one inherited mutation and one somatic mutation, as opposed to de novo mutation requiring two independent somatic mutations
- **Somatic mutations:** occur in body cells; not inherited; acquired over lifetime through interactions with carcinogens and other mutagens; majority of human cancers result from accumulated somatic mutations
- **Tumor sequencing studies:** compare germline normal DNA to tumor DNA to identify abnormalities in cancer cell genomes; in both sporadic cancers and cancer predisposition syndromes, mutations accumulating in tumor suppressor genes particularly important
- **Tumor suppressor genes:** normally suppress cell growth by variety of mechanisms; mode of activity of many such genes remains undiscovered; some tumor suppressor genes encode transcription factors — proteins that regulate RNA transcription of other genes; example — protein product of TP53 gene binds directly to DNA; in turn leads to expression of genes that can inhibit cell growth and promote cell death; other tumor suppressor genes code for proteins active in cell cycle control; example — CDKN2A gene encodes P16 protein that inhibits cells from entering DNA synthesis (S) phase of cell cycle; inhibitory effect lost if both alleles of CDKN2A mutated, allowing DNA synthesis to progress unchecked; both copies of tumor suppressor gene must be lost or mutated to lead to cancer; loss of one copy of tumor suppressor gene predisposes cell to cancer; remaining copy adequate to suppress cell proliferation; germline mutation in tumor suppressor gene results in only one functional copy of gene in all cells; loss or mutation of second copy leads to cancer

Oncogenes: proto-oncogenes — genes involved in regulation of normal cell growth; encode proteins that function as growth factors, growth factor receptors, signal transducers relaying messages from receptor to cell surface, and nuclear transcription factor proteins binding to DNA and regulating gene activity; normal proto-oncogenes essential for homeostasis of normal cells; overexpressed or mutated proto-oncogenes can become oncogenes; results in unregulated cell growth and transformation; oncogene expression usually dominant; only single mutation in one allele needed for cancer development; some oncogenes known to predispose to hereditary cancer syndrome; example — germline mutations in RET proto-oncogene lead to multiple endocrine neoplasia type 2, a hereditary syndrome associated with medullary thyroid cancer and other endocrinopathies; germline mutations in proto-oncogenes MET and CDK4 also lead to inherited cancer syndromes

DNA mutations promoting tumorigenesis: revealed by both germline and somatic defects in different DNA repair systems; example — Lynch syndrome cancer predisposition syndrome affecting approximately one out of every 300 individuals in North America; caused by deficiency in DNA mismatch repair

Mismatch repair: repairs single-base substitution mutations and small insertion deletion mutations; when deficient, DNA mutation rates increased by >100-fold; leads to tumorigenesis in cells lining GI tract; epithelial cells lining colon divide rapidly, approximately every 3 days; particularly vulnerable to increased DNA mutation rates

Homologous recombination DNA repair: repairs double-stranded DNA breaks; includes tumor suppressors BRCA1, BRCA2, PALB2, RAD51, and other genes; DNA double-strand breaks occur frequently during normal cellular homeostasis; scarless DNA repair — homologous recombination system repairs double-stranded breaks without leaving any residual mutation

at repair site; when inactivated, other backup repair mechanisms take over; after repeated cell division cycles, mutations at sites of double-stranded breaks occur all over genome; cells dividing episodically with high velocity particularly vulnerable; hormonally responsive cells such as those in breast or ovary responding to monthly menstrual cycle particularly susceptible to double-stranded break repair mutations

Nucleotide excision repair: repairs damage caused by exogenous sources such as ultraviolet light; typically used for larger lesions such as thymine dimers caused by ultraviolet radiation; these mutations occur on single strands; usually cause distortions in double-stranded helix and disruptions in transcription or regulation of genes; repair starts with removal of whole lesion and proceeds by filling in gap using complimentary strand as template for repair; inherited defects in nucleotide excision repair mechanism cause xeroderma pigmentosum and related disorders; xeroderma pigmentosum — autosomal recessive disorder in which individuals have predisposition to numerous skin tumors due to sensitivity to ultraviolet light

Immune system: plays important role in tumor suppression; adaptive immunity includes T cells; innate immunity includes macrophages and NK cells; adaptive and innate immunity can help sculpt tumors during cancer evolution, sometimes even before tumors are macroscopically detectable; observational studies demonstrate mice or patients immunodeficient in adaptive immunity such as T cells have increased incidence of certain types of cancer, particularly virally induced cancers such as human papillomavirus or hepatitis B viral-positive tumors; overall process of how tumors sculpted by adaptive and innate immune system called cancer immune-editing; also sometimes called immunosurveillance or immunoselection; initial studies proposing immunoediting largely drawn from studies of chemically induced tumors in immunodeficient animals such as mice

Major histocompatibility complex (MHC): more recent studies evaluating landscape of specific mutations carried by individual tumors paired with host MHC human leukocyte antigen (HLA) alleles provide additional evidence that tumor-specific changes in MHC-mediated antigen presentation affect tumor growth in patients; almost all homeostatic nucleated human cells decorated by class I MHC molecules in cell surface membrane; these molecules present proteasomal-degraded cytosolic eight- to 11-amino acid peptides to CD8+ cytotoxic T cells for recognition; different dendritic cell populations encountering tumor cells can act as antigen presenting cells, presenting these tumor antigens in the context of the class II MHC; cross-presentation by dendritic cells expands and activates cytotoxic CD8+ T cells and CD4+ helper T cells, promoting cytotoxic CD8+ T-cell expansion; class I MHC (HLA) encoded by three genes, HLA-A, B, and C; highly polymorphic; different allele combinations of HLA-A, B, and C create significant diversity between individuals as to which antigens can be presented to CD8+ T cells

Impact: early in their development, cancer cells typically retain HLA alleles; can be recognized and eliminated by immune cells if they present neoantigens — mutated host proteins; cancer cells may also sometimes overexpress homeostatic antigens found in normal tissues; example — mucin 1 (MUC 1) or herceptin (HER2/neu growth factor receptor); varying degrees of effect on central tolerance, which can prevent tumorigenesis from becoming macroscopically detectable; recent molecular epidemiology studies show human tumors paired with patient host HLA from >10,000 tumors, such as those in cancer genome atlas, have neoantigens with higher predicted HLA-neoantigen binding affinities; indicative of higher likelihood of presentation of CD8+ T cells that were significantly more likely to experience mutations that decrease HLA affinity of targeted neoantigens; studies also revealed recurrent oncogenic mutations such as KRAS, B-RAF, or IDH1 collectively present on >35% of all solid tumors and many hematologic tumors, which have low predicted HLA binding affinities; paired tumor-normal studies provide important new evidence that immunologically invisible human mutations are under evolutionary selection pressure during early tumorigenesis

Summary: tumorigenesis depends on intrinsic cell autonomous changes such as mutations; can be stochastic and random or accumulate with aging and impaired DNA repair systems; immune system also able to recognize tumor mutations and control growth of malignant cells after transformation

Proteomics: genomics launched precision medicine revolution; has yielded breakthrough markers for risk prognosis and prediction of chemotherapy response; use of molecular profiling to select cancer patients for precision medicine therapies and targeted chemoprevention can result in response rates >80% in some cases; most markers used in patient selection paradigm have been from genome-based assays; example — evaluating DNA mutations, rearrangements, or amplifications; not all genomic markers demonstrate outstanding ability to predict treatment outcomes in clinical studies; thus, proteomics has become area of increased interest for complementary, specific protein targets for drugs and chemopredictive tests; while genomics defines potential gene products, proteomics better reflects mechanistical activity in individual cells, thought of as protein motors; example — protein expression as consequence of translational control and degradation or regulation of protein activity through post-translational modifications

Immunoblotting: majority of protein quantification still done by antibody-based immunoassays; conventional western immunoblots widely used to quantify proteins in research settings; despite improvements, immunoblotting still slow to perform; standardization challenging

Enzyme-linked immunosorbent assay (ELISA): uses two complementary antibodies against same protein — sometimes referred to as sandwich ELISA — considered gold standard for measurement of individual proteins and body fluids for clinical diagnostics for >50 years

Immunohistochemistry: method of choice for protein quantification in clinically relevant tissues such as formalin-fixed tumors

Challenges: all antibody-dependent assays face same fundamental challenges associated with availability, quality, affinity, and specificity of antibodies; example — clinically important assays for estrogen receptor beta and programmed cell death ligand 1 have

faced significant antibody performance issues; can be difficult to discriminate between isoforms and variants found in tissues using antibodies, though these may be most important signatures of disease state; example — estrogen receptor (ER) critical cancer driver and drug target in breast cancer; several small molecule inhibitor therapies inhibiting ER; different isoforms of ER due to alternative messenger RNA splicing; antibody used to differentiate ER- positive from ER-negative breast cancer; critical distinction leading to different targeted and chemotherapy regimens with ER blocking therapies such as tamoxifen or raloxifene; this antibody potentially prone to misidentifying patients as ER-positive; androgen receptor protein isoform variants that do not bind dihydrotestosterone such as androgen receptor variant 7 common in prostate cancer; can lead to misidentification of patients prescribed androgen blocking therapies such as enzalutamide for tumors with androgen receptors that do not respond to any ligand

Performance: antibodies recognize six to 15 amino acid epitopes forming specific three-dimensional shapes; several molecules, including proteins, protein modifications, and non-protein molecules such as lipids or glycosaminoglycans, can have cross-reactivity, thus compromising accuracy of antibody quantification and undermining reproducibility; antibody performance also context-dependent; validating assay in one experimental setting does not reflect performance in all settings

Mass spectrometry: comparatively new technology for protein analysis; well established for analysis of small molecules in clinical settings; example — establishing structure and presence of drugs such as aspirin or other commonly used medications; has only recently been applied to quantification of proteins for clinical use; uses relative and absolute quantification techniques; able to have agnostic approach to proteins and proteomics without depending on antibodies; mass spectrometry-based proteomics provides high analytical specificity and isoform discrimination and has validation for new biomarkers in the "protein that is often neglected" area; use has increased significantly in past few decades with identification of peptide fragment ion spectra using database searches and introduction of high sensitivity analysis; example — using nano liquid capillary or tandem mass spectrometry; multiple reaction monitoring mass (MRM) spectrometry offers antibody-independent proteomic assays; MRM mass spectrometry assays have shorter development times than many anybody-based protein assays and have extensive multiplexing capabilities; also have improved speed sensitivity in quantitative precision for protein assays; MRM assays conducted using triple quadrupole mass spectrometers, which only have limited resolution and mass accuracy; reliable identification of target peptide usually requires concurrent analysis of standard; use of peptide-specific internal standards fits definition of definitive quantification standards established by US FDA and other regulatory agencies; possible to calculate absolute quantitative protein concentration values for unknown samples using characterized reference standard with calibration curve

High mass accuracy based parallel reaction monitoring (PRM) mass spectrometry: similar or improved performance; added advantage of high resolution; fragment ion spectra can be filtered post-acquisition to obtain specific ion traces almost devoid of noise; targeted assays can be multiplex to encompass large numbers of proteins to generate new biological information and meaningful picture of specific assays relevant to cancer

OVO1 mass spectrometry assay: determines risk of ovarian cancer in patients with pelvic masses; test capitalizes on ability to define quantification of 7 proteins simultaneously; first FDA-approved mass spectrometry-based proteomic biomarker assay; many more in development

Development: mass spectrometry-based proteomic assays also being developed for early cancer detection; liquid biopsy involves blood draw to identify plasma components that can be used to improve cancer surveillance and early detection; liquid biopsy using cell-free DNA now FDA- and CLIA- (clinical laboratory improved amendments) approved for monitoring advanced cancers for detection of DNA-mutation precision medicine targets; for early detection, proteomics has additional dimension used to aid liquid biopsy cancer surveillance; example — liquid biopsy interception assay CancerSEEK utilizes proteomic and cell-free DNA components; proteomic profiling improves accuracy of cancer detection sensitivity and specificity beyond what cell-free DNA can provide in liquid biopsy; first example of combined genomic and proteomic diagnostic test in advanced stages for FDA approval; FDA Center for Biologics Evaluation and Research (CBER) has established special FDA US National Cancer Institute clinical proteomics program; goal of advancing introduction of FDA-approved proteomic clinical diagnostic tests

Summary: proteomics mechanistically closer to cancer cell growth, metastasis, and progression than genomics; anticipated proteomic and combined genomic-proteomic assays will supplant pure genomic tests using precision medicine as cotheragnostic tests for cancer therapies; proteomics provides important additional source of data for challenging diagnostic tests such as detection of early stage cancers; can be fewer than one molecule of cell-free DNA available per detection in 20 ccs of blood, depending on malignancy; additional modalities such as proteomics improve sensitivity; targeted mass spectrometry proteomics has potential to better meet requirements for clinical validation; underused; currently used more in biological research; changing technologies from mass spectrometry antibody-based approaches at validation stage introduce uncertainty as to whether any validation failure is due to biomarker or technical performance; using targeted mass spectrometry validation will help resolve ambiguities in results from antibody tests; anticipate large increase in number of available proteomic tests

Metastasis: metastasis, and consequences of its treatment, greatest contributor to death from cancer; cancer therapy has largely concentrated on druggable targets in primary cancer tumorigenesis pathways such as receptor tyrosine kinases like epidermal growth factor receptor; uses

sequential and combination therapies to minimize drug resistance; metastasis-related growth beyond primary cancer causes death for vast majority of patients; metastatic colonization — progressive growth of cancer cells at foreign location beyond site of tumor cell origin

Adjuvant treatment: combined with surgery; patients have surgery to remove primary tumor in absence of visible distant metastases; patients receive additional targeted or cytotoxic chemotherapy to prevent metastatic colonization; chemotherapy often added in patients with tumors with cells that have spread to lymph nodes but not to other organs; has substantial survival benefit; examples — stage III colorectal and breast cancer and malignant melanoma; patients with resected lymph nodes found to carry tumor cells treated with full-force cytotoxic and targeted chemotherapies to kill every last cell that has spread to lymph nodes or elsewhere but has not manifested as clinically observable disease

Prognosis: diagnosis of metastatic cancer indicates terminal illness for overwhelming majority; patients initially diagnosed with localized disease often experience excellent 5-year survival; those with regional disease at diagnosis, eg, those with spread to regional lymph nodes, have lower survival overall but, excluding patients with bladder or prostate cancer, often have survival gains, as shown by data from the 2010 to 2020 reporting period; however, only colorectal, esophageal, lung, and oral cancer out of 12 types of cancer assessed had associated gains in survival of patients with distant metastases at time of diagnosis, and these had improvement <5% overall; 5-yr survival of several types of cancer, including ovarian, prostate, and uterine cancer, decreased for metastatic patients from 2010 to 2020; reasons not understood at present

Pathology: tumor cells begin metastasis by invasion of tissue surrounding primary tumor; cancer cells traverse normal tissue in groups of single cells using reversible adhesion, proteolytic destruction, and motility; after local invasion, tumor cells can enter bloodstream directly or via lymphatic system; traversal of bloodstream most frequently ends in arrest at first capillary bed encountered at distant site; tumor cells then extravasate from bloodstream and arrive at distant sites of metastasis; pre-metastatic niche — metastatic sites can be altered by bone marrow-derived cells before tumor cell arrival; cellular composition, immune status, blood supply, extracellular matrix, and other aspects of metastatic site can be altered to favor colonization

Dormancy: paused state of metastasis; certain cancers have prolonged periods of dormancy where small numbers of cells, often thought to be single cells, can live for many years; example — breast cancers can recur with same molecular characteristics of primary tumors after 10 to 13 years of complete response and disappearance of all macroscopic disease

Site of metastasis: can influence choice of therapy; most pronounced in tumors crossing blood-brain barrier into central nervous system, the brain and spinal cord; HER2/neu ERBB2-positive receptor — important growth factor-promoting cell surface protein; most common in breast adenocarcinoma; also expressed by other cancers; ERBB2-positive tumor present in central nervous system cannot be treated with anti-ERBB2 monoclonal antibodies, which cannot pass through blood-brain barrier; target drugs must penetrate central nervous system to treat central nervous system metastasis of breast cancers; example — ERBB2-inactivating small molecules used as chemotherapy

Prevention and treatment of cancers in bone: bone complications sometimes referred to as skeletal-related events; defined as radiation to bone, pathological fracture, surgery to bone, and spinal cord compression; bone-targeted therapies include RANKL ligand-binding monoclonal antibody denosumab and zoledronic acid, which can be incorporated into matrix of bone tissue; both prostate and breast cancers frequently metastasize to bone and promote skeletal-related events such as anemia, thrombocytopenia, and leukopenia; denosumab and zoledronic acid among targeted chemotherapy drugs; do not attack tumor cells but prevent prostate or breast cancer cells from resorbing essentially normal bone matrix surrounding tumor cells; both prostate and breast cancer patients can benefit from reduced skeletal-related events from therapies targeted at bone extracellular matrix despite different biologies and cytotoxic chemotherapy regimens of the two cancers

Tumor diagnostics and precision medicine: presence of metastasis can cause different subclonal evolution at different sites; different mutations or epimutations develop at some sites of metastasis but not others

Liquid biopsy: emerging technology developed in past 15 years; highly sensitive in detecting DNA mutations; first applied to detect fetal genetic alterations in pregnant women; concentration of cell-free DNA in pregnancy can approach 10%; adapted for use in precision oncology; tumor DNA in patients with advanced cancer can reach up to 25% of all cell-free DNA in plasma; for patients with early stage cancers, concentration can be much lower; sometimes <1%; if only one site of tumor biopsied and sequenced for precision medicine targeted therapy, it may not reflect resistance mutations at other sites of metastasis; example — KRS mutations conferring resistance to epidermal growth factor receptor inhibitors; may be benefits to using liquid biopsy to integrate different mutations present at multiple sites

Procedure: typically involves isolating plasma from blood in special tubes to separate completely from normal blood cells and cell-free isolate DNA from plasma; also uses PCR amplification of panels of specific mutation hotspots or whole genes followed by purification of PCR-amplified DNA in deep next-generation sequencing of gene panels

Use in metastatic disease: monitoring tumor response to therapy in advanced cancer patients; liquid biopsy showing increases or decreases in specific mutations present in tumor reveals efficacy of targeted therapy; example — therapies targeting BRAF V600E; potential replacement for surgical tumor biopsies; use in adjuvant setting post-resection to monitor minimal residual disease and recurrence after surgical resection of primary tumor; can monitor growth and metastasis in other sites; early detection in patients with small numbers of circulating tumor cells in early stage cancers; also used to monitor metastatic disease; example — monitoring heavy smokers for appearance of new lung cancers instead of using spiral CT; concentration of cell-free DNA can be very low

in small tumors; additional types of cancer-specific data such as epigenetic or proteomic markers used to augment cell-free DNA detection

Summary: metastasis main cause of death for most patients with solid tumors; new targeted therapies specifically attack tumor cells and microenvironment to prevent metastasis from occurring or spreading; anticipated that liquid biopsy will become more important to integrate totality of mutation-carrying sites in metastatic patients to understand optimal therapies; example — patients may have mutation at one site in KRAS that would obviate use of epidermal growth factor receptor inhibitors; in contrast, patients with no detectable mutation would have positive treatment in other contexts

Suggested Reading

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Familial Cancer Syndromes

James Church, MD, *Colorectal Surgeon, Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, OH*

Cancer: caused by loss of regulation of cell division, growth, and differentiation; cellular functions usually tightly controlled by multiple overlapping molecular fail-safe systems that protect against developing cancer; when controls fail, cells become capable of growing abnormally, invading adjacent tissue, and spreading to distant organs to set up colonies in foreign environments

Control: mechanisms regulating cell division, growth, and differentiation consist of molecular pathways involving numerous proteins; each protein coded for by gene — segment of DNA holding code for particular protein; ≈30,000 genes in human genome; genes coding for proteins involved in growth regulation include tumor suppressor genes that produce proteins inhibiting cell growth and proto-oncogenes producing proteins encouraging growth

Oncogenesis: loss of function of tumor suppressor gene or abnormal activation of proto-oncogene can abnormally accelerate cell growth; tumor suppressor genes represent brake; proto-oncogenes represent accelerator; growth of cell inappropriately fast when brake fails; clone of cells produced if stem cell suffers change in function; each cell then has abnormal growth, prolonged survival, and enhanced differentiation; growth regulation becomes increasingly abnormal as clones accumulate dysfunction in other tumor suppressor genes and proto-oncogenes; affected cells can invade and metastasize; stem cells never die in cellular terms; keep dividing and producing new cells to populate organ; eg, in base of crypts of colon, there are stem cells that keep dividing, producing colonocytes, which progress up the colonic crypts over 4-5 days, then die and are shed into lumen; organs with most rapidly dividing stem cells most prone to acquiring mistakes in cell DNA, mutations, and development of cancer; these organs include large intestine, liver, skin, lung, pancreas, white blood cells, small bowel, esophagus, testis, and thyroid; sporadic cancers in these organs relatively common; generally develop at later age; takes many decades for cell clones to accumulate number of genetic mutations required to achieve transformation of normal cell into malignant cell

Hereditary cancer: in some patients, cancer develops at an unusually early age and can be seen in multiple relatives in same family; suggests inherited deleterious mutation in key tumor suppressor gene or proto-oncogene; present in patient germline in oocyte in women or spermatocyte in men; inherited germline mutations present in nucleus of every cell of affected child

Syndrome of cancer predisposition: syndrome — collection of medical signs, symptoms, and diseases in patient and family often associated with particular disease or disorder; growth control progressively lost; progress to cancer accelerated as clones of cells containing initial mutation accumulate more genetic abnormalities; hereditary cancer syndromes typically feature multiple benign and malignant tumors occurring in young patients and affecting several organs; positive history of signs, symptoms, and diseases in family; most syndromes of hereditary cancer feature autosomal dominant inheritance, where each child of an affected patient has 50% chance of being affected regardless of gender

Genetic testing: each syndrome has one or more mutated gene causing clinical manifestations; genetic diagnosis confirms clinical suspicion and allows for triage of at-risk relatives of affected patients; role of clinician to protect affected family members from developing advanced and untreated cancers by means of surveillance programs; genetic testing for hereditary cancer syndrome indicated when patient presents with signs and symptoms suggestive of syndrome; these include developing cancer at unusually young age, having strong family history of cancer, or multiple benign or malignant manifestations characteristic of particular syndrome; patient referred for genetic counseling to explain nature of genetic testing, risks and benefits, and financial and social implications of results; current testing usually done with genetic panels; panel test includes sequencing of group of 20 to 30 or more genes including all genes implicated in clinical presentation of patient; Medicare covers cost of FDA-approved genetic testing panels; testing available and affordable for most patients; after test results obtained, patient meets again with genetic counselor to have implications of results explained and plan surveillance or treatment strategy based on results

Results: panel tests covering multiple genes increase chances of positive result but also chance that significance of results will be hard to determine; testing explains clinical situation if classical gene mutation found that is in agreement with clinical manifestations of syndrome; implications well known and treatment can proceed; however, sometimes mutation is found in gene not typically associated with clinical presentation that initiated test; variant of unknown significance — mutation detected that is not considered harmful; potentially confusing results must be interpreted by genetic counselor; in presence of positive results, triage at-risk relatives by screening their DNA for same mutation; family mutation same in every affected person in family

Triaging of relatives: second situation in which genetic testing for hereditary cancer syndromes performed; screen for specific family mutation rather than sequencing number

of different genes; simpler, quicker, and cheaper; negative result in proband means genetic testing not suitable for that family; negative genetic test does not mean patients do not have syndrome; simply means test did not demonstrate it; some families develop certain syndromes in unknown ways; still have syndrome but mutation not found; genetic testing unhelpful in these circumstances; every at-risk family member of affected person should be screened; if positive in proband, genetic testing used to tell members of family not at risk that they do not require aggressive screening

Hereditary breast and ovarian cancer:

Genetic mechanisms**:** common hereditary cancer syndromes; due to mutations in BRCA1 and BRCA2 genes; genes have role in DNA repair; control double-strand breaks in DNA; when proteins not produced because of gene mutations, DNA develops multiple mistakes due to failure of double-strand break repair; mistakes lead to mutations in other genes; encourage instability and lack of control of cell growth; produce neoplasms and other tumors; accounts for about 5% to 10% of breast cancers; syndromes relatively common because breast cancer common; inheritance of mutations in BRCA genes is autosomal dominant with incomplete penetrance; penetrance is percentage of patients with mutation who actually develop disease; can vary up to ≈70% to 80% depending on age; mutation does not guarantee disease; chances of breast cancer increased over general population by several fold

Indications for testing: patient with strong family history of breast cancer should have breast cancer genetic panel testing including BRCA genes; 25% to 28% of patients with strong family history of breast cancer carry germline mutation; other indications for testing include family member with BRCA1 or 2 gene mutation linked to breast cancer, personal history of breast cancer at age 45 or younger, personal history of bilateral breast cancer, and personal history of triple negative breast cancer diagnosed under age 60; triple negative breast cancer tests negative for estrogen receptors, progesterone receptors, and excess HER2 proteins

Characteristics of BRCA1 and BRCA2 cancers: BRCA1 cancers typically triple negative breast cancers; mean age of onset age 40; BRCA2 cancers typically have post-menopausal presentation and are associated with male breast, prostate, pancreas, and gastrointestinal cancers, including gallbladder, bile duct, and stomach cancers, and melanoma; mean age of development of BRCA2 cancers 43 years; invasive ductal cancers in breast; BRCA1 mutations also associated with ovarian and fallopian tube cancer; other indications for testing of BRCA1 and BRCA2 include Ashkenazi Jewish heritage, personal history of breast cancer, personal history of breast cancer at age 46 to 50 with close family member diagnosed with breast cancer or aggressive prostate cancer, personal history of breast cancer and close family member diagnosed with breast cancer at age 50 or younger, and personal history of breast cancer and two or more close family members diagnosed with breast cancer at any age; personal or family history of ovarian, pancreatic, aggressive or metastatic prostate, and male breast cancer also suggestive and indication for testing

Management: patient found to have germline mutation in BRCA1 or BRCA2 should receive aggressive screening; includes breast MRI yearly beginning between ages 20 and 30, depending on age of diagnosis in relatives; earlier diagnosis in a relative should prompt earlier breast cancer surveillance; pelvic ultrasound and pelvic exam to evaluate ovaries twice yearly; careful prostate screening in men with BRCA2 mutation; oral contraceptive therapy can reduce risk of ovarian cancer in women with BRCA1 mutation; tamoxifen useful therapy for first breast cancer in BRCA2 carriers and second cancer in both mutations; prophylactic surgery can be contemplated for breast and ovarian cancer on individual basis, depending on presentation

Li-Fraumeni syndrome: germline mutation in P53 gene — key gene involved in coordinating DNA repair by controlling cell division, cell cycle arrest, and processes of DNA repair and apoptosis; apoptosis — programmed cell death occurring when DNA damage too severe to be repaired or incompatible with repair; mistakes in DNA replication during cell division go unrepaired when gene not working; results in multiple mutations in multiple genes; mutations in gene found in 60% to 80% of cases meeting criteria; inherited in autosomal dominant pattern; rare; incidence unknown

Diagnosis: three clinical criteria; all three required; sarcoma age <45, first degree relative with any cancer at <45, and another first or second degree relative diagnosed with any cancer <45 or sarcoma at any age; sarcomas and cancers of breast, brain, or adrenals and leukemia or lymphoma characteristic findings; penetrance of mutation varies according to age and type of mutation; 22% of cancers occur in children between zero and 15 years; tend to be in adrenal cortex, choroid plexus, striated muscle, and brain; half of cancers occur in adults between age 16 and 50; include breast, osteosarcoma, soft tissue sarcomas, leukemia, colon, rectal, and lung cancer; in adult phase, between ages 51 and 80, pancreatic and prostate cancers predominate; 50% overall develop cancer by age 30; 90% by age 70

Management: avoidance of radiation, comprehensive annual physical examination, breast cancer screening beginning at age 25, colonoscopy beginning no later than age 25, and targeted organ surveillance based on family pattern of cancer

Familial adenomatous polyposis (FAP): germline mutation in tumor suppressor APC — gene involved in wingless (Wnt) pathway of growth control; loss of APC protein akin to turning on growth-encouraging pathway and leaving it on; mutations present in >85% of patients with clinical manifestations; penetrance close to 100%; patients with germline mutation highly likely to develop clinical symptoms and signs of disease; inherited in autosomal dominant pattern; ≈25% of patients have no family history; develop mutation de novo at conception; FAP occurs about once in every 12,000 births; accounts for ≈1% of colorectal cancers

Clinical manifestations: mainly colorectal polyposis, gastroduodenal polyposis — fundic gland polyps in stomach; adenomas in duodenum, and desmoid disease — benign tumors of fibrous tissue causing severe symptoms by rapid growth and effect on adjacent organs; multiple other extracolonic manifestations include hepatoblastoma in infants, medulloblastoma, and thyroid, small bowel, adrenal, and renal cell cancer; Gardner's

syndrome — osteoma, epidermoid cysts, desmoid disease, and extra teeth also part of FAP

Indications for testing: >10 cumulative adenomas; patients with cancers of colon and rectum developing under age 50; FAP categorized according to number of polyps present in colon; attenuated FAP has <100 synchronous adenomas; mild FAP — 100 to 1000; profuse FAP — >1000; clinical presentation varies according to position of mutation and gene, although these do not account for all clinical variations

FAP management: prime responsibility of clinician is stopping cancer development; second is allowing patient to have as normal a life as possible; be strategic when making decisions about surgery; 40% of patients with FAP develop desmoids, which tend to occur after abdominal surgery; in patient with family history of desmoid disease, be cautious about surgery and be certain no other option exists; colonoscopy recommended on yearly basis starting at puberty or age 10 or 11 to control cancer risk; esophagogastroduodenoscopies beginning in early 20s to control upper GI tract cancer; continue as necessary, depending on stage or severity of duodenal polyposis; thyroid ultrasound at diagnosis and regularly throughout life; GI tract remains under surveillance after prophylactic surgery; depends on how much bowel left behind and location of remnant

Surgical options for FAP: in patients whose colonic polyp number and size suggest cancer risk, options include colectomy with ileorectal anastomosis, proctocolectomy with ileal pouch-anal anastomosis, or proctocolectomy and end ileostomy; less disturbance of quality of life with ileorectal anastomosis, but risk of rectal cancer remains; patient must be surveilled on yearly basis; patients who have pelvic pouch made out of terminal ilium have less risk of rectal cancer, although small level of risk remains at anal transition zone; have markedly abnormal bowel habits including multiple loose stools and potential issues with defecation and incontinence; patients who develop severe duodenal adenomatosis at risk of developing duodenal cancer; usually concentrated around duodenal ampulla; ampullectomy and pancreas-preserving duodenectomy or Whipple operation sometimes performed to treat or prevent cancer in duodenum; close observation sometimes needed

Desmoid disease: common; occurs in ≈31% of patients with FAP; treated based on stage; stage one — <10cm stable and asymptomatic tumor; stage two — mildly symptomatic, slowly growing; stage three — tumor more rapidly growing and >10cm; stage four — tumor >20cm and very rapidly growing, generally resistant to usual therapies and can be life threatening

Lynch syndrome: sometimes called hereditary mismatch repair; involves mutations in four mismatch repair genes — MSH2, MLH1, MSH6, and PMS2; another gene in close vicinity called EPCAM also produces deficient DNA repair; inherited in autosomal dominant fashion; penetrance varies by genotype and age; cancer more likely in older patients; average age of patients at cancer diagnosis ≈46 years; one in 279 in population will develop Lynch syndrome; accounts for about 2% to 3% of all colorectal cancers; Lynch syndrome sometimes referred to as hereditary non-polyposis colorectal cancer (HNPCC); two syndromes sometimes referred to as if equivalent; not accurate, as Lynch syndrome is genetic diagnosis, while HNPCC is clinical diagnosis

Hereditary nonpolyposis colorectal cancer vs Lynch syndrome: HNPCC is clinical diagnosis based on Amsterdam criteria — three affected relatives in family, two of which are first degree of third; affected patients have colorectal cancer or other Lynch syndrome-related cancers such as pancreatic or biliary, endometrial, gastric, small bowel, transitional cell, brain, and skin; familial polyposis must be excluded; additionally, one of three must be diagnosed <50 years of age; criteria developed to reflect autosomal dominant inheritance pattern; not particularly sensitive, as family sizes are decreasing and surveillance decreases incidence rate of cancer; some patients with HNPCC have Lynch syndrome germline mutation; others do not; patients with HNPCC subject to intensive surveillance; receive Lynch syndrome testing; may have genetic mutation not picked up by available tests; thus, presence of Amsterdam criteria increases chance patient has autosomal dominant disease

Genetics of Lynch syndrome: MSH2, MLH1, MSH6, and PMS2 have different associated clinical phenotypes; MSH2 and MLH1 aggressive forms with high rates of cancer and recurrent cancer after first cancer removed; ≈70% to 80% lifetime risk of colon cancer; MSH6 much less aggressive, with lower rates of colon cancer but higher rates of endometrial cancer; 30% to 35% lifetime risk of colon cancer; PMS2 least clinically aggressive with relatively low rates of colorectal cancer — ≈15% lifetime risk; cancers developing from hereditary DNA mismatch repair tend to be right-sided and have microsatellite-unstable genetic profile; DNA mismatch repair genes normally repair mismatches in DNA that happen during cell division and DNA replication; microsatellites — areas of DNA that have multiple repeated bases of abnormal lengths; develop when mismatches not repaired; gene with microsatellites prone to developing mutations in many genes; mutations produce small fragments of protein when transcription and translation occur; fragments immunogenic; microsatellite-unstable tumors stimulate host defense response; marked response can occur in cancer when host defense response enhanced by PD-1 blockade, such as with Keytruda antibody; discovery of this mechanism is major step forward; only cancers with microsatellite instability suitable for treatment with immune therapy with Keytruda

Diagnosis: made in patients who already have colorectal cancer by testing for microsatellite instability or doing immunohistochemistry to evaluate for mismatch repair proteins in tissue; evidence of Lynch syndrome if mismatch repair gene not expressed in cancer or if cancer has microsatellite instability; sometimes cancers develop sporadic microsatellite instability; further testing usually needed; strong family history another reason to test for mutation in mismatch repair genes; Amsterdam-criteria positive family history indication for genetic testing for Lynch syndrome; usually done with panel of genes including DNA mismatch repair and other genes related to hereditary colorectal cancer

Treatment of Lynch syndrome: put patients with germline mutation on active surveillance protocol starting with colonoscopy at 20 to 25; depends on phenotype of

disease in family; if other family members develop colorectal cancer young, patients with mutation but no disease should start surveillance young; examination of stomach and duodenum starts at age 35, as do pelvic exams and ultrasounds of uterus and adnexa in women; administer skin check, because patients develop malignant skin tumors; urinalysis sometimes done to diagnose early transitional cell cancers; colonoscopy only screening and surveillance test shown beneficial; prophylactic colectomy offered when patients reach certain age in presence of family history of aggressive cancers; prophylactic hysterectomy and oophorectomy offered when women have reached age at which reproduction no longer contemplated; preference to offer total colectomy with ileorectal anastomosis when Lynch syndrome patients develop cancer; extended resection helps patients avoid metachronous colorectal cancer; removal of remaining colon still possibility but not generally done if patients have segmental colectomy and diagnosis of Lynch syndrome made later; patients undergo intensive colonoscopic surveillance in hopes of preventing metachronous cancer by removing polyps; rate at which adenomas become malignant in Lynch syndrome accelerated compared to sporadic situation

Cowden syndrome: germline mutation in PTEN — tumor suppressor gene involved in coordination of apoptosis and growth control and regulation; germline mutation that produces tumors in variety of tissues; autosomal dominant inheritance; patients fulfilling diagnostic criteria for Cowden syndrome have ≈80% chance of having PTEN mutation; incidence of one in 200,000; primary manifestations include breast cancer, seen in 85% of mutation carriers, follicular carcinoma of thyroid in 35%, endometrial cancer in 28%, and carcinoma of large intestine; patients also develop multiple polyps of multiple histologies such as fibromas, lipomas, ganglioneuromas, and adenomas of hyperplastic polyps in colon; develop multiple skin lesions including trichilemmomas and acral lesions

Diagnosis: major diagnostic criteria include breast cancer, follicular thyroid cancer, endometrial carcinoma, and macrocephaly; minor criteria include benign thyroid lesions, intellectual disability, with IQ <75, hamartomatous intestinal polyps, fibrocystic breast disease, genitourinary tumors, including renal cell cancer, genitourinary malformations, and uterine fibroids; patients with combinations of these clinical signs should be tested for PTEN mutation; should undergo yearly thyroid ultrasound and skin check from time of diagnosis with positive test; monthly breast self-examination recommended; annual breast screening with mammogram and/or MRI; annual transvaginal ultrasound with endometrial biopsy; begin colonoscopy at age ≈35; continue depending on degree of polyposis; undergo renal imaging with CT or MRI every 2 years beginning at age 40

Multiple endocrine neoplasia (MEN): divided into MEN types 1 and 2; different syndromes with different genes involved

MEN 1: autosomal dominant inherited disease; due to mutation in MEN 1 gene; mutation 95% penetrant; mutation found in 70% to 90% of patients fulfilling diagnostic criteria; ≈10% of patients develop mutation without family history; de novo mutation probably happening at conception; frequency about one in 30,000; characteristic clinical manifestations include pituitary adenomas, parathyroid hyperplasia, angiofibromas, lipomas, and functioning pancreatic tumors secreting gastrin or other pancreatic hormones; ≈50% of affected patients develop symptoms and signs by age 20; almost 95% by age 40

Diagnosis: criteria include two of three classical tumors in family; familial MEN 1 defined in individual with at least one first degree relative with one or more classic endocrine tumor or single organ involvement with MEN tumor and germline pathogenic variant; surveillance recommended in patients diagnosed with MEN 1; serum prolactin from age five, serum calcium for effects of parathyroid hyperplasia from age eight, fasting serum gastrin from age 20, MRI of head from age five and every 3 to 5 years to evaluate for pituitary adenomas, abdominal CT or MRI from age 20 and every 3 to 5 years, chest CT from age 20, and OctreoScan from age 20 and every 3 to 5 years

MEN 2: germline mutation in RET proto-oncogene; occurs in about one in 40,000; ≈50% of affected patients have no family history; de novo mutation; manifestations of germline RET mutation include medullary thyroid cancer with pheochromocytomas, parathyroid hyperplasia, and neuromas; some patients have Marfan habitus without having Marfan syndrome; genetic testing should be sought if patient has family history of two of three — medullary thyroid cancer, pheochromocytoma, or parathyroid adenoma — or if patient presents with one of the three tumors; manifestations treated as appropriate

Hereditary diffuse gastric cancer (HDGC): germline mutation in CDH1 gene; found in 30% to 50% of families with clinical phenotype suggesting syndrome; autosomal dominant inheritance; rare syndrome; only 1% of all gastric cancers; syndrome suggested in presence of two or more cases of stomach cancer in family, at least one diffuse; family member with gastric cancer before age 50; personal or family history of both diffuse gastric cancer and lobular breast cancer and one patient diagnosed before age 50; two or more cases of lobular breast cancer in family diagnosed under age of 50; patient diagnosed with multiple different lobular breast cancers before age 50; or patient with diffuse gastric cancer and personal or family history of cleft lip or palate; these patients should undergo genetic testing for CDH1 gene; cancer panel suggested; lifetime risk of gastric cancer in an affected patient 70% for men and up to 83% in women; affected women also face lifetime risk of lobular breast cancer of 39% to 52%

Management: prophylactic gastrectomy generally most effective approach to cancer risk;; surveillance can be falsely negative because diffuse gastric cancers tend to be submucosal; rare that indications of cancer present early in course of disease; even surveillance biopsies can be falsely negative; since total gastrectomy morbid operation, intense surveillance can be offered with up to 70 biopsies taken at each gastroscopy; women should do breast self-examination every month and have breast MRIs on yearly basis

Von Hippel-Lindau (VHL) disease: dominant inheritance of germline mutation in VHL gene; occurs in about one in 36,000 births; mutation has 90% penetrance; patients affected with mutation in their germline have 90%

chance of developing manifestations of disease over lifetime; mean age of diagnosis 26; ≈20% of patients de novo mutations without family history; indications for genetic testing include positive family history of VHL disease with at least one case of hemangioblastoma, pheochromocytoma, or renal cell cancer; without family history, any individual needs two of these tumors to suggest disease

Presentation: headaches, problems with balance and walking, dizziness, limb weakness, angiomatosis, hemangioblastomas, pheochromocytomas, renal cell cancer, pancreatic cysts, endolymphatic sac tumors, and cystadenomas of epididymis in men or broad ligament of uterus in women; strokes, heart attacks, and cardiovascular disease common due to blood vessel involvement throughout body; spinal hemangioblastomas found in up to 60% of patients; each manifestation treated as appropriate

Suggested Reading

Norton JA, et al: Multiple endocrine neoplasia: genetics and clinical management. *Surg Oncol Clin N Am.* 2015 Oct;24(4):795-832; **Valdez JM, et al:** Li-Fraumeni syndrome: a paradigm for the understanding of hereditary cancer predisposition. *Br J Haematol.* 2017 Feb;176(4):539-52; **Waller A, et al:** Familial adenomatous polyposis. *J Pediatr Genet.* 2016 Jun;5(2):78-83.