RHODE ISLAND
MEDICAL JOURNAL


Anthony E. Mega, MD


Fred J. Schiffman, MD

Updates in Hematology/Oncology

ANTHONY E. MEGA, MD
FRED J. SCHIFFMAN, MD, MACP
GUEST EDITORS

Declining Cancer Rates, Inclining Local Expertise: We Are Pointed in the Right Direction but Work Remains

ANTHONY E. MEGA, MD; FRED J. SCHIFFMAN, MD, MACP
GUEST EDITORS

Each year, the American Cancer Society estimates cancer incidence and death rates and compiles data on a number of relevant cancer statistics. The last report provides more than a ray of optimism. In 2016–2017, cancer death rates over the last measured period fell 2.2%. This represents the greatest decline in any one-year period since statistics have been kept. Today's good news is the result of decades, if not centuries, of basic research, clinical trials and preventive strategies. Skilled scientists, dedicated healthcare providers, public health workers, educators and policy makers (certainly not from a single political party) deserve credit here. Even diligent parents and grandparents who have implored their children and grandchildren not to smoke have made a contribution! Many years of innovation and comprehensive care throughout the country has led to a 27% decline in cancer mortality over nearly three decades. This translates into nearly 3 million lives saved – approximately the population of Chicago.

What is the data from Rhode Island (RI)? Cancer incidence rates in both RI men and women, as well as cancer mortality rates, exceed the national averages. Most striking is the higher cancer incidence in RI women compared to the national average, 458.1/100,000 age-adjusted population versus 419.3/100,000 age-adjusted population. In women, this represents the third highest cancer incidence. Some of this is attributable to RI women having the highest incidence of bladder cancer and third highest incidence of lung cancer in the United States. The difference in per capita mortality between the state and national average for both men and women is much less pronounced.

Manuscripts from the current edition of the *Rhode Island Medical Journal* (RIMJ) exhibit the expertise needed to make a difference in providing excellent life-saving care. These articles highlight the expertise of our Brown University/Lifespan colleagues as they address selected common and problematic oncologic and hematologic illnesses. We have also included a description of the newly established Sickle Cell Disease Center since many caregivers in the Lifespan Cancer Institute minister to patients with this challenging disease as well.

In their article, "Current Indications for Consideration of Evaluation for Hereditary Cancer Predisposition Syndromes and How They Can Change Management," **DR. LAUREN J. MASSINGHAM** and **DR. ANDRE DE SOUZA** review the dynamic evolution of hereditary cancer predisposition syndromes. The authors estimate that 5–10% of cancers are due to hereditary predisposition with substantial association with the more common malignancies of breast, prostate, ovarian and colon cancers. These malignancies are commonly understood as "hereditary." Less known is the inter-relationship among the malignancies; for example, the increased risk in men to develop more virulent forms of prostate cancer if they carry a BRCA2 gene. This possibility may have been suggested by a family history of breast or ovarian cancer. In addition, the inclusion of pancreatic cancer, an often lethal cancer, as a malignancy within the hereditary predisposition syndromes is highlighted.

The authors point out that a number of institutions provide genetic counseling for patients and family members. But as the indications for genetic counseling and testing expand, will the RI medical community be able to meet the needs? Currently, RI does not license genetic counselors while 25 states do, including neighboring states of Connecticut and Massachusetts. Licensure ensures that the licensees have the minimal degree of competency necessary to ensure that public health, safety and/or welfare are protected. Also, licensing can influence reimbursement of services subsequently impacting availability. Bills have been introduced in the RI state legislature without passage. Given the increasing complexity of cancer genetics and the expanding indication for counseling, we urge our legislative bodies to reassess this issue.

DR. ROBERT SOKOLIC, in his article, "The Sickle Cell Disease Multidisciplinary Clinic (SCDMDC) at the Lifespan Cancer Institute," provides a detailed description of the mission of the clinic. Prior to the SCDMDC inception in late 2017, sickle cell patients transitioning into adulthood were faced with a loss of the comprehensive care as they moved from the Pediatric SCD program at Hasbro's Tomorrow Fund Clinic. While the estimated number of SCD patients in RI is comparatively low, (150–200), their medical needs are complex and "resource-intense." Adding to the complexity are the social vulnerabilities of this group of patients. Dr. Sokolic describes three vital components of SCDMDC: patient-centered care, multidisciplinary delivery and high-touch frequency. While all valued aspects of care delivery, it is the high-touch care that has the potential to be most impactful. It is through frequent contact with caring personnel that relationships and trust are gained with the SCD

patient. This will encourage patients to participate in health maintenance strategies and interventions that will most significantly affect immediate and long-term health.

In their contribution, "Non-Small Cell Lung Cancer in the Era of Personalized Medicine: Molecular Tests that Matter," **DR. CHRISTOPHER DEL PRETE** and **DR. CHRISTOPHER G. AZZOLI** discuss precision medicine influencing therapeutics in lung cancer, which continues to be the leading cause of cancer death in men and women. In 2003, gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, became the first targeted therapy approved for the treatment of non-small cell lung cancer (NSCLCA). Since that time, more than 20 new agents, in the categories of targeted therapy and immunotherapy have gained approval for treatment of metastatic NSCLCA. The authors provide a roadmap to personalized management in order to select the best agent based on cancer cell characteristics of an individual's lung malignancy. In spite of the therapeutic evolution leading to improved survival statistics in NSCLCA, an ounce of prevention should remain one of our priorities as we counsel our patients and children of the harm of tobacco use.

The Nobel Prize for Medicine or Physiology 2018 was awarded to James P. Allison of the University of Texas MD Anderson Cancer Center and Tasuku Honjo of Kyoto University for their discovery of therapies that inhibit negative immune regulation. The medications which were based upon this foundational research inhibit CTLA-4 and PD-1 checkpoint proteins, enabling T cells to target and attack cancerous cells. **DR. ANDREW HSU**, **DR. LAUREN MENDELSON**, and **DR. KHALDOUN ALMHANNA** in their article, "Immune Checkpoint Inhibitors in the Treatment of Gastrointestinal Malignancies: A Review of Current and Future Therapies," remind us of incremental advancements of cancer therapy. While immunotherapy provides benefit to selected patients with gastrointestinal malignancies, the authors note its limited effectiveness, perhaps due to the immunosuppressive tumor cells microenvironment. They point out future directions of trials combining therapies to enhance the immune response. Trials like these often start as Phase I trials with some being offered locally via the planned Phase 1 therapy clinics soon to be established at The Miriam and Rhode Island Hospitals under the auspices of the Lifespan Cancer Institute.

Two contributions provide us with concise reviews of two common malignancies, acute myeloid leukemia (AML) and prostate cancer. **DR. ARI PELCOVITS** and **DR. RABIN NIROULA** in their contribution, "Acute Myeloid Leukemia: A Review," provide insight into the complex heterogeneity of AML. No longer is diagnosis and treatment based solely on the appearance of myeloblasts in the microscopic assessment of the peripheral blood and bone marrow. Genomic signatures directing therapy require highly specialized care. At Rhode Island Hospital, leukemia patients are managed by hematology malignancy specialists. Inpatient care is on a dedicated leukemia service with care transitioned to a leukemia outpatient care team.

The annual RI incidence of prostate cancer is 104 per 100,000 men. In spite of fluctuations in PSA screening recommendations, prostate cancer remains the most common non-cutaneous malignancy in men. In "Prostate Cancer Therapeutics and Their Complications: A Primer for the Primary Care Provider," **DR. ZACHARY BROWNLEE**, **DR. ANDRE DE SOUZA**, **DR. PAUL P. KOFFER**, **DR. THOMAS A. DIPETRILLO** and **DR. ANTHONY E. MEGA** point out the interplay between prostate cancer treatment and a multitude of general health issues such as osteoporosis, cardiovascular disease and diabetes. The team approach of care is adopted at the Genitourinary Cancer Multidisciplinary Clinic at Lifespan Cancer Institute. At this multidisciplinary clinic at The Miriam Hospital, prostate cancer patients meet a team of providers, including urology, radiation oncology, medical oncology, psychiatry, genetics, Phase I research team, sexual health experts combined with support from social work, nurse navigation, survivorship nursing, and nutrition. Care plans are developed and shared with the patient's primary care provider to maintain health, wellness and quality of life for the patient.

In addition, **DR. RANI CHUDASAMA** and **DR. PETER BARTH**, in their contribution, "Risk Stratification of Precursors to Multiple Myeloma in 2020," point out the significant advances in the management of plasma cell disorders, attributed primarily to novel myeloma-directed therapies as well as improved imaging techniques, analysis of the genetic evolution of plasma cell disorders (PCDs), and clinical trials exploring the treatment of pre-symptomatic stages of PCDs. In their article, they explore recent advances in the risk stratification of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma.

The official state motto of Rhode Island is simply "Hope." In our opinion, the authors of articles in this issue have provided us the rays of optimism that embody hope in the delivery of cancer care in our state. Of note, four of the authors are trainees from the Brown hematology/oncology fellowship program and one trainee is from the radiation oncology training program. Scholarly commitment from young professionals adds to the hope.

Acknowledgment

We would like to express our gratitude to the leaders of the Division of Hematology/Oncology and the Lifespan Cancer Institute, (especially Dr. Howard Safran, Dr. David Wazer, and Ms. Susan Korber) for their unwavering support, which has made the world class care we aspire to deliver into reality for our patients and their families.

Guest Editors

Anthony E. Mega, MD; Associate Professor of Medicine, Associate Professor of Surgery, Warren Alpert Medical School of Brown University; Lifespan Cancer Institute, Providence, RI.

Fred J. Schiffman, MD, MACP; Sigal Family Professor of Humanistic Medicine, Vice Chairman of Medicine, Warren Alpert Medical School of Brown University; Medical Director of the Lifespan Cancer Institute; Associate Physician-in-Chief, The Miriam Hospital, Providence, RI.

Current Indications for Consideration of Evaluation for Hereditary Cancer Predisposition Syndromes and How They Can Change Management

LAUREN J. MASSINGHAM, MD; ANDRE DE SOUZA, MD

ABSTRACT

Our current understanding of the genetic mechanisms that underly cancer pathogenesis is rapidly expanding. Hereditary cancer predisposition syndromes are important to recognize for diagnostic and treatment decision-making but also for family members so they will benefit from surveillance and treatment options. This brief review gives primary care and oncology caregivers a summary of the evolution of hereditary cancer predisposition syndromes, indications for consideration of testing and therapy of patients and families.

KEYWORDS: cancer, genetic, hereditary, BRCA, Lynch

BACKGROUND

Approximately 1.7 million individuals were diagnosed with cancer in the United States in 2018 and it is a leading cause of death nationwide.[1] In Rhode Island, between 1995 and 2016, there were approximately 6100 new cancer diagnoses annually.[2] According to the National Cancer Institute, some of the most common cancers diagnosed include breast cancer, prostate cancer, colon cancer, melanoma and pancreatic cancer.[1] One of the most prolific areas of cancer research involves the identification of pathogenic variants (mutations) in genes that alter the function. These gene changes can be somatic (most common) or germline. It is estimated that about 5–10% of cancers are due to hereditary predisposition. Genetic abnormalities vary with tumor type. For example 24% of ovarian cancers, 8–10% of pancreatic cancers, 12% of metastatic prostate cancers, and 17% of early onset colorectal cancers are associated with mutations.[3-6] Hereditary cancer predisposition syndromes have been associated with significantly increased lifetime risk of development of cancer and their identification is critical for patients and families.

Breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) were the first genes to be linked to hereditary cancer syndromes. *BRCA* are correlated with early onset and/or concurrent breast and ovarian cancers. *BRCA1* and *BRCA2* genes were initially cloned in 1994.[7] In 1996, *BRCA1/2* sequencing became clinically available. Shortly thereafter, genetic testing for hereditary colon cancer (Lynch syndrome) became available. In 2010, with the introduction of next generation sequencing (NGS), significant advances have been made in gene discovery, decreasing the time required for results and making genetic testing more affordable. Today, high penetrance genes are defined as those that confer a greater than 5-fold lifetime risk of cancer in comparison with the general population risk. Moderate penetrance genes incur a 2-3-fold increased risk of cancer.

The aim of this brief review is to provide an update on the current indications and implications of germline genetic testing for hereditary predisposition syndromes and to discuss specific surveillance and therapeutic options. We will also describe how the selection of treatment based on molecular biomarkers has taken oncology to the age of precision medicine.

INDICATIONS FOR GENETIC EVALUATION FOR HEREDITARY CANCER SYNDROME

There are many different hereditary cancer predisposition syndromes. **Table 1** provides a summary of common cancer types and criteria to identify individuals at a high risk of a hereditary predisposition who might benefit from genetic evaluation and counseling.[8-9] The National Comprehensive Cancer Network (NCCN) has criteria for identification of those who are at a higher risk for hereditary breast and ovarian syndrome and Lynch syndrome.[10-11] Other tools include Chompret criteria for Li Fraumeni syndrome, the Melanoma Cancer Syndrome Assessment Tool, and *PTEN* risk calculator for *PTEN*-Hamartoma syndrome for other hereditary cancer syndromes in addition to *BRCA* and Lynch syndrome. In general, features that are concerning for a hereditary cancer predisposition syndrome include early age of onset, multiple primary tumors in one individual, cancers with high-risk qualities (such as triple negative breast cancer or medullary thyroid cancer) or multiple cancers in successive generations. Colonic polyposis can also raise concern for a hereditary predisposition. **Table 2** provides a summary of the current polyposis burden recommendations for genetic evaluation and counseling.

Advances in gene sequencing and evolving understanding of cancer susceptibility risk attributed to pathogenic variants will likely refine current genetic testing criteria. For example, germline genetic testing for pediatric cancer has demonstrated that in 8.5–14% of pediatric cases, a hereditary

Table 1. Common cancer indications and criteria that warrant genetic evaluation for hereditary cancer predisposition

Basal cell carcinoma (BCC)	> 5 BCC
	BCC diagnosed at < 30 y
Brain cancer	Family history of cancer: • Lynch syndrome related cancer* • Li Fraumeni**
	Subependymal giant cell astrocytoma
	Medulloblastoma and ≥10 adenomatous colon polyps • ≥10 adenomatous colon polyps • Findings of Neviod basal cell carcinoma syndrome***
Breast cancer (female)	Breast cancer diagnosed ≤45 y
	Triple negative breast cancer diagnosed ≤60 y
	Ashkenazi Jewish Ancestry
	Breast cancer and family history of cancer: • Ovarian cancer • Male breast cancer • Pancreatic cancer • Metastatic prostate cancer
	Breast cancer diagnosed ≤ 50 y and family history of: • Breast cancer • Prostate cancer
Breast cancer (male)	Personal history or family history of a close relative
Colorectal cancer	Colon cancer diagnosed ≤ 50 y
	Colorectal cancer with mismatch repair deficiency on tumor screening
	Two primary Lynch syndrome related cancers* in the same person
	Colon cancer diagnosis with first or second degree relative with a Lynch syndrome related cancer* diagnosed ≤ 50 y
	Colon cancer diagnosis and family history of 2 other with a Lynch syndrome related cancer*
Endometrial cancer	Endometrial cancer diagnosed ≤ 50 y
	Endometrial cancer with mismatch repair deficiency on tumor screening
	Two primary Lynch syndrome related cancers* in the same person
	Endometrial cancer with first or second degree relative with a Lynch syndrome related cancer* diagnosed < 50 y
	Endometrial cancer diagnosis family history of 2 other Lynch syndrome related cancers* regardless of age
Gastric cancer	Diffuse gastric cancer dx < 40 y
	Diffuse gastric cancer and lobular breast cancer in the same person
	Personal/family history of ≥ 2 cases of gastric cancer or lobular breast cancer (one dx < 50)
	Personal/family history of gastric cancer and 2 other Lynch syndrome related cancers at any age
Leukemia	Leukemia at <18 y with a second primary cancer
	Leukemia at <18 y with a sibling with a childhood cancer
	Leukemia and a family history of ≥2 Li Fraumeni associated cancer** (one diagnosed ≤45y)
Melanoma	≥ 3 primary melanomas in the same person
	Personal/family history ≥ 3 diagnoses of melanoma or pancreatic cancer
Ovarian cancer/fallopian tube, primary peritoneal	Personal history or family history of a close relative
Pancreatic cancer	Personal history or family history of a close relative
Prostate cancer	Metastatic prostate cancer

	High grade prostate cancer (Gleason ≥7) with one of the following:
	• Ashkenazi Jewish
	• >1 close blood relative with
	  ◦ Breast cancer diagnosed ≤50 y
	  ◦ Ovarian cancer
	  ◦ Pancreatic cancer
	• ≥2 close blood relatives with breast cancer or prostate cancer at any age

Renal cancer	Renal cancer diagnosed at ≤45 y
	Bilateral or multifocal renal cancer
	Renal cancer and a family history of renal cancer
	Renal cancer and a history of: • Skin leiomyoma, fibrofolliculoma or trichodiscomas • Pneumothorax • Pheochromocytoma/paraganglioma • Hemangioblastoma of retina, brainstem, cerebellum or spinal cord • Early onset uterine fibriods (<30 y)
Thyroid cancer	Medullary thyroid cancer
	Papillary thyroid cancer (cribriform-morular variant)

* Lynch syndrome related cancers: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (typically glioblastoma), biliary tract, small intestinal, sebaceous adenomas, sebaceous carcinoma, keratoacanthoma

** Li Fraumeni syndrome related cancers: soft tissue sarcoma, osteosarcoma, early onset breast cancer, brain cancer, colon cancer

*** Nevoid basal cell carcinoma syndrome: BCC diagnosed < 30 y, >5 BCC, macrocephaly

Table 2. Colonic polyposis burden that warrants genetic evaluation for hereditary cancer predisposition

> 10 adenomatous colon polyps
3–5 juvenile polyps
≥ 2 Peutz-Jegher polyps
≥ 5 serrated polyps proximal to the sigmoid colon (two polyps ≥ 10 mm)
≥ 20 serrated polyps of any size distributed throughout the colon

predisposition has been identified.[12-13] Additionally, the American Society of Breast Surgeons released a consensus guideline that recommends genetic testing for all patients with a new diagnosis of breast cancer.[14] This recommendation was based in part on a study which compared the yield of genetic testing for those with breast cancer who meet and fail to meet the National Cancer Center Network (NCCN) criteria for *BRCA1/2* testing.[15] Patients who met NCCN criteria for germline testing had a 9.39% yield with a large multicancer 80 gene panel. In comparison, patients who did not meet the NCCN criteria for germline testing had a 7.92% yield. Since the difference between the diagnostic yield was not statistically significant, the suggestion is to test all new diagnoses of breast cancer, which could double the number of patients with a clinically actionable result.[15]

GENETIC EVALUATION AND COUNSELING

The gold standard for identifying and testing those at risk for a hereditary cancer predisposition syndrome includes pretest and posttest counseling by professionals, such as genetic counselors, geneticists or oncologists trained in genetics. Part of the evaluation includes utilization of risk assessment tools which are moderately to highly accurate in predicting the likelihood of a germline pathogenic variant. Some examples of these include the International Breast Cancer Intervention Study (IBIS) or BRCAPRO for hereditary breast cancer, and PREMM5 for hereditary colorectal cancer. The benefits of pretest counseling includes: increased understanding of cancer risk, decreased worry about cancer, decreased anxiety, and decreased depression.[16] Face-to-face counseling is the ideal method to educate patients and families before and after testing is performed. As germline genetic testing becomes more and more specialized, the genetics experts can focus upon the most comprehensive, informative and cost-effective testing. If in-person counseling is not available, there are now alternative methods for providing advice and including video methods and telegenetics services.

GERMLINE GENETIC TESTING OPTIONS

The patient affected by cancer should be the first member of the family to be tested by a genetic panel as they are the most informative family member. If that person refuses or is unable to perform the testing, then consideration of testing family members is appropriate. Typically, a blood or saliva sample is collected. A skin biopsy may be necessary if the individual has had an allogenic stem-cell transplant or has a hematologic malignancy. Results typically take 3–4 weeks to return but a STAT panel that includes highly penetrant genes with a 1 week turnaround can be obtained for urgent therapeutic decision making.

MANAGEMENT

Depending upon the cancer predisposition syndrome identified, the lifetime risk of developing cancer does vary. High penetrance hereditary cancer genes are associated with a high lifetime risk of cancer. Some examples of genes that have been identified as high penetrance include *BRCA1*, *BRCA2*, *CDH1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *PTEN*, *TP53*, *RET,* and *STK11*. These genes are typically tumor suppressor genes and management recommendations that include surveillance and therapeutic options are tailored to the specific syndrome.

For example, functionally impaired *BRCA1* or *BRCA2* genes cannot repair double-stranded DNA breaks (the DNA repair or homologous recombination system), leading to genomic instability, accumulation of mutations, and cancer predisposition. In general, the risk for breast cancer is 45-65% by the age of 70 years for a pathogenic variant in either *BRCA1* or *BRCA2*.[17-18] Due to this risk, some women consider a risk-reducing mastectomy. Breast cancer specific mortality has been shown to be decreased by 81-100% after mastectomy.[19] Options for *BRCA1* and *BRCA2* management for women include: clinical breast examination every 6 months starting at the age of 25 years, increased breast screening starting at age 25 years with annual breast MRI and at the age of 30 years addition of a mammogram with consideration of tomography staggered every 6 months from the MRI. Individuals with a *BRCA* pathogenic variant or likely pathogenic variant also have the option of a risk-reducing mastectomy and salpingo-oopherectomy.[10] These can be considered after completion of child bearing. There are also specific recommendations for men carrying *BRCA1* or *BRCA2* pathogenic variants as well, including self and clinical exam starting at age 35 years and consideration of prostate cancer screening starting at age 45 years.[10] Currently there are no specific recommendations for women or men regarding increased melanoma or pancreatic cancer screening but this can be individualized.[10]

The overall goal of precision medicine is to utilize molecular changes to individualize care and choose therapies that are more effective and have fewer side effects. Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as effective agents for the treatment of *BRCA*-mutated tumors. PARP inhibitors repress a salvage gene repair system in *BRCA*

deficient cancers, leading to irreparable DNA damage in these tumor cells and tumor cell death.[20] Three PARP inhibitors were approved in the maintenance or sequential treatment of relapsed epithelial ovarian with or without *BRCA* mutations. Recently, Phase III studies of metastatic *BRCA*-mutated triple negative breast (OLYMPIAD), pancreatic (POLO) and castrate resistant prostate cancers (PROfound) have demonstrated clinically significant improvements in delaying symptomatic or radiologic progression of tumors.[21-23]

Moderate penetrance hereditary cancer genes are associated with a moderate lifetime risk of cancer. Some examples of genes that have been identified as moderate penetrance include: *ATM*, *BARD1*, *CDKN2A*, *CHEK2*, and *RAD51D*. These genes are also typically involved in the DNA repair or homologous recombination aspects of cell function. Recommendations are tailored to the specific pathogenic variant as it may implicate distinct natural history. For example, recommendations for *ATM* and *CHEK2* currently include increased screening starting at age 40 years, annual mammogram with consideration of tomography, and breast MRI staggered 6 months from the mammogram. For these two genes there are currently no surgical recommendations (for breast or ovarian cancer risk). There are also some moderate penetrance genes that do have prophylactic surgical options. *RAD51D* is associated with ovarian cancer and the NCCN currently recommends consideration of risk reducing salpingo-oopherectomy at age 45–50.[10]

FAMILY MEMBER RISK

Identification of a hereditary cancer predisposition can affect patient management, but it is also of critical importance for family members. Once a pathogenic variant or likely pathogenic variant has been identified in an individual, typically his/her first-degree relatives should be offered the opportunity to consider testing. Exceptions to this rule include minors, who, unless the hereditary cancer predisposition syndrome includes childhood onset cancers and screening (such as *TP53* and Familial Adenomatosis Polyposis), should hold off on testing until they reach adulthood and can make their own informed decision.[24] If a first-degree relative refuses testing or is unavailable, second-degree relatives can consider testing. An important implication of testing a family member who is unaffected by cancer is insurance discrimination. In the United States, citizen protection from health insurance discrimination is enforced by the genetic information nondiscrimination act (GINA). However, life insurance, disability insurance and long-term care insurance are entities exempted from GINA.

VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Typically, when completing genetic testing, pretest counseling includes discussion of three possible results. A positive result is described as a finding of inherited a pathogenic or likely pathogenic variant in a hereditary cancer predisposition gene. A negative result is a finding of no detected gene alterations. In this situation the origin of cancer is most likely somatic and may be secondary to environmental or multifactorial causes. The third possibility is the finding of a variant of uncertain significance. This is a gene alteration that has not been reported in the literature before or does not have enough evidence to classify it as pathogenic or benign. Therefore, it is non-diagnostic. The recommendation is to update patients (especially with consistent family history of cancers) of the pathogenicity of the VUS as the scientific evidence accumulates. Family testing is sometimes helpful to sort out the significance of the result to learn if it tracks with other family members with disease. Otherwise, family testing is not recommended for their clinical management.

SOMATIC TESTING

Somatic testing, or tumor testing, has been increasingly utilized in oncology. Tumor testing often identifies multiple pathogenic/likely pathogenic variants that have evolved in the cancer and may be potential targets for treatment. Sometimes a change is identified on somatic testing that is concerning for a germline change. It is important to note that germline testing should be considered based on the patient's clinical and family history, not solely on somatic testing.

CONCLUSIONS

The field of cancer genetics and the testing techniques are quickly evolving. Some of the available panels can now test up to 100 genes. This has important implications for patients with cancer since patient and family diagnostic and therapeutic plans may be impacted.

In Rhode Island, there are multiple institutions that provide genetic services which can be utilized when there is a patient who presents with a personal or family history suggesting a hereditary predisposition. This gives the individual and their family members the opportunity to personalize their management (precision medicine), complete earlier/increased surveillance and/or consider prophylactic therapies to reduce their risk of developing cancer or improve outcomes.

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Authors

Lauren J. Massingham, MD; Division of Genetics, Department of Pediatrics, Warren Alpert Medical School of Brown University; Hasbro Children's Hospital, Lifespan Cancer Institute at Rhode Island Hospital and the Miriam Hospital, Providence, RI.

Andre De Souza, MD; Division of Oncology, Department of Internal Medicine, Warren Alpert Medical School of Brown University; Lifespan Cancer Institute at Rhode Island Hospital and the Miriam Hospital, Providence, RI.

Correspondence

Lauren Massingham, MD
Department of Pediatrics, Division of Genetics
593 Eddy St, MOC Suite 460
Providence, RI 02903
401-444-8361
Fax 401-444-3288
lmassingham@lifespan.org

The Sickle Cell Disease Multidisciplinary Clinic at the Lifespan Cancer Institute

ROBERT SOKOLIC, MD, FACP

KEYWORDS: Sickle cell disease, multidisciplinary clinics, health-care delivery

Sickle cell disease (SCD) is one of the world's most common monogenic disorders, affecting about 100,000 people in the United States. The illness is manifested by sudden, unpredictable and severe bouts of pain, termed vaso-occlusive episodes (VOEs). In addition to the classic presentation of severe VOEs, SCD leads to end-organ damage in multiple systems (**Table 1**). This damage is cumulative, and ultimately leads to a decreased average lifespan and quality of life.[1] As is the case for many genetic diseases, pediatricians have been at the forefront of research and treatment for SCD. Nevertheless, as patients with SCD mature into adulthood, they face the unique problems of adults, along with the accumulating burden of symptoms and end-organ damage from hemoglobinopathy, and care in adult medicine practices becomes appropriate. Current guidelines for the management of SCD call for the care of patients with SCD to be coordinated throughout the lifespan and across care settings as in the patient-centered medical home model.[2]

Table 1. Systemic Effects of SCD

Organ or System	Manifestations of end-organ damage
Nervous system	Stroke, neurocognitive impairment, psychiatric disease, neuropathic pain
Eyes	Retinopathy
Heart	Cardiomyopathy, congestive heart failure, cardiomegaly, valvulopathy
Lungs	Interstitial lung disease, pulmonary hypertension, intrapulmonary shunt
Liver	Hepatopathy, gallstones, nausea, constipation
Immunohematologic system	Hemolysis, thromboembolic disease, hyposplenism
Genitourinary system	Isosthenuria, acute kidney injury, chronic kidney disease, papillary necrosis, renal medullary carcinoma, priapism, erectile dysfunction
Skeleton	Avascular necrosis, osteoporosis, compression fractures
Skin	Leg ulcers
Social function	School and work absenteeism, interrupted education, underemployment, underinsurance

Data on the number of patients with SCD in Rhode Island are scarce. Nevertheless, one can arrive at a rough estimate based on the number of African Americans in Rhode Island and the known prevalence of SCD in the African American population. There are about 60,000 people of African descent in Rhode Island.[3] The prevalence of SCD in African Americans is about 1 in 365.[4] The expected number of patients with SCD is therefore about 150 to 200 patients. Hasbro Children's Hospital (HCH) has long had a clinical program in SCD, but no similar multidisciplinary clinic has existed for adults whose care was divided among different community and academic hematologists in Rhode Island.

In the last quarter of 2017, The Lifespan Cancer Institute (LCI) established the SCD Multidisciplinary Clinic (SCDMDC). The clinic was modeled after two successful programs within the Lifespan Academic Medical Center – the Pediatric SCD program at Hasbro's Tomorrow Fund Clinic and the various disease-centered multidisciplinary clinics within LCI. The first patients were cared for in the clinic on January 2, 2018. The mission of the SCDMDC is to facilitate the achievement by patients with SCD of their self-identified life and health-care goals, while mitigating as much as possible the impact of SCD on achieving these goals. The SCDMDC uses three strategies to facilitate care of adult patients with SCD: patient-centered care, multidisciplinary care, and high-touch care.

Patient-centered care is foundational in SCD. By the time they have reached adulthood, most patients with SCD have extensive experience with the health care system, and this experience has left lasting impressions for both good and ill.[5] As with any other specialty clinic, the first visit to the SCDMDC is concerned with gathering records and clarifying the patient's previous disease history. But, in addition to collecting the medical facts, such as number and frequency of hospitalizations, previous treatments and end-organ damage, time is spent elucidating the patient experience of SCD. Certain aspects of the clinical presentation and pathophysiology of SCD make discussion and validation of the patient's experience of disease particularly important.

Despite its prevalence among African-Americans, South Asian-Americans and Arab-Americans, SCD as a whole is

considered to be a rare disease.[6] Patients with SCD are frequently cared for by practitioners with little personal experience with the disease.[7] Furthermore, the episodic nature of VOEs contributes to frequent emergency treatment, and this often comes from nurses and doctors who do not know the patient personally. The primary symptom of VOEs, pain, is entirely subjective. Successful treatment of acute exacerbations of SCD-related pain requires a foundation of trust between the patient and health-care providers. The provider must trust that the patient's description of his or her symptoms is accurate. In turn, the patient must trust that the provider will accept the patient's description of his or her symptoms without objective correlation to laboratory tests or imaging studies. Such deep trust can be built over multiple patient encounters during an ongoing provider-patient relationship, but is often difficult to achieve when providing care to an unfamiliar patient or receiving care from an unfamiliar practitioner.[8] For this reason, patient-centered care relies on providing care within the context of a familiar practitioner-patient relationship. Patients in the SCDMDC are encouraged to receive urgent care within LCI, either through unscheduled visits to their primary practitioner or through parenteral treatment in the LCI infusion suite. In either setting, patients have a better chance of being cared for by someone whom they know and who knows them personally. If patients cannot be cared for within LCI, they are encouraged to present to the emergency department of a Lifespan hospital. In order to facilitate consistent care in this less familiar setting, each patient in the SCDMDC has a personalized plan for treatment of VOEs in his or her chart. This plan includes documentation of the patient's baseline analgesic regimen as well as analgesic suggestions for unscheduled care in the emergency department and if admitted to the hospital. Plans are readily visible in a care co-ordination note in the patient's electronic medical record.

Another aspect of patient-centered care in the SCDMDC is collaborative development and prioritization of goals. While the SCDMDC staff identifies specific treatment goals within the first few provider-patient encounters based on the extent and severity of end-organ damage, patients of the SCDMDC may have more immediate goals such as relief of symptoms. Furthermore, there are only a few therapies known to be helpful in SCD, and all these therapies have significant shortcomings in terms of effectiveness and adverse events. Therapy for SCD typically must be initiated at low doses and titrated up slowly before it can be expected to lead to clinical benefit, whereas side effects are often noticeable shortly after starting therapy. Given these difficulties with the therapeutic tools available to patients with SCD, patients may be reluctant to accept recommended therapies based on prior experiences. Typically, early prioritization of patient goals, such as symptom management, is necessary prior to beginning treatment based on practitioner-identified goals, such as initiation of disease-modifying therapy and prevention of end-organ damage.

Table 2. Disease-specific treatments of SCD

Treatment	Advantages	Disadvantages
Hydroxyurea	Extends life, reduces VOEs, inexpensive	GI discomfort, leg ulcers, leukemogenic, cytopenias
Transfusion	Prevents stroke in children	Hemosiderosis, alloimmunization, vascular access
Glutamine	Reduces VOEs	Nausea, expensive
Crizalinzumab	Reduces VOEs	Expensive, vascular access, infusion reactions
Voxelotor	Increases hemoglobin	No demonstrated effect on VOEs, expensive
Allogeneic hematopoietic cell transplantation	Curative	Expensive, upfront morbidity and mortality, not available for SCD in Rhode Island

VOE – vaso-occlusive episode

Finally, patient-centered care requires offering the full range of therapies for SCD. Until 2017, there was only one approved drug for SCD. Since then, three new drugs have been approved. With respect to non-drug therapy, supportive care includes both simple and exchange transfusion, while hematopoietic cell transplantation (HCT) remains the only curative treatment for SCD. Every patient who is interested in the procedure is offered referral to an HCT program or to the SCD gene therapy program at Boston Children's Hospital.[9] All other disease-specific therapies are available directly through the SCDMDC at Rhode Island Hospital. Individualized treatment plans use any of these therapies either as single agents or in combination. Because there are no experimental data comparing any therapy for SCD to another, the most appropriate sequencing and combination of treatments is unclear. Selection of treatments is based on the known advantages and disadvantages of each therapy (**Table 2**) but ultimately requires a shared decision-making process in which the patient is the ultimate arbiter of which therapies will be used.

The second strategy used for all patients in the SCDMDC is multidisciplinary care. SCD can affect almost any organ system, and most typically affects multiple systems.[1] Specialists from many different disciplines are required to provide comprehensive care. The dedicated clinic staff of the SCDMDC includes three physicians, two nurse practitioners, two social workers, two patient navigators, a pharmacist, an infusion nurse, a psychologist and a chaplain. A nurse coordinator leads the clinic. Weekly pre-clinic and post-clinic meetings are organized to co-ordinate care among the different disciplines. Monthly meetings of the SCDMDC steering committee are dedicated to systematic issues and to the discussion of complicated patients.

In addition to the above-mentioned core clinical staff, the SCDMDC has developed working relationships with practitioners in other key disciplines, including pain and palliative care, psychiatry, cardiology, pulmonology, nephrology, acupuncture, music and art therapy, emergency medicine, hospital medicine and orthopedics. Colleagues at the Lifespan Recovery Center have been available to treat the few patients with substance use disorder while the patients remain on indicated narcotic analgesics, a problem that is notoriously complicated to treat.[10]

Such complex multidisciplinary and longitudinal care requires considerable co-ordination. Patients of the SCDMDC are strongly encouraged to identify primary care providers and are typically referred to a primary care practice if no such provider has been identified.

The third strategy used by the SCDMDC is high-touch care. Care is based on the 2014 NHLBI expert panel report on evidence-based management of SCD.[4] Where the evidence is not clear, the SCDMDC tends to favor screening for known complications of SCD. After the first few visits, it is often the case that several opportunities for screening and treatment are identified. Patients are usually followed monthly until these interventions have been provided or deferred. Thereafter, patients are followed monthly during titration of treatments. Patients with complicated pain management needs, such as patients on high doses of opiates, patients whose opiates are being tapered and patients with co-morbid substance abuse, are typically seen weekly, whereas patients with very complicated analgesic regimens requiring parenteral treatment may be seen several times a week. In the last case, the LCI infusion nurses and advanced practice providers lead care. When patients are on stable therapy, they are seen 2–4 times per year. Patients admitted to hospital are cared for by the RIH house staff and inpatient physicians with consultation from SCDMDC physicians and frequent visits from other clinic staff.

The LCI SCDMDC is now 2 years old. Approximately 60 patients have been treated, with anecdotal benefit to several patients. One clinic patient has died in the last two years. Overall, hospital days have been reduced by about 30% and the number of ER visits for SCD has been reduced by about 50%. Research collaborations have been initiated with the Department of Emergency Medicine and with other SCD centers in New England, as part of the American Society of Hematology SCD Research Network. The staff of the SCDMDC continues to strive to build on these accomplishments. Patients with SCD can be referred to the MDC via the main LCI number, 844-222-2881.

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Author

Robert Sokolic, MD, FACP; Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University; Lifespan Cancer Institute, Providence, RI.

Correspondence

Robert Sokolic, MD
593 Eddy Street, APC Building
Providence, RI 02903
401-444-4538
Fax 401-444-4184
Robert.Sokolic@lifespan.org

Non-Small Cell Lung Cancer in the Era of Personalized Medicine: Molecular Tests that Matter

CHRISTOPHER DEL PRETE, MD; CHRISTOPHER G. AZZOLI, MD, FASCO

ABSTRACT

The diagnosis and treatment of lung cancer is entering a new era. With increasingly advanced diagnostic tools, we are more able than ever to pinpoint genetic changes in tumor cells that allow us to treat with highly effective, targeted therapy. In a growing number of patients, we are able to avoid cytotoxic therapies altogether. The recent advent of immunotherapy has led to a similar paradigm shift. This article will review the latest advances in tumor tissue and blood biomarkers directly as they relate to available treatments. Specifically, we will review activating and sensitizing gene mutations, gene fusions, PD-L1 tumor score, and close with an appraisal of the rapidly advancing field of peripheral blood biomarkers.

KEYWORDS: Non-Small Cell Lung cancer, peripheral blood biomarkers, molecular tests, immunotherapies

INTRODUCTION

Lung cancer is one of the most common, and by far the deadliest form of cancer in both men and women in the United States. In 2019, it is estimated that 228,150 Americans will be diagnosed with lung cancer and 142,670 will die of the disease, accounting for approximately 25% of all cancer-related deaths, and making lung cancer, all by itself, the second leading cause of death in America after heart disease. The five-year overall survival rate for all-comers with non-small cell lung cancer is 15% or less.[1]

Amidst these grim statistics, a paradigm shift is underway in the diagnosis and treatment of advanced lung cancer. Increasingly, molecular tests performed on tumor tissue, and/or peripheral blood are driving therapeutic decision-making. In the context of metastatic disease in particular, therapies that target molecular pathways or harness the immune system to attack tumor cells are replacing traditional cytotoxic chemotherapies. These newer therapies are less toxic, more effective, and better differentiate malignant cells that carry particular mutations, protein expression, or immune susceptibilities compared to normal cells. This review will focus on the ever-expanding role of biomarkers in the selection of a growing array of gene-targeted drugs and immunotherapies for the treatment of advanced non-small cell lung cancer. It is essential that all physicians have an awareness of the current biomarker landscape in lung cancer to better manage patients with this common disease.

LUNG CANCER HISTOLOGY

After obtaining a tissue biopsy, the next step in the diagnosis of non-small cell lung cancer is to categorize the predominant histologic subtype. This is accomplished by histopathologic examination, though often aided by both immunohistochemical (IHC) and genetic analyses. The results of this pathologic analysis categorize non-small cell lung cancer into histologic subtypes: adenocarcinoma, squamous cell carcinoma, large cell neuroendocrine carcinoma, sarcomatoid or pleiomorphic carcinoma, undifferentiated, and mixed histologies. The vast majority of targetable mutations occur in the adenocarcinoma subtype. However, due to the potential to mis-categorize a small biopsy specimen, and the phenomenon of mixed histology, small biopsy specimens should be given the benefit of the doubt and tested for targetable mutations.[2]

ACTIVATING AND SENSITIZING GENE MUTATIONS

Activating mutations occur in genes that code for intracellular proteins or receptors which drive cancer cell growth, survival, invasion and metastatic spread. They are analogous to a switch stuck in the "on" position, indifferent to the negative feedback that regulates normal cell behavior. In general, lung cancers driven by an activating oncogene are particularly virulent. So patients with such a cancer would have a poor prognosis if untreated. However, cancer cells carrying activating mutations also have a particular vulnerability. These cancers have been described as, "oncogene addicted," meaning that they rely solely on a particular growth signal for survival, and that blocking this signal can trigger cell death.[3] Thus, the gene mutation both activates cancer growth, and also makes the cancer sensitive to a single gene-targeted drug. This paradigm provides the therapeutic rationale behind many of today's targeted therapies. With proper diagnosis, lung cancers which may have a worse prognosis if untreated are flipped to dramatically better prognosis on appropriate treatment.

Targetable activating, sensitizing mutations can be identified in approximately one third of patients with lung

adenocarcinoma, and one fifth of unselected patients with NSCLC.[4,5] As a general rule, the presence of an activating, sensitizing mutation is more common in NSCLC in patients who never smoked cigarettes.[6] However, 90% of lung cancer patients are former or active smokers, and these mutations may still be found in heavy smokers. The clinical impact is such that you do not want to miss them, and patients should be tested for these gene mutations regardless of their smoking history.

EGFR MUTATIONS

The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family of cell membrane receptors which relays growth signals from the surface of the cell to the nucleus via downstream proteins including RAS, PI3K, mTOR and MAPK. This growth signal leads to a variety of anti-apoptotic and proliferative effects within the cell.

Approximately 10% of NSCLC patients will be found to have an activating mutation in *EGFR*, and most of these make the cell sensitive to drugs which block the signal. Over 90% of these mutations are substitution mutations in exon 21 and in frame deletions in exon 19.[7] The prognosis varies with the specific mutation, but in general the presence of an *EGFR* mutation is felt to be a favorable prognostic factor because the drugs blocking EGFR signal are so effective. A recent large cohort study of 1,656 patients with advanced NSCLC and *EGFR* mutation treated with targeted therapy revealed a median overall survival of 30 months and a 3- and 5-year survival of 40% and 20% respectively.[8] This represents a dramatic improvement in overall survival compared to patients with advanced NSCLC lacking an *EGFR* mutation.

Multiple tyrosine kinase inhibitors (TKIs) have been developed that target *EGFR* mutations including afatinib, erlotinib, gefitinib, and osimertinib, all of which are pills taken once daily. It is important to note that these drugs are considered first-line mono-therapeutic agents and as such are used in lieu of traditional chemotherapy or immunotherapy. While effective initially, these drugs do not cure the disease and inevitably cancer cells arise which are resistant to the drug. Resistance to EGFR TKIs can be caused by secondary mutations in *EGFR* which prevent the drug from binding to the protein, or by activation of bypass tracts which stimulate cell growth independent of EGFR.[9] Better initial treatments are being developed by studying the genetic mechanisms of acquired resistance to targeted therapy.

ALK TRANSLOCATIONS

Translocations in the anaplastic lymphoma kinase (*ALK*) gene are both activating, and drug sensitizing. These translocations occur in approximately 3–7% of NSCLC cases and are associated with an excellent response rate to ALK TKIs, ranging from 57 to 74%.[10] Thus, similar to *EGFR* mutations, targeted therapy outperforms systemic chemotherapy by a wide margin in the vast majority of ALK-positive patients. Gene translocations can be harder to find than gene mutations, and require techniques which look at chromosomes (fluorescence in situ hybridization (FISH), or protein immunohistochemistry (IHC)). More sophisticated genetic testing using next-generation sequencing can routinely detect both gene mutations and chromosomal alterations. Whether the *ALK* gene fusion is detected by FISH, IHC or next-generation sequencing, there are a number of drugs which are commercially available to target ALK-positive lung cancer, including alectinib, brigatinib, ceritinib, crizotinib and lorlatinib. Patients with advanced ALK-positive lung cancer treated with serial ALK inhibitors have a median survival time measured in years.[11]

ACTIVATING-SENSITIZING GENE FUSIONS IN ROS1, NTRK, MET AND RET

Like *ALK*, other genes can be activated by chromosomal translocations. ROS1, or c-ROS oncogene 1, is a receptor tyrosine kinase which drives 1–2% of NSCLC patients. The tyrosine kinase domains of ROS1 and ALK are highly conserved, meaning drugs such as crizotinib, ceritinib and lorlatinib are effective in both ROS1 and ALK-positive lung cancers. In a similar story of overlapping efficacy, the drug entrectinib was recently FDA-approved for the treatment of lung cancers with either ROS1, or neurotrophic tyrosine receptor kinase (NTRK) genetic changes. The TRK proteins function during normal physiology as receptors for nerve growth factors, and when activated by gene fusions can drive lung cancers, as well as certain breast cancers and sarcomas. Both entrectinib and larotrectinib are FDA-approved for NTRK-positive lung cancer. RET and MET gene rearrangements are also both activating, and sensitizing; however, there are no FDA-approved drugs specific for these gene targets. Discovery of these genetic changes should prompt enrollment in a clinical trial, or off-label use of a drug approved for some other purpose (cabozantinib, lenvatinib and vandetinb for RET, and crizotinib for MET). Retrospective cohorts of ROS1-positive lung cancer include patients still alive at 5 years.[12] Because NTRK, MET and RET fusions are relatively rare, there is less known about long-term outcomes in these patients.

BRAF V600E

The BRAF proto-oncogene codes for a kinase that when mutated activates the MEK signaling pathway, leading to anti-apoptotic signaling and proliferation. *BRAF* mutations are common in melanoma, but are found in only 1–3% of NSCLC. The combination of dabrafenib and trametinib is FDA-approved for the treatment of advanced lung cancer with *BRAF* V600E with response rates of 60%, and progression-free survival of 10 months.[13,14] It is important to note that, unfortunately, most *BRAF* mutations in lung cancer are not of the targetable V600E type. There is no targeted therapy for *BRAF* non-V600E, and patients with these mutations have a poor prognosis, with a reported 3-year survival rate of 0% compared to 24% of those with a V600E mutation.[15]

Notably, in contrast to the driver mutations discussed so far, *BRAF* mutations are more common in smokers.

KRAS

The most common activating mutations in NSCLC are in the oncogene KRAS. Activating *KRAS* mutations are found in approximately 25–35% of patients with NSCLC and, like BRAF, are more common in current or former smokers. KRAS mutations are generally associated with poor outcomes, at least in part because there are currently no gene-targeted drugs available. Excitingly, this is likely to change with the development of inhibitors to the specific mutation, *KRAS* G12C, which occur in approximately 13% of lung adenocarcinomas and can be blocked by small molecules which bind covalently and exclusively to the mutant protein.[16]

PD-L1

PD-L1 (programmed death-ligand 1) is a transmembrane protein expressed on tumor cells, stromal cells and macrophages that binds to PD-1 receptors on cytotoxic T-cells and effectively turns them off, halting anti-tumor effect. Thus, PD-L1 can be understood as a mask that cancers wear to hide from the immune system. (Please see the accompanying article by Hsu, et al in this edition of the RIMJ, "Immune Checkpoint Inhibitors in the Treatment of Gastrointestinal Malignancies: A Review of Current and Future Therapies.")

The class of drugs that target this mechanism – also known as immune checkpoint inhibitors (ICPIs – includes pembrolizumab, nivolumab, atezolizumab and durvalumab. These monoclonal antibodies disrupt T-cell recognition of PD-L1, thereby enabling T-cell attack on tumor cells.

Due to the growing role of these therapies in modern oncology, and lung cancer in particular, it is now the standard of care in advanced non-small cell lung cancer to test all biospecimens for PD-L1 by immunohistochemical staining. After the stain has been applied, a pathologist calculates the proportion of tumor cells which are positive for PD-L1. The KEYNOTE-024 trial compared standard chemotherapy to pembrolizumab in patients with advanced NSCLC in the first-line setting in patients with a PD-L1 score of ≥50%, and who tested negative for *EGFR* or *ALK* genetic changes. The median overall survival (OS) in the immunotherapy group was not reached, but is estimated to exceed 24 months compared this to the typical 12-month median OS in patients treated with chemotherapy. The overall response rate to pembrolizumab was 45%, compared with 28% treated with chemotherapy.[17] Subsequent trials have combined chemotherapy with pembrolizumab and demonstrated survival benefit regardless of PD-L1 score.[18,19] However, the best biomarker package for selecting single-agent pembrolizumab remains testing negative for *EGFR* and *ALK* genetic changes and having a PD-L1 score ≥ 50%. These patients can avoid first-line cytotoxic therapy altogether, in favor of immunotherapy alone. More recent phase 3 data shows that the combination of low-dose ipilimumab + nivolumab (CTLA4 + PD1 blockade) is superior to chemotherapy even in PDL1 negative patients. This combination is not yet FDA-approved, perhaps because adding CTLA4 blockade adds side effects, and the overall survival comparison in the PDL1 negative cohort was not statistically significant because it was not part of the study's statistical testing hierarchy (no alpha allocation). Also, ipilimumab + nivolumab was not reported to be superior to nivolumab alone for PD-L1 > 1%, and not reported to be superior to chemotherapy + nivolumab for PD-L1 negative patients.[20]

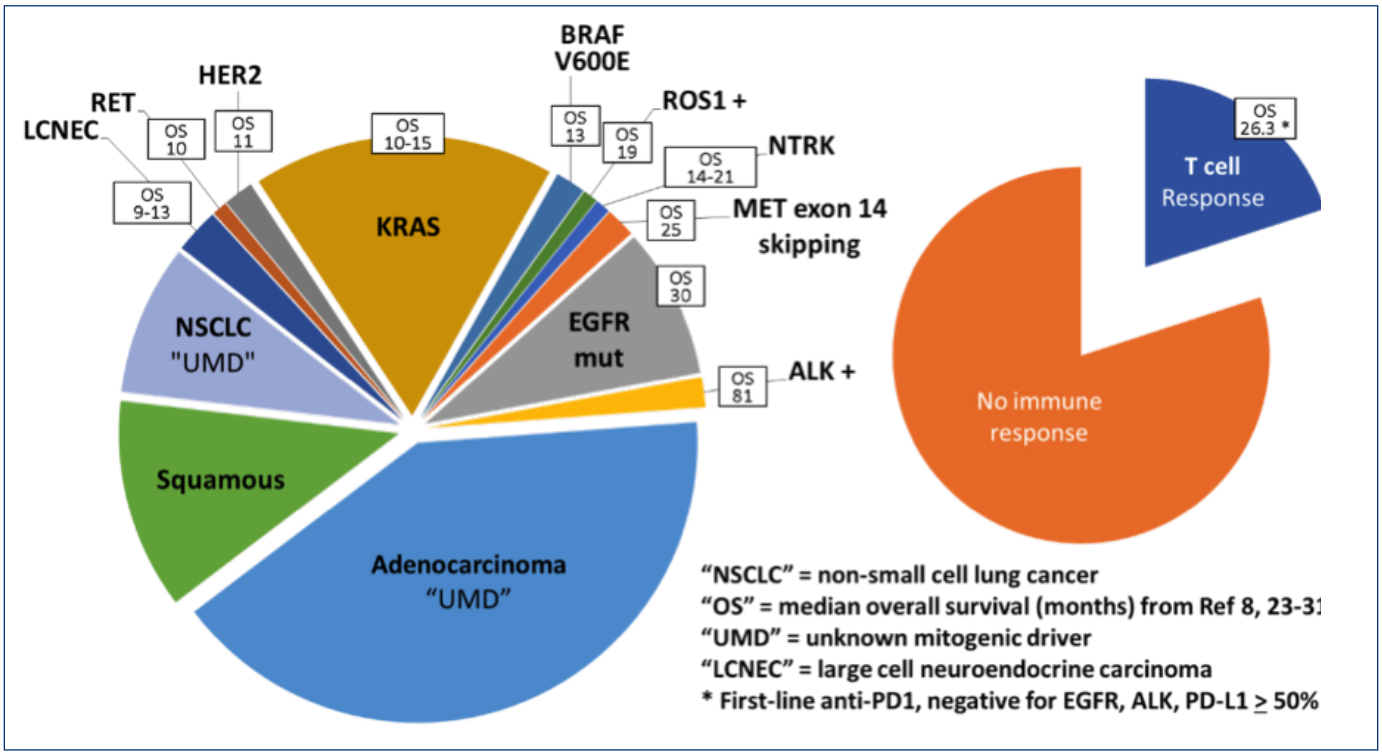
FINDING MUTATIONS IN THE BLOOD

The molecular tests discussed so far rely on biopsy tissue to allow analysis of chromosomes, unique oncoproteins by IHC, and to obtain the tumor DNA for genetic analysis. The drugs which target these genes are then prescribed by medical oncologists to patients with advanced lung cancer as systemic therapy. It stands to reason that these same biomarkers may be found in the blood in patients with advanced disease. In fact, most patients with advanced non-small cell lung cancer will have circulating tumor DNA which can be detected in the blood. Blood-based testing is becoming increasingly popular and can speed up the process of molecular testing.[21] The problem is that up to 20% of patients with these diagnoses do not have circulating tumor DNA, and therefore extracting DNA from biopsy tissue for molecular testing remains the gold standard.

There is no blood test to select patients for immune therapy. Doctors and scientists at Brown University are studying extracellular vesicles which are found in both blood and saliva and can be used to classify metastatic cancers and tumor-host immune interactions. Extracellular vesicles – including exosomes (30–100 nm) and microvesicles (100–1000 nm) – are cell-derived membranous structures which originate from endosomes or are shed from the plasma membrane, and are involved in multiple cellular processes including intercellular communication and intercellular exchange of proteins, lipids and genetic material. Recent discoveries in immunology and cancer biology have established exosomes as an important mechanism by which cancer cells manipulate the tumor microenvironment and avoid immune-mediated elimination.[22]

A recent study looking at the role of extracellular vesicles in patients with melanoma found that melanoma cells release PD-L1-positive exosomes to amplify immunosuppressive signals to CD8+ T cells which would otherwise be limited to cell-to-cell contact. Since these exosomes can be isolated and measured in plasma and saliva, their detection and quantification can be used to distinguish clinical responders from non-responders to immune therapies.[23] Specifically, patients with metastatic melanoma responding to anti-PD1 immunotherapy (pembrolizumab) demonstrated increased levels of PD-L1 on circulating exosomes within 6 weeks of initiation of therapy. Ongoing research at Brown will evaluate exosomes as biomarkers of immune response in patients with advanced lung cancer.

Figure 1. Stage IV NSCLC: Clinically Relevant Subgroups



CONCLUSIONS

The treatment of advanced non-small cell lung cancer is evolving rapidly. Medical oncologists now prescribe a wide array of targeted therapies and immunotherapies based on biomarker science, making long-term survival possible in the context of a universally fatal disease. These advances depend on matching the right patient with the right drug, and have redefined non-small cell lung cancer as an ever-evolving collection of clinically relevant subgroups based on histology, molecular pathology results, and observed benefit from immune therapy (**Figure 1**). This paradigm has resulted in a feedback loop of discovery and therapeutic progress. In this way, molecular pathology will continue to redefine non-small cell lung cancer into subgroups with unique treatment opportunities and, with continued progress, the potential for using drug therapy for cure.

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Authors

Christopher Del Prete, MD; Department of Medicine, Division of Hematology/Oncology,Warren Alpert Medical School of Brown University, Providence, RI.

Christopher G. Azzoli, MD, FASCO; Associate Professor of Medicine, Warren Alpert Medical School of Brown University; Director of Thoracic Oncology, Lifespan Cancer Institute, Providence, RI.

Correspondence

Christopher Del Prete, MD
593 Eddy Street, George 310
Providence, RI 02903
cdelprete@lifespan.org

Immune Checkpoint Inhibitors in the Treatment of Gastrointestinal Malignancies: A Review of Current and Future Therapies

ANDREW HSU, MD; LAUREN MENDELSON, DO; KHALDOUN ALMHANNA, MD, MPH

ABSTRACT

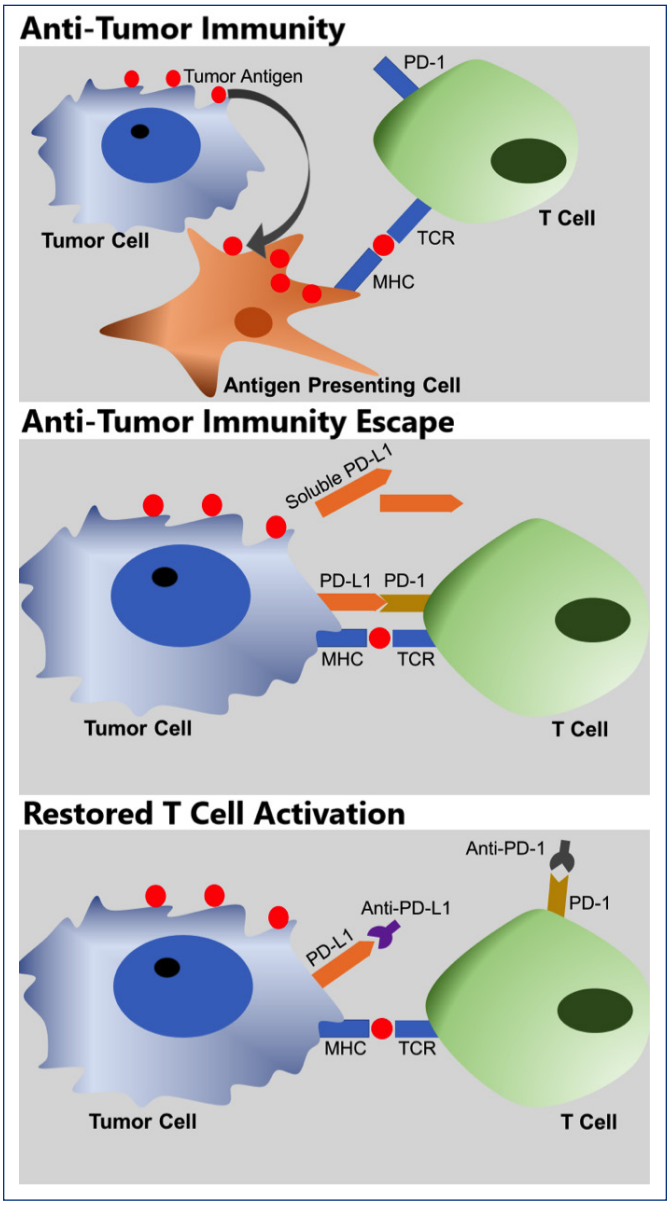
Gastrointestinal cancers are some of the most common malignancies worldwide. Traditional chemotherapy has been disappointing in improving overall survival in patients with unresectable or metastatic disease. The dawn of immunotherapy has led to emerging strategies in incorporating immune checkpoint inhibition either as single agents or in combination when treating gastrointestinal cancers. In this review, a general overview of the state of immunotherapy in the treatment gastrointestinal cancers is first provided. Subsequently, a review of the FDA-approved uses of immunotherapy in gastric, gastroesophageal, hepatobiliary, pancreatic and colorectal cancers will be provided followed by a glimpse into future treatment directions.

KEYWORDS: immunotherapy, checkpoint inhibitors, gastrointestinal malignancies, PD-1, PD-L1

INTRODUCTION

Escape from the immune system is a well-recognized feature of cancer. Despite numerous genetic and epigenetic changes, cancers are able to escape immune destruction by inducing T-cell tolerance through the expression of inhibitory signals. This leads to dysfunctional T-cell signaling by terminating an immune response after antigen activation. Programmed cell death protein-1 (PD-1) is a key immune checkpoint on activated T-cells that can be exploited by tumor cells through the expression of PD-1 ligand (PD-L1) leading to the evasion of immune destruction. Inhibition of PD-1/PD-L1 is thought to restore anti-tumor immunity (**Figure 1**). The incorporation of immunotherapy in the treatment of cancer has been considered a major scientific and medical breakthrough since the first immune checkpoint inhibitor (ICI) was approved in the United States for the treatment of metastatic melanoma in 2011.[1] Since then, multiple antibodies targeting PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have gained FDA approval in numerous malignancies, thereby reshaping the treatment landscape of cancer. (Please see the accompanying article within this issue of the RIMJ, "Non-Small Cell Lung Cancer in the Era of Personalized Medicine: Molecular Tests that Matter")

Figure 1. (Top) Activation of cytotoxic T-cell through presentation of tumor antigen; (Middle) Immune evasion by tumor cell through secretion of PD-L1; (Bottom) Restored T cell activation. See text for details



Gastrointestinal (GI) malignancies account for approximately 35% of all cancer-related mortality, making them one of the most common groups of malignancy worldwide.[2]

Due to the insidious nature of these malignancies, a large portion of patients have unresectable or metastatic disease at time of diagnosis, and the opportunity for cure through surgical resection is lost. Furthermore, traditional chemotherapy treatment has been disappointing with a dismal 5-year survival in stage IV disease. Immunotherapy has been evaluated in GI malignancies as single agents and in combination leading to limited approval in the second-line setting (after failure of initial therapy) for gastric, gastroesophageal, hepatic, and colorectal cancers. The role of these agents in the neoadjuvant or adjuvant setting is currently being investigated. Unlike in lung cancer or melanoma, the response rates to immunotherapy in GI malignancies are relatively low. Response rates for ICI monotherapy is approximately 5%–30% in gastroesophageal cancers, 10%–20% in hepatobiliary cancers, 30%–50% in mismatch repair-deficient (dMMR) colorectal cancer, and no clinical benefit in pancreatic cancer.[3-9] Furthermore, PD-1/PD-L1 status and tumor mutation burden (TMB) have not aided in predicting response to ICIs.

One explanation as to why GI malignancies are thought to have such relatively low response rate to ICI monotherapy is the tumor microenvironments that hinder the infiltration of immune cells.[10] Tumor microenvironments create what is termed as "cold tumors," leading to ineffective T-cell activation and/or penetration of the stroma/parenchyma to reach the tumor.11 There has been increasing interest in combining ICIs with immunotherapeutic small molecules, targeted therapy, chemotherapy, radiation, or other immunotherapies to convert "cold tumors" into "hot tumors" by altering the tumor microenvironment and enhancing immune efficacy and T-cell penetration.[11]

The combination of different modalities with immunotherapy is thought to lead to enhanced efficacy through the promotion of apoptosis causing increased antigen presentation or direct disruption of the tumor matrix increased antigen exposure and T-cell infiltration.[12] In particular, the combination of ICIs with other immunotherapies is thought to enhance antigen presentation and processing, decrease the secretion of immunosuppressive cytokines and suppressor cells, and enhance T-cell infiltration by targeting different immune checkpoints.[11,13] However, one predictable limitation in combining immunotherapies is the increased incidence of immune-related adverse effects.

Since the first ICI was FDA-approved for the treatment of metastatic melanoma in 2011, hundreds of new drugs have entered the market for the treatment of various conditions. In 2018 alone, 59 new drugs gained FDA approval.[14] The aim of this review article is to focus on the currently studied, FDA-approved uses of ICIs in the treatment of GI malignancies and review ongoing studies examining the combination of ICIs with traditional chemotherapy, immunotherapeutic small molecules, targeted therapy, and/or other immunotherapies.

IMMUNOTHERAPY IN THE TREATMENT OF GASTRIC AND GASTROESOPHAGEAL CANCER

Currently, first-line treatment of metastatic gastric and gastroesophageal cancers consists of chemotherapy alone or in combination with trastuzumab in patients with HER-2 positive disease. Second-line treatment includes taxanes and/or irinotecan with ramicurumab in patients who are eligible for vascular endothelial growth factor (VEGF) targeted therapy. The overall outcomes are still poor with survival of less than a year. Of note, ICIs first gained approval in metastatic gastric and esophageal cancers with microsatellite instability (MSI). In general, patients whose tumors demonstrate high microsatellite instability (MSI-H) have a better prognosis.

Pembrolizumab was FDA approved in 2017 for the treatment of chemotherapy-refractory (defined as progression after two lines of therapy), PD-L1-positive gastroesophageal cancers. The approval was based upon the findings in KEYNOTE-059, a phase II, global, open-label, single-arm, multicohort study that enrolled 259 patients. Patients received pembrolizumab 200mg intravenously every three weeks until disease progression. Objective response rate (ORR) was 11.6% with a complete response rate of 2.3%. The ORR was 15.5% and 6.4% in patients with PD-L1 positive and PD-L1 negative tumors, respectively.[4] More recently, the FDA approved pembrolizumab for patients with recurrent, locally advanced or metastatic, squamous cell carcinoma of the esophagus (ESCC) whose tumors expressed PD-L1 (Combined Positive Score [CPS] $\geq$ 10) based upon KEYNOTE-181. KEYNOTE-181 was a randomized, open-label trial that enrolled 628 patients with recurrent, locally advanced or metastatic esophageal cancer who progressed on or after one line of systemic treatment for advanced or metastatic disease. Patients were randomized to receive either pembrolizumab every three weeks or the investigator's choice of traditional chemotherapy. The hazard ratio for overall survival (OS) in ESCC whose tumors expressed a PD-L1 CPS $\geq$ 10 was 0.64. Median OS was 10.3 months and 6.7 months in the pembrolizumab and control arms, respectively.[15] Another trial that supported these findings with pembrolizumab was KEYNOTE-180, a single-arm, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least two prior systems treatments for advanced disease. In this trial, and in the 35 patients with ESCC expressing PD-L1 CPS $\geq$ 10, ORR was 20% and response durations ranged from 4.2 to 25.1 months.

On the other hand, nivolumab, another PD-1 inhibitor, was evaluated in the treatment of esophageal cancer in CheckMate-032. This phase I/II compared the combination of two immunotherapies (nivolumab and ipilimumab, a CTLA-4 inhibitor), nivolumab monotherapy, and placebo in patients with esophageal cancers who had failed second-line therapy. This trial showed improved ORR and progression free survival (PFS) in the combination group versus the monotherapy group. However, as expected, the combination group experienced more treatment-related toxicities.[16] In another trial, ATTRACTION-02 examined nivolumab monotherapy in the second-line setting and resulted in an 11% ORR, 27.3% 12-month OS, and 10.6% 24-month OS.[17] The results of this trial led to the approval of nivolumab monotherapy in Asia only.

The use of immunotherapy in the front-line treatment has not been successful – in the phase III trial, KEYNOTE-062, the combination of pembrolizumab with chemotherapy versus chemotherapy alone was examined in PD-L1-positive gastroesophageal cancers. The results only trended towards improvement in outcomes, particularly in patients with higher PD-L1 expression, but did not achieve statistical significance.[18] Currently, several trials are examining immunotherapy in combination with chemotherapy in the adjuvant and neoadjuvant setting and its role in maintenance therapy.

IMMUNOTHERAPY IN THE TREATMENT OF HEPATOBILIARY CANCER

For the purposes of this review, we will address the use of ICIs in hepatocellular carcinoma (HCC) and cholangiocarcinoma/gallbladder cancer only. Currently, first-line treatment for unresectable or metastatic HCC includes sorafenib and more recently, lenvatinib. Until recently, there was not an established second-line treatment following sorafenib failure.

The efficacy of nivolumab in HCC was examined in CheckMate-040, a phase I/II study that enrolled patients with advanced HCC and Child-Pugh A or B cirrhosis who progressed or were intolerant to sorafenib. Forty-nine of the 255 patients assessable for response had an objective anti-tumor response to nivolumab, corresponding to an 18.2% ORR. The benefits of nivolumab were observed in sorafenib-naïve and sorafenib-experienced patients.[19] Based upon this data, nivolumab was FDA-approved for the treatment of HCC in patients who had previously failed sorafenib.

In another similar phase II trial, KEYNOTE-224 evaluated pembrolizumab in patients previously treated with sorafenib resulting in a 17% ORR.[20] A confirmatory study was recently presented at the 2019 American Society of Clinical Oncology (ASCO) meeting: KEYNOTE-240. This trial enrolled 413 patients with advanced HCC with Child-Turcotte-Pugh A cirrhosis after progression or intolerance to sorafenib. Patients were randomized to pembrolizumab versus placebo. Although this study showed improvements in median OS (13.9 versus 10.6 months) and PFS (3 versus 2.8 months), the findings were not statistically significant because pre-specified efficacy boundaries were not reached. Response rates were higher for pembrolizumab compared to placebo (18.3% versus 4.4%).[21]

A phase Ib study examined atezolizumab, a PD-L1 inhibitor, in combination with bevacizumab, a VEGF inhibitor, in the first-line setting for advanced HCC with up to Child-Pugh B7 cirrhosis. Preliminary data revealed a 34% ORR with one complete response and a median PFS of 14.9 months.[22] Given these promising results, the phase III IMbrave150 trial is currently underway and examining the combination of atezolizumab with bevacizumab versus sorefenib.[23] Currently, there are several other ongoing trials that are examining multiple immunotherapy combinations in the front-line treatment of HCC. CheckMate-459 is examining the combination of nivolumab with sorafenib in the front-line setting. Unfortunately, preliminary data suggests that there is no statistically significant improvement in OS when compared to sorafenib alone.[24] LEAP-002 is a phase III trial currently underway and that is examining the use of pembrolizumab with lenvatinib in the front-line setting.[25]

In unresectable or metastatic biliary tract cancers, first-line treatment includes gemcitabine with a platinum agent (e.g. cisplatin, oxaliplatin). Of note, patients who are dMMR or MSI-H (microsatellite instability – high) have been found to have higher response rates to PD-1/PD-L1 inhibition. Unfortunately, only a minority of patients with biliary tract cancers are MSI-H or dMMR – 5% of gallbladder cancers; 5–13% of extrahepatic cholangiocarcinoma; and 10% of intrahepatic cholangiocarcinoma.[26] Based upon the results of a study by Le, et al. in 2017, pembrolizumab gained approval for use in unresectable or metastatic solid tumors that were dMMR or MSI-H. This trial evaluated patients with dMMR malignancies and resulted in a 53% ORR across twelve different tumor types including HCC and biliary tract cancers.[27] Currently, there are several trials examining the combination of ICIs with standard chemotherapy in the second-line setting.

IMMUNOTHERAPY IN THE TREATMENT OF PANCREATIC CANCER

First-line treatment for unresectable or metastatic pancreatic cancer consists of one to four drug regimens built upon a backbone of either a fluoropyrimidine or gemcitabine – dependent upon the patient's age and performance status. Prognosis of advanced pancreatic cancer is very dismal, and survival is less than a year. Pancreatic cancer is traditionally considered non-immunogenic – the majority of patients derive little clinical benefit from ICIs.[28-30] The exception to this rule is pancreatic cancers that are found to be MSI-H or dMMR, which only accounts for 1.2% of pancreatic cancers.[31] One theory to explain the disappointing response rates to ICIs is due to the immunosuppressive tumor microenvironment of pancreatic cancer along with the poorly vascularized and dense surrounding connective tissue that hinders immune cell infiltration.[32] Currently, pembrolizumab is approved in the second-line setting only in pancreatic cancers that are MSI-H or dMMR.

Given the disappointing responses to ICI monotherapy, there has been significant interest in combining immunotherapy with different treatment modalities in the hopes of increasing tumor immunogenicity. Thus far, the majority of trials that have examined the use of ICIs in combination with standard cytotoxic regimens have not resulted in significantly improved response rates when compared to the standard cytotoxic regimens alone.[33-35] Another potential strategy to increase tumor immunogenicity is to use a pancreatic cancer vaccine (GVAX) – created from irradiated, allogeneic pancreatic cancer cells which are then modified to induce a tumor antigen response by a host's immune system. Currently, there are ongoing trials examining the use of GVAX with and without ICIs; however, to date, the results have been mixed.[36, 37]

IMMUNOTHERAPY IN THE TREATMENT OF COLORECTAL CANCER

The treatment of metastatic colorectal cancer (mCRC) has been evolving through the last decade. Currently, first-line treatments for unresectable or mCRC include cytotoxic regimens built upon a fluoropyrimidine backbone in combination with targeted therapy. Immunotherapy has been approved for the treatment of mCRC patients whose tumors are MSI or dMMR, which accounts for 15% of CRCs and plays a significant role in predicting a response to ICI therapy.[38, 39]

Pembrolizumab was examined in the second-line setting for mCRC patients who were MMR-deficient (dMMR) and MMR-proficient. In MMR-proficient patients, there was a 0% ORR with an 11% disease control rate (DCR); however, dMMR patients exhibited a 40% ORR with a 78% DCR to pembrolizumab monotherapy. These findings led to the FDA-approval of pembrolizumab in the second-line setting for MSI-H or dMMR mCRC.[26] Nivolumab combined with ipilimumab and nivolumab monotherapy have also been approved for second-line use for MSI-H or dMMR mCRC based on CheckMate-142 which showed a 55% ORR in the dual ICI cohort and a 31% ORR in the monotherapy cohort.[3,40] Of note, those that received dual ICI had received two or more lines of therapy and showed response regardless of PD-1/PD-L1 status, KRAS wild-type, BRAF mutation, or history of Lynch syndrome.[40] Given these promising results from CheckMate-142 regarding dual ICI therapy, there has been much interest in combining ICIs with other treatment modalities in the hopes of improved response rates.

An ongoing phase II trial is combining standard cytotoxic chemotherapy with pembrolizumab in the front-line setting for patients with mCRC irrespective of MMR status. Preliminary data demonstrates a 53% ORR.[40] Other studies have looked into combining ICIs with a VEGF inhibitor (i.e. bevacizumab) with standard chemotherapy in patients who had not received a platinum (i.e., oxaliplatin) containing regimen or without standard chemotherapy in patients who were oxaliplatin-refractory. This has resulted in an 8% ORR without standard chemotherapy and a 36% ORR with standard chemotherapy.[42] Based upon the promising results from a phase I trial, IMblaze370 examined the use of an ICI with a MAP kinase enzyme (MEK) inhibitor in hopes of upregulating antigen presentation leading to increased T-cell tumor accumulation in microsatellite stable (MSS) or MSI-low (MSI-L) mCRC patients who had progressed after two or more lines of therapy. Unfortunately, no statistically significant difference was found in survival when compared to standard therapy.

CONCLUSION

The introduction of immunotherapy has led to major changes to the treatment paradigms of many cancers. ICIs have made their way into front-line treatment regimens in melanoma and lung cancer. In GI malignancies, the changes to the treatment paradigms have been more modest – treatment with ICIs are mostly reserved for use in the second-line or beyond, and usually in the setting of PD-1/PD-L1 positivity, MSI-H, or dMMR tumors. However modest, these second-line ICIs give patients reasonable options following progression of their disease that were not available a few years ago.

Why the responses to ICI monotherapy are relatively low in GI malignancies include the immunosuppressive tumor microenvironments and the complex stroma/parenchyma of tumors preventing immune cell infiltration that is necessary for a robust immune response. As a result, the logical next step has been combining ICIs with other treatment modalities such as: standard cytotoxic chemotherapy to help break down the tumor stroma/parenchyma to help expose tumor antigens, increase antigen presentation, and enhance immune cell infiltration: or combine one ICI with another ICI to help enhance the immune response through different mechanisms and/or dampen the immunosuppressive tumor microenvironment.

With an increased understanding of the underlying mechanism of the immune system and how it interacts with the tumor microenvironment, new studies are being devised to assess the safety and efficacy of these combinations on a smaller scale prior to pursuing larger phase III trials.

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Authors

Andrew Hsu, MD; Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University, Lifespan Cancer Institute, Rhode Island Hospital, Providence, RI.

Lauren Mendelson, DO; Department of Medicine, The University of Massachusetts Medical School, Worcester, MA.

Khaldoun Almhanna, MD, MPH; Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University, Lifespan Cancer Institute, Rhode Island Hospital, Providence, RI.

Correspondence

Khaldoun Almhanna, MD
Lifespan Cancer Institute
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
401-606-4694
Fax 401-444-8918
Kalmhanna@lifespan.org

Acute Myeloid Leukemia: A Review

ARI PELCOVITS, MD; RABIN NIROULA, MD

ABSTRACT

Acute myeloid leukemia (AML) is a malignancy of the stem cell precursors of the myeloid lineage (red blood cells, platelets, and white blood cells other than B and T cells). Like other malignancies, it is due to genetic variations that lead to neoplastic changes and clonal proliferation. AML remains a rare malignancy, accounting for only 1.2% of all new cancer diagnoses in the United States per year, but it accounts for close to one third of all leukemias diagnosed.* For much of the 20th and early 21st century treatment paradigms were unchanged with survival curves remaining stagnant for many decades. Recent changes in our understanding of the genetic variations in the disease have led to some promising new therapies with hopes for improved outcomes in the future. Below we review the definitions, diagnosis and classification of AML and how this affects the evolving treatment paradigm of AML.

KEYWORDS: acute myeloid leukemia, bone marrow, stem cell transplantation

DEFINITION/DIAGNOSIS/CLASSIFICATION

AML is a disease of the bone marrow, a disorder of hematopoietic stem cells due to genetic alterations in blood cell precursors resulting in overproduction of neoplastic clonal myeloid stem cells. While extramedullary manifestations can occur (e.g. myeloid sarcomas, leukemia cutis), the underlying disease is due to abnormalities in hematologic cellular production. A small subset of cases have identified causative factors such as prior chemotherapy or certain chemical exposures, but the large majority are due to genetic alterations, through chromosomal abnormalities or isolated gene mutations, without clear causative agents.[1] Delineating these genetic abnormalities is important in risk stratifying patients and determining appropriate treatment.

Patients with AML will initially present in a myriad of ways. Some cases of disease will be discovered on routine blood work while others may present with symptomatic complications such as infection, bleeding or disseminated intravascular coagulation. Bone marrow examination is paramount for both establishing the diagnosis as well as obtaining tissue for analysis to better classify the AML subtype and prognostic severity.

The World Health Organization in its 2016 updated guidelines distinguishes six groups of AML: (1) AML with recurrent genetic abnormalities, (2) AML with myelodysplasia-related changes, (3) Therapy-related myeloid neoplasms, (4) AML Not Otherwise Specified, (5) Myeloid sarcoma, and (6) Myeloid proliferations related to Down syndrome.[2] The diagnosis is made by the presence of ≥20% blasts in the peripheral blood or in the bone marrow, or through the presence of unique genetic abnormalities found in the bone marrow regardless of blast count [t(8;21), inv(16), or t(15;17)].[3]

AML is further classified into three prognostic risk groups: favorable, intermediate, and adverse [**Table 1**].[3] These are based on both cytogenetics and relatively recent recognition of molecular diseases subsets that are distinct from the

Table 1. Risk Profile Categories as Determined by Molecular and Cytogenetic Abnormalities

Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1;
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD/low FLT3-ITD
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD(high)
	Wild-type NPM1 without FLT3-ITD/ low FLT3-ITD (normal karyotype)
	t(9;11)(p21.3;q23.3)MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype
	Monosomal karyotype
	Wild-type NPM1 and high FLT3-ITD
	Mutated RUNX1
	Mutated ASXL1
	Mutated TP53

Adapted from Blood 2017 129:424-447

contribution of cytogenetic risk. These newly recognized molecular subsets have different responses to standard therapeutics. The prognostic groups predict the response to standard therapy and survival in one large retrospective analysis of patients under the age of 55, the overall survival rate at 5 years was 44%, however when broken down by risk profile the overall survival rates were 64%, 41%, and 11% for favorable, intermediate, and adverse risk respectively.[4] The overall survival decreases when older adults are included but the stratification of survival remains constant.

TREATMENT

The treatment of AML involves initial induction therapy and post-remission therapy. Goal of induction therapy is to achieve complete remission (CR) with preferably no measurable residual disease (MRD). Studies have shown improved survival in patients who achieve CR irrespective of the type of induction therapy.[5] Choice of initial induction treatment depends on functional status of the patient (which is best measured by performance status and comorbidities), biological status of the disease (best measured by prognostic risk groups and recently recognized molecular profile of leukemia cells) and goals of the patient. The two commonly used induction therapies in acute myeloid leukemia include 1) Cytotoxic chemotherapy with or without targeted therapies and 2) Hypomethylating agents with or without targeted therapies.

INDUCTION CHEMOTHERAPY

Favorable and Intermediate Risk Disease

For all patients with AML with the goal of cure and who are medically fit enough to tolerate chemotherapy, the backbone of therapy has not changed for 50 years, with upfront treatment consisting of a continuous infusion of cytarabine over 7 days with the addition of an anthracycline, typically daunorubicin, given daily for the first 3 days. This induction therapy, known colloquially as 7+3, leads to complete disease response in up to 80% of patients with favorable risk disease and 50–60% complete response in those with intermediate adverse risk disease.[6]

The outcomes have improved with addition of various targeted drugs to the traditional 7+3 induction chemotherapy in the favorable and intermediate risk groups. Gemtuzumab ozogomycin (GO) is a monoclonal antibody against CD-33 (a protein that is expressed in myeloid leukemia cells). Addition of GO to standard chemotherapy in patients with favorable and intermediate risk disease decreases the risk of relapse and in some studies improves overall survival (OS). The magnitude of benefit is higher in favorable risk disease than in intermediate risk disease.[7] This has made obtaining early cytogenetic and molecular studies on patients with a new diagnosis of the upmost importance as GO is added to the first day of therapy for patients with favorable risk disease who are CD-33 positive.

Midostaurin is an oral multi-targeted tyrosine kinase inhibitor active in patients with a FLT3 mutation. FLT3 mutations initiate oncogenic signal transduction in about 25–30% of patients with AML. There are 2 types of FLT3 mutation; Internal tandem duplication and tyrosine kinase domain. Addition of midostaurin to standard 7+3 chemotherapy in patients with FLT3 mutation has improved survival, from a median of 25 to 74 months.[8]

Adverse Risk Disease

Adverse risk disease is an unmet need in AML. The outcomes with standard 7+3 chemotherapy remain unsatisfactory. Complete remission (CR) rate is only about 40% and median overall survival is in the range of 12–18 months. Even with allogenic hematopoietic stem cell transplantation (see below), almost half of the patients relapse. Patients are therefore usually referred for clinical trials if there is one available, due to these lower rates of survival. Recently two therapies, CPX351 and venetoclax with a hypomethylating agent, have shown better results than the standard therapy in patients with adverse risk disease.

CPX 351 is a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio of cytarabine and daunorubicin. The liposomal encapsulation leads to prolonged exposure to the two drugs. CPX 351 showed significantly improved response rates and improved survival compared to 7+3 chemotherapy in patients with adverse risk disease (i.e. therapy-related AML, AML with MDS related changes).[9]

Venetoclax is an oral highly selective inhibitor of the anti-apoptotic protein BCL-2. BCL2 is thought to mediate resistance to standard therapy in patients with adverse risk AML. Venetoclax was studied with hypomethylating agents (decitabine and azacitadine) as a backbone in patients with adverse risk disease. Even in elderly patients and patients with poor cytogenetics and adverse molecular mutations, the outcomes were better with venetoclax plus hypomethylating agents than hypomethylating agents alone.[10] Median overall survival in these preliminary studies was approximately 15 months, significantly improved from the historical median survival of approximately 10 months with the use of hypomethylating agents alone.[11]

POST-REMISSION THERAPY

The goal of post-remission therapy is to prevent relapse of the disease. The two commonly employed strategies are additional post remission cytotoxic chemotherapies (such as high or intermediate dose cytarabine) with or without targeted therapies, or allogenic hematopoietic stem cell transplantation (Allo SCT). The choice of therapy is determined by the unique risks and benefits provided by each treatment

arm. The risk of non-relapse mortality (NRM) is high with Allo SCT; however, the risk of disease relapse is reduced. Furthermore, there is increased morbidity with Allo SCT (such as chronic graft vs host disease, secondary malignancies, or infection from chronic immunosuppression).

The absolute decrease in the risk of disease relapse has to be more than the risk of NRM to justify Allo SCT as post-remission therapy. All patients with adverse risk profiles and most of the patients with intermediate risk meet this criteria.[12,13] Patients with favorable risk profiles, however, are able to remain free from relapse at high enough rates with chemotherapy alone such that the risks of Allo SCT are not justified. Therefore, in favorable risk group, induction therapy is followed by definitive consolidation therapy with high dose cytarabine (HiDAC).[14]

FUTURE DIRECTIONS

Over the last decade, there have been significant advancements in the genomic profiling of AML. This has resulted in exciting opportunities to create genomically defined targeted therapies for patients with AML. Some of the therapies like FLT3 inhibitors, Isocitrate dehydrogenase (IDH) 1 and 2 inhibitors have been tested in clinical trials and are now the standard of care in patients who harbor these mutations. There are other targeted agents directed against various mutations seen in AML that are currently being investigated in clinical trials. One ongoing multicenter trial is sponsored by the Leukemia and Lymphoma Society in the United States and is known as the "BEAT AML" trial. Patients are assigned to targeted therapies based on their genomic profile, with the hope that the results of this and several other trials will provide important information regarding the clinical benefits of genomically defined targeted therapies in AML.

CONCLUSION

Acute myeloid leukemia remains a rare but lethal malignancy. Our understanding of the disease has progressed significantly, and new and evolving therapies are providing hope for improved survival and less toxic treatment. Early diagnosis with rapid analysis of cytogenetic and molecular abnormalities (e.g. NPM1, FLT-3) are paramount in tailoring best therapy for patients, especially in light of new treatment modalities that rely on cytogenetic and molecular testing. Chemotherapy remains the backbone of treatment with stem cell transplantation still the best hopes for cure in many patients with adverse cytogenetic risk profiles.

*SEER Cancer Stat Facts: Acute Myeloid Leukemia. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/amyl.html

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Authors

Ari Pelcovits, MD; Alpert Medical School of Brown University, Division of Hematology-Oncology, Rhode Island Hospital, Providence, RI.

Rabin Niroula, MD; Alpert Medical School of Brown University, Division of Hematology-Oncology, Rhode Island Hospital, Providence, RI.

Correspondence

Rabin Niroula, MD
Rhode Island Hospital, 593 Eddy Street, Providence, RI, 02903
844-222-2881
Fax 401-444-2330
rabin_niroula@brown.edu

Prostate Cancer Therapeutics and Their Complications: A Primer for the Primary Care Provider

ZACHARY BROWNLEE, MD; ANDRE DE SOUZA, MD; PAUL P. KOFFER, MD;
THOMAS A. DIPETRILLO, MD; ANTHONY E. MEGA, MD

INTRODUCTION

Prostate cancer is the most common malignancy in men and the second leading cause of cancer mortality in men. Even with evolving alterations in the screening guidelines, the annual number of prostate cancers per year in the United States remains substantial. The majority of men diagnosed with prostate cancer will die of other causes. Many men will face survivorship issues related to prior therapies. In addition, advanced prostate cancer has a long natural history with continuous exposure to therapies that have impactful effects on overall health. The primary care provider is an integral participant in the care team for the prostate cancer patient. The goal of the ensuing discussion is to provide an educational primer on prostate cancer therapeutics and potential consequences of therapy.

RADIATION THERAPY

Radiation techniques have evolved, resulting in a reduced rate of acute and late toxicities.[1] Radiation therapy primarily is delivered by two methods: external beam radiation treatment (EBRT) and brachytherapy. Most men treated with EBRT for localized prostate cancer, either primary treatment or salvage treatment after surgery, have an excellent prognosis with cancer specific survival longer than 10 years. Therefore, monitoring for acute and late toxicities from treatment is paramount. We herein discuss the pattern and timing of toxicities associated with radiation treatment for prostate cancer. Of note: many men receiving EBRT for treatment of prostate cancer also receive androgen deprivation therapy (ADT). The effects of ADT will be discussed in a separate section.

Typical acute toxicities of EBRT include fatigue, urinary symptoms and gastrointestinal symptoms. Acute cutaneous toxicity, as often seen in radiation for breast cancer, is exceedingly rare in prostate cancer as the skin is spared significant radiation. Fatigue is the most common symptom of radiation therapy, occurring in 40–80% of patients treated. Fatigue often arises within the first several weeks of radiation therapy and may last several months beyond the completion of radiation therapy. Severity of fatigue varies but the majority of patients are able to maintain a full work schedule. Incontinence is less likely to occur with radiation therapy than prostatectomy; however, dysuria, urinary frequency and nocturia are more common. Symptoms can mimic urinary tract infection and urinalysis may often reveal microscopic hematuria and even the presence of WBCs. Antibiotic therapy is indicated only in the uncommon circumstance in which bacteria is noted and cultured. Typical acute GI toxicities during radiation therapy include intermittent loose stools or diarrhea. Common management strategies include use of anti-diarrheal agents and dietary/nutritional changes. Data supporting the benefit of nutritional changes is overall weak but strategies that have shown efficacy include fat restriction, lactose restriction, fiber supplementation, or a combination of the above.[2] Acute toxicity predicts late gastrointestinal events.[1,3]

The Prostate Testing for Cancer and Treatment (ProtecT) trial assessed toxicity outcomes in 1600 men randomized to active surveillance, radical prostatectomy, or EBRT with short term ADT. The toxicity analysis distinguished the toxicities of prostatectomy and EBRT as compared to the non-treatment patients. Patients receiving EBRT reported no increase in urinary incontinence as opposed to all patients immediately postoperative. Although higher rates of voiding symptoms and nocturia were noticed at 6 months post-radiation treatment, at one year the rates were similar to active surveillance patients. Reports on erectile quality after EBRT revealed decreased erection quality at 6 months with a continued erection quality decline over the 6-year follow-up period. Overall long-term erectile dysfunction rates in radiation patients were similar to what was experienced by active surveillance patients. Patients with erectile dysfunction after treatment should be referred to a multidisciplinary clinic where patients receive care from medical, surgical and psychology providers. A multidisciplinary Men's Health Clinic is available for patients at the Lifespan Cancer Institute. Increased rates of rectal bleeding were shown after radiation therapy after 2 years of follow-up. There was no increase in fecal incontinence.[4]

There are significant differences between brachytherapy and external beam radiation therapy. Only selected patients are considered appropriate for brachytherapy as primary treatment. Since minimal radiation is delivered beyond the prostate capsule, brachytherapy is offered only for the best prognostic categories. Placement of the brachytherapy seeds is done in an operating room with patients under general anesthesia. Patients must be in good health in order to undergo this invasive procedure. Anticoagulation and

anti-platelet therapy need to be discontinued for the procedure. Toxicities also differ between the two radiation methods. When compared to active surveillance patients, there was a clinically significant increase in urinary obstruction and irritation scores at 3 and 12 months for brachytherapy but only at 3 months for external beam radiation therapy. At 24 months, all patients had similar rates. Patients with significant pre-existing urinary symptoms or large prostate glands (greater than 40cc–60cc) have increased rates of irritative urinary symptoms after brachytherapy and are more appropriate patients for EBRT. There was no relative effect on urinary continence seen in either radiation arm. Clinically significant increased bowel problems were seen in the external beam population at 3 months. No increased bowel problems were seen with brachytherapy. While in many studies erectile function is better for patients receiving brachytherapy as opposed to EBRT, other studies do not show a substantial difference.[5,6] Finally, there are safety guidelines that are given to patients after brachytherapy that restrict prolonged, close contact (such as sitting on the lap) with young children and pets for patients receiving brachytherapy, as the seed implants emit radiation for several months after placement. During this time, brachytherapy patients will set off alarms on security detectors and patients should forewarn security officials by showing proper documentation.

Later toxicities (greater than 6 months from treatment) occur in approximately 10% of patients who had received EBRT. The most common late gastrointestinal effect is proctitis. This typically presents with rectal bleeding and less commonly rectal urgency or tenesmus. First-line treatments include oral agents such as pentoxyfylline, vitamin A, metronidazole, 5-ASA as well as topical agents such as sucralfate, hydrocortisone, and formalin. Endoscopic approaches include argon plasma coagulation or heater probe or laser. Hyperbaric oxygen treatments may also be helpful in refractory cases.[7,8] Currently, hydrogel rectal spacers are used to reduce the radiation dose exposure to the rectum. Current data is mixed on clinical effectiveness of rectal spacers while it certainly increases the cost of treatment and exposes the patient to an additional invasive procedure. The most common late genitourinary effect is radiation cystitis. It usually presents as self-limited gross hematuria that can be persistent and severe. Treatment options include conjugated estrogens, pentosan polysulfate, or topical formalin. Referral to urologic consultants is recommended for endoscopic cautery or laser ablation and to exclude other causes of hematuria. Rarely, bleeding leads to the need for transfusion support and hospitalization for bladder irrigation. If severe bleeding persists, the patient may require a surgical diversion and/or cystectomy. Hyperbaric oxygen treatments may also be helpful in refractory cases, usually referred by radiation oncologists.[9,10]

Therapeutic ionizing radiation has the risk of radiation-induced secondary malignancies. In prostate radiation, the most common secondary malignancies are bladder cancer, colorectal cancer, and pelvic sarcomas. Secondary hematologic malignancies, such as acute leukemias and myelodysplastic syndromes, are relatively uncommon. Malignancies typically develop 5 to 20 years following treatment. Smoking enhances the risk of bladder cancer. Retrospective historical data noted a 6% increase in relative risk of secondary solid tumor after radiation relative to surgery. The relative risk was increased to 15% for those who survived more than 5 years after treatment and to 34% for those who survived greater than 10 years. The estimated absolute risk of radiation-induced solid tumor was 1 in 290 with rates as high as 1 in 70 in men surviving more than 10 years after treatment.[11] A more recent SEER analysis by Krasnow and colleagues revealed an increased secondary malignancy risk at 10 years risk from 1.9 to 2.7% and at 20 years from 3.6 to 5.4%. This risk was most increased in patients younger than 55 years even after adjusting for competing risk factors and life expectancy.[12] The risk appears to be dependent on treatment technique and "conformity" (precise radiation field) as demonstrated in a third SEER database review by de Gonzalez and colleagues. This demonstrated a statistically significant decrease in secondary rectal cancers with 3D conformal technique compared with 2D planning. There were also decreased rates of colon cancer and leukemia with brachytherapy relative to external beam radiation.[13] There are currently no secondary malignancy screening recommendations for men that have received radiation therapy to the prostate/pelvis, but a primary care physician should be aware of this risk and work up any concerning symptoms such as hematuria or hematochezia.

ANDROGEN DEPRIVATION THERAPY

The main drivers of prostate cancer cell growth and survival are androgens. Androgen deprivation therapy (ADT) is the backbone of therapy for patients with various presentations of prostate cancer. It is the cornerstone of treatment of incurable, metastatic disease. ADT slows down progression to metastatic disease in patients with non-metastatic disease and a rising PSA after local treatment (biochemical relapse). ADT is an adjunctive treatment to radiation for certain higher-risk patients with prostate cancer being treated with curative intent. ADT is also utilized in select cases after prostatectomy as adjuvant therapy. The duration of ADT can vary from 4 months to continuous ADT depending on the clinical situation and treatment objectives. In general, the longer the duration of ADT the more troublesome the adverse effects.

Androgen deprivation therapy can be achieved by bilateral orchiectomy or luteinizing hormone release hormone (LHRH) therapy. In the United States, medical castration through LHRH antagonist or agonist injections is more commonly employed. Degarelix is a LHRH antagonist

administered as monthly subcutaneous injections. Degarelix achieves castration, defined as serum testosterone levels of less than 50 ng/dL, within 3 days. Since it has a relative rapid onset of action, it is often the choice for patients with acute complications of prostate cancer, such as urinary obstruction, severe bone pain or spinal cord compression. Degarelix requires monthly injection and has a 40% rate of local injection reactions. Leuprolide is a LHRH agonist that induces castration in 2 to 4 weeks. It has a lower rate of local injection reaction (1%) than degarelix. It may be given monthly or every 3, 4 or 6 months. Leuprolide can cause an initial testosterone surge that may accelerate the growth of prostate cancer cells in the first 2 to 4 weeks after its administration. Thus, it requires concurrent androgen receptor antagonism to prevent exacerbated bone pain, spinal cord compression and urinary obstruction from prostate tumor growth. The most common oral antagonist receptor antagonist in current use is bicalutamide. Bicalutamide has an elimination half-life of 7 days; therefore, a lead-in of 14 days is usually sufficient to address the testosterone surge.

Androgen deprivation therapy has been linked to metabolic syndrome. Testosterone suppression induces skeletal muscle mass loss. This happens in part due to downregulation of insulin growth factor receptors and regulation of transcription factors associated with skeletal muscle programmed death. Lean muscle mass loss is implicated in insulin resistance and subsequent hypercholesterolemia and hyperglycemia. Upregulation of lipoprotein lipase is also observed in the castrate state. Hypertension is thought to be a result of a higher basal level of endothelin-1, a hormonal vasoconstrictor.[14] Studies have shown that the risk of diabetes in patients on ADT is increased by 44% compared to matched control patient cohort not receiving ADT. The risk for coronary artery disease and for myocardial infarct is increased 16% and 11% respectively. Effect on cardiovascular mortality is mixed and inconclusive.[15] Degarelix may have a lower risk of cardiac events at 1 year compared with leuprolide in men with pre-existing cardiovascular disease, based on a retrospective study.[16] An ongoing prospective American study (the PRONOUNCE trial) is assessing longer-term, cardiovascular outcomes in patients on degarelix versus leuprolide. The time of a cardiovascular event from the initiation of ADT does affect risk, with a decline in risk with passage of time.[17] Physical activity has been shown to decrease the risk for cardiovascular events in men on ADT.[18]

Bone loss is a known adverse effect of ADT. This is due to dysregulation of Receptor Activator of Nuclear Factor Kappa beta (RANK) and its ligand (RANKL), both important for bone resorption.[19] RANKLs are secreted by osteoblasts and bind to RANK on osteoclasts to activate osteolysis. The RANKL monoclonal antibody denosumab blocks this interaction. Men on ADT are at higher risk for bone fractures. A baseline Dual-Energy X-ray Absorptiometry (DEXA) scan should be obtained at the onset of ADT. Thereafter, DEXA scans are recommended every 1–2 years. Men with osteoporosis at baseline or after androgen deprivation therapy should be treated with the RANKL blocker denosumab 60 mg intravenously every 6 months or the intravenous bisphosphonate zoledronic acid 4 mg yearly or the oral bisphosphonate alendronate 70 mg weekly.[20,21] Bisphosphonate treatment is contraindicated in patients with severe renal impairment and should be used with caution in patients with mild to moderate renal impairment. Men who are older than 50 years old with osteopenia and a World Health Organization FRAX score (available online) predicting a 10-year risk of hip fracture equal or above 3% or major osteoporosis-related fracture equal and above 20%, should be treated in a similar manner. A baseline 25-OH vitamin D level is recommended. Patients who are deficient in vitamin D require appropriate replacement therapy. Decrease of alcohol consumption, smoking cessation and exercise are important to counteract bone resorption and men should be counseled to adopt these beneficial, lifestyle measures.

Men with bone metastasis are at risk for pathological fractures, spinal cord compression and bone pain; collectively referred to as skeletal-related events (SREs). ADT compounds the risk of SREs by activating osteoclasts.[19] Bisphosphonates and RANKL inhibitors have shown to delay skeletal-related events but only in men with metastatic bone lesions and castrate-resistant disease (mCRPC).[22] Dosing bone protective agents for mCRPC patients is frequent; thus, increasing the risk of osteonecrosis of the jaw (ONJ) to 2%–4%. Dental preventative care is important in preventing ONJ and dental providers need to be informed that men are receiving therapy. Dental extractions increase the risk of developing ONJ and should occur only as a necessity. If a tooth extraction is required, bone protective agents should be held for an extended period. Other common side effects from these agents include myalgias and arthralgias, flu-like symptoms, hypocalcemia for denosumab and renal insufficiency for zoledronic acid.

In summary, skeletal-related events and metabolic syndrome figure among the most significant long-term adverse effects of androgen deprivation therapy. It is the role of the health care providers to recognize the magnitude of the skeletal and cardiovascular risks associated with these important prostate cancer therapies. By mitigating contributing cardiovascular factors and reinforcing fracture prevention, primary care providers have an opportunity to promote bone and cardiovascular health.

ANTI-ANDROGEN AGENTS

Over the last two decades, a significant change in the management of prostate cancer is the development of new therapeutics for mCRPC and the expansion of their roles in the treatment of metastatic castrate sensitive prostate cancer (mCSPC). The scope of this discussion will be limited

to the two most commonly utilized anti-androgen agents: abiraterone acetate and enzalutamide.

Abiraterone acetate was approved for the treatment of mCRPC in 2011 and mCSPC in 2018. In both circumstances, abiraterone improves overall survival and progression-free survival with its bigger impact in mCSPC, which has placed the drug earlier in the treatment paradigm.[24] The mechanism of action of abiraterone is unique. Abiraterone is an androgen biosynthesis inhibitor, that impedes 17 α-hydroxylase/C17,20-lyase (CYP17). CYP 17 catalyzes the formation of dehydroepiandrosterone (DHEA) and androstenedione. Treatment with LHRH agents and orchiectomy reduces testosterone production from the testis only, with abiraterone providing added blockade from the adrenal glands and prostate cancer cells. Absorption of abiraterone increases if administered with fats and it should be administered on an empty stomach. A significant consequence of treatment with abiraterone is development of mineralocorticoid excess syndrome (MES) as a result of accumulated CYP 17 substrates being shuttled to the mineralocorticoid pathway. This can lead to complications of hypertension, fluid retention and hypokalemia. Co-administration of prednisone at 5mg to 10mg per day mitigates MES but adds the toxicities of continuous steroid administration. Even with prednisone administration, hypertension remains a common adverse effect. In an analysis of 5445 patients from 5 studies, the overall incidences of all-grade hypertension and high-grade hypertension (grade 3 and 4) were 21.9% (95% CI: 13.6–33.2%) and 10.2% (95% CI: 6.9–11.6%) respectively.[25] Of note, there is no standard management of abiraterone treatment-related hypertension. Finally, abiraterone was associated with a statistically significant 76% (RR 1.76) increase in the risk of high-grade cardiac disorder adverse events (95% CI: 1.12-2.75 RR; $p = 0.01$) and in a 28% (RR 1.28) increase in all-grade cardiac disorder adverse events (95% CI: 1.06-1.55; $p = 0.01$). [26]

Enzalutamide was approved for the treatment of mCRPC in 2012, non-metastatic or M0 CRPC in 2018 and mCSPC in 2019.[27] Similar to abiraterone, enzalutamide impacts overall survival and progression-free survival in these indications; moving to an earlier point in the treatment paradigm. Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Like abiraterone, it is combined with ADT. Enzalutamide's most common adverse effect is fatigue. Enzalutamide is associated with less hypertension when compared to abiraterone and is not associated with a statistical increase in cardiac events.[26] However, there is a small risk of seizures (0.1%–1%) and is not recommended for patients with a history of seizures. Finally, falls have been associated with enzalutamide.

Drug-drug interactions can occur with either abiraterone or enzalutamide. Abiraterone inhibits liver cytochrome P450 (CYP)-dependent enzymes CYP2C8 and CYP2D6, which are involved in the metabolism of approximately 25% of all drugs. Thus, abiraterone may increase plasma levels of CYP2C8 substrates including amiodarone and carbamazepine and CYP2D6 substrates, including amitriptyline, oxycodone and risperidone. Enzalutamide induces CYP3A4, CYP2C9 and CYP2C19, which metabolize up to 50% of medications. Importantly, enzalutamide may decrease plasma levels of warfarin and clopidogrel. As always, cross-referencing medications for drug-drug interactions remains a critical component of patient care requiring cross discipline communication among providers.

CONCLUSION

The aging of our population and the high prevalence of prostate cancer will result in an increase in prostate cancer patients actively treated and prostate cancer survivors. Proper long-term surveillance of prostate cancer patients involves the monitoring of late gastrointestinal, genitourinary and sexual side effects, the surveillance for secondary malignancies associated with radiation therapy, monitoring for cardiovascular disease, diabetes and osteoporosis. In summary, awareness of the timing, frequency and severity of these effects helps the clinician to provide high quality care for the man with prostate cancer.

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Authors

Zachary Brownlee, MD; Tufts Medical Center, Boston, MA.

Andre De Souza, MD; Division of Oncology, Department of Internal Medicine, The Warren Alpert Medical School of Brown University; Lifespan Cancer Institute at Rhode Island Hospital and The Miriam Hospital, Providence, RI.

Paul P. Koffer, MD; Assistant Professor of Radiation Oncology, The Warren Alpert Medical School of Brown University, Providence, RI; Radiation oncologist, Lifespan Cancer Institute at Rhode Island Hospital, Providence, RI.

Thomas A. DiPetrillo, MD; Clinical Director of Radiation Oncology at Rhode Island and The Miriam hospitals; Associate Professor of Radiation Oncology at The Warren Alpert Medical School of Brown University, Providence, RI; Adjunct Associate Professor at Tufts University School of Medicine, Boston, MA.

Anthony E. Mega, MD; Associate Professor of Medicine, Associate Professor of Surgery, Warren Alpert Medical School of Brown University; Lifespan Cancer Institute, Providence, RI.

Correspondence

Anthony E. Mega, MD
Lifespan Cancer Institute
The Miriam Hospital
Fain Building
164 Summit Ave., Providence, RI, 02906
844-222-2881
Fax 401-793-7603
amega@lifespan.org

Risk Stratification of Precursors to Multiple Myeloma in 2020

RANI CHUDASAMA, MD; PETER BARTH, MD

ABSTRACT

With advances in the treatment of plasma cell disorders, there have also been improvements in the risk stratification of these diseases. There are currently no screening recommendations for monoclonal gammopathy of unknown significance (MGUS); however, new studies are analyzing the role of screening for patients age 40–75 who are African American or have a family history of multiple myeloma (MM). Patients with smoldering multiple myeloma (SMM) have an increased risk of progression to MM when compared to MGUS. Data have shown that evaluation of bone marrow biopsy, full body MRI and free light chain ratios can identify high-risk SMM patients. Current investigation into early initiation of treatment for patients with SMM who do not meet criteria for MM showed improvement in time to progression. By continuing to evaluate clinical markers of disease burden, physicians can risk stratify patients to identify those at highest risk for progression to MM.

KEYWORDS: multiple myeloma, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, risk stratification

INTRODUCTION

Over the past decade there have been significant advances in the management of plasma cell disorders. These developments are attributed primarily to novel myeloma-directed therapies, but also due to improved imaging techniques, analysis of the genetic evolution of plasma cell disorders (PCDs), and clinical trials exploring the treatment of pre-symptomatic stages of PCDs. Here we will explore recent advances in the risk stratification of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma. Of note, the evaluation of less common plasma cell disorders such as AL amyloidosis, Waldenström macroglobulinemia, POEMS syndrome, and monoclonal gammopathy of renal significance, is beyond the scope of this manuscript.

MGUS

MGUS is most often a diagnosis made in patients with a presentation concerning for multiple myeloma, but an alternative diagnosis is made to explain their presenting symptoms (e.g. renal failure due to dehydration, hypercalcemia due to hyperparathyroidism, iron deficiency anemia, etc.). The laboratory evaluation for plasma cell disorders includes a serum protein electrophoresis (SPEP), serum immunofixation (SIFE), serum free light chains (SFLC), quantitative immunoglobulin levels (IgG, IgA, IgM), and urine protein electrophoresis in patients with protein present on urinalysis. In order to be consistent with MGUS, the monoclonal protein must be <3 g/dL with <10% plasma cells present on a bone marrow biopsy. Both the quantity and quality of monoclonal protein are used to estimate risk of progression to myeloma in MGUS. The presence of 1. A non-IgG isotype, 2. Monoclonal protein > 1.5g/dl, or 3. An abnormal serum free light chain ratio have been found to increase risk of progression to myeloma. Patients with none, one, two, or all three risk factors have a 20-year risk of progression to multiple myeloma of 2%, 10%, 18%, and 27%, respectively.[1] In patients with low-risk MGUS (none of the aforementioned risk factors), bone marrow examination and skeletal survey can safely be deferred.[2,3] In all patients diagnosed with MGUS, regardless of risk category, the risk of progression to multiple myeloma remains linear, rather than logarithmic or exponential.

While MGUS is present in over 3% of patients aged 50 or older[4], there are currently no screening recommendations for the disease given the significant anxiety surrounding the diagnosis, the lack of curative therapy, and the low risk of progression to multiple myeloma. Investigation into who may benefit from screening for a monoclonal protein is ongoing with the current PROMISE study analyzing the role of screening in patients age 40–75 who are African-American or have a first-degree relative with multiple myeloma, MGUS, SMM, or Waldenström macroglobulinemia.

SMOLDERING MULTIPLE MYELOMA

Historically, those patients who do not have "CRAB" symptoms (hyper**c**alcemia >1 mg/dL above upper-limit of normal, **r**enal insufficiency with CrCl < 40 mL/min, anemia with hemoglobin value <10 g/dL, or one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT) attributable to multiple myeloma, yet have ≥10% clonal bone marrow plasma cells on bone marrow examination or ≥3 g/dL of serum monoclonal protein are diagnosed with smoldering multiple

myeloma. This intermediate diagnosis reflects the increased risk of progression to symptomatic multiple myeloma compared to MGUS and thus can help guide clinicians on how to appropriately monitor these patients. Unlike the linear risk associated with MGUS over time, patients with smoldering multiple myeloma follow a logarithmic curve of progression to symptomatic multiple myeloma: 10% risk per year for the first five years following diagnosis, 3% risk per year for the following five years, and a subsequent 1% risk per year.[5]

Given the significant morbidity associated with symptoms of multiple myeloma, namely renal dysfunction, pain, and/or fracture associated with bone lesions, significant effort has been dedicated to identifying those patients with SMM who are very likely to progress. Long-term follow-up of SMM patients in a Mayo Clinic cohort revealed that the presence of >60% clonal plasma cells on bone marrow examination represents an ultra-high risk group of smoldering myeloma with a 95% risk of progression at two years.[6] Advances in MRI technology have allowed for a study of whole-body MRI in 149 patients with SMM found that two or more focal lesions on whole-body MRI indicated a 70% risk of progression to multiple myeloma at two years.[7] Subsequently, a retrospective study of free light chain levels in 586 patients with smoldering multiple myeloma discovered that an involved-to-uninvolved free light chain ratio of 100:1 or greater predicted a 72% risk of progression to multiple myeloma within two years.[8] These three studies led to the incorporation of three new diagnostic criteria for multiple myeloma by the International Myeloma Working group (IMWG): 1. Bone marrow clonal plasma cells >60%; 2. Involved-to-uninvolved free light chain ratio >100:1 (also requiring the involved free light chain absolute level >100 mg/L); and 3. >1 focal lesion on MRI studies.

More recently, focus has shifted toward identifying SMM patients who do not meet the aforementioned criteria for multiple myeloma who would benefit from early initiation of therapy. The Spanish PETHEMA group published a phase 3, open-label, randomized trial of lenalidomide and dexamethasone versus observation in high-risk SMM (defined as SMM plus >95% phenotypically aberrant plasma cells in the bone marrow plasma cell compartment with reduction of at least 25% below the lower-limit of normal in one of the two uninvolved immunoglobulins) in 2016.[9] Patients in the intervention arm had a significantly longer time to progression (HR 0.24, 95%CI 0.14–0.41) as well as a significant improvement in overall survival (0.43, 95%CI 0.21–0.92). Unfortunately, the risk stratification method using multi-parameter flow cytometry is of limited availability in many practices and is not routinely performed. Early results from an ongoing Eastern Cooperative Oncology Group Study (E3A06) have confirmed the expected improvement in time to progression, without overall survival data available. This trial uses routinely available markers of high-risk SMM of > 20% clonal bone marrow plasma cells, >2 g/dL monoclonal protein or involved-to-uninvolved free light chain ratio of >20:1.

CONCLUSION

As basic science advances our understanding of the evolution from the asymptomatic precursor disease of MGUS to symptomatic multiple myeloma, clinical research is investigating the benefits of treating patients earlier in their disease course with the hope of preventing morbidity. The convergence of these two processes is the development of a safe and effective cure for plasma cell disorders at diagnosis. Until that time, the use of clinical markers of disease burden can help physicians risk stratify patients in order to counsel on appropriate testing, referral, follow-up, and treatment.

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Authors

Rani Chudasama, MD; Alpert Medical School of Brown University, Division of Hematology Oncology, Rhode Island Hospital/The Miriam Hospital, Providence, RI.

Peter Barth, MD; Assistant Professor of Medicine, Alpert Medical School of Brown University, Division of Hematology-Oncology, Rhode Island Hospital/The Miriam Hospital, Providence, RI.

Correspondence

Peter Barth, MD
Lifespan Cancer Institute
The Miriam Hospital
Fain Building, 2nd Floor
164 Summit Ave., Providence, RI, 02906
401-793-7151, Fax 401-793-2855
peter_barth@brown.edu