Hematologic Malignancies

KENNETH C. ANDERSON, MD, on
Changing the Paradigm

“A ‘revolution’ of therapies for hematologic malignancies”

GU Cancer PCP Pneumonia in Patients with Metastatic Prostate Cancer
Cassandra Duarte, MD; Danielle Gilbert, BA; Alison D. Sheridan, MD; Sarah D. Weisdack, PharmD; and Elaine T. Lam, MD, FACP

GI Cancer Hepatocellular Carcinoma Clinical Quandary
Alejandro Gabutti, MD; Sherrie Bhoori, MD; Tommaso Cascella, MD; and Marco Bongini, MD

Immunotherapy The Relationship Between Checkpoint Inhibitors and the Gut Microbiome and its Application in Prostate Cancer
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CHAIRMAN’S LETTER

Improving Outcomes in Multiple Myeloma

Dear Reader,

The oncology treatment landscape continues to evolve at a rapid pace, and nowhere is that evolution more apparent than in the field of hematologic malignancies and multiple myeloma. In this issue of ONCOLOGY, we spoke with Kenneth C. Anderson, MD, program director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics at the Dana-Farber Cancer Institute, about the current trends in multiple myeloma treatment and the novel therapies that are providing better and more durable outcomes, and allowing patients to live more meaningful lives. “It is said that patients’ survival [has] improved at least 3- to 4-fold,” Anderson said about the impact of these therapies. “That is a conservative estimate, because many patients on maintenance therapy truly do have myeloma as a chronic illness and grow old and die of something else.”

While Anderson talks enthusiastically about the treatment breakthroughs happening right now, he also raves about those that are yet to come. “I think there is literally a revolution in terms of novel therapies for hematologic malignancies, and that includes the leukemias, lymphomas, [and] multiple myelomas. Multiple new targeted agents, [many] new immune agents, and especially CAR T cells… are being tested in all 3 [hematologic malignancies],” he notes.

Also in this issue, we feature 2 review articles. The first discusses the increased incidence of Pneumocystis jirovecii pneumonia in patients with solid tumors, a condition which arises due to immunosuppression caused by chemotherapy regimens and the use of corticosteroids to manage their complications. Our second review looks at the rapidly growing use of checkpoint inhibitors in oncology, and the possible underlying factors within the gut microbiome and tumor microenvironment which lead to treatment success or failure.

For this month’s clinical quandary, you will read about the case of a 64-year-old woman with hepatocellular carcinoma recurrence after liver transplantation. What is her best treatment option? Read on to find out.

Within these pages, you will also find highlights from the 17th Annual Winter Lung Cancer Conference® and the Society of Gynecologic Oncology’s 25th Annual Winter Meeting.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

- Mike Hennessy, Sr.
Chairman and Founder of ONC’s parent company, MJH Life Sciences

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Exploring New and Novel Treatments in Neurofibromatosis

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Upon successful completion of this activity, you should be better prepared to:

- Describe the pathophysiologic rationale for the use of targeted therapies in patients with neurofibromatosis
- Evaluate recent clinical trial findings regarding the efficacy and safety of targeted therapies for neurofibromatosis
- Discuss the potential benefits and risks associated with the treatment of neurofibromatosis

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**Neurofibromatosis**

(NF) is an autosomal dominant disorder characterized by peripheral nerve sheath tumors. The tumors are usually benign, but malignancy can develop and be a significant cause of morbidity and mortality. Patients with NF are at increased risk for gliomas, especially pilocytic astrocytomas of the optic nerve. They are also at increased risk for leukemia. Potential consequences of NF include blindness, deafness, disfigurement, bone abnormalities, disabling pain, and learning disabilities.

NF is usually diagnosed in childhood or early adulthood. There are 3 distinct types. NF type 1 (NF1) is the most common and occurs in 1 in 3000 persons. The features of NF1 include café au lait spots and neurofibromas on or under the skin and freckling of the armpits or groin. Patients may also have bone deformities. About 50% of patients with NF1 have learning difficulties. Patients with NF1 are at increased risk for central and peripheral nervous system tumors. Plexiform neurofibromas are benign peripheral nerve sheath tumors that usually develop in early childhood. The potential complications include pain, disfigurement, neurologic dysfunction, compression of vital structures, and malignant transformation. Surgical resection is the standard approach to management. However, in many cases, complete surgical resection is not feasible.

NF type 2 (NF2) involves bilateral vestibular schwannomas, and hearing loss and occurs in 1 in 25,000 to 30,000 persons. The growth of vestibular schwannomas causes progressive hearing loss. There is no effective treatment for tumors that recur or continue to grow despite surgery and/or radiation. Surgery and radiotherapy can cause worsening of hearing loss and further nerve damage. Thus, there is a need for new therapies that either delay tumor progression or cause tumor shrinkage.

The third type of NF is schwannomatosis, which is characterized by painful schwannomas, usually on the spinal or peripheral nerves. Although there is no cure for NF and treatment options are limited, effective therapies are on the horizon. Encouraging results have been found with certain therapies that target the pathways involved in the pathogenesis of NF. Targeted therapies that have been evaluated in NF include MEK 1/2 inhibitors, multikinase inhibitors, mTOR inhibitors, anti-VEGF monoclonal antibodies, focal adhesion kinase 1 inhibitors, and hedgehog pathway inhibitors.

NF1 is caused by a germ-line mutation in the tumor suppressor **NF1** gene that causes decreased levels of neurofibromin. The absence of neurofibromin leads to dysregulation of the RAS/RAF/MEK/ERK signaling pathway, resulting in tumor growth. Neurofibromin also negatively regulates activity in the mTOR pathway, suggesting a potential role for treatment with mTOR inhibitors.

Agents that target RAS signaling and other pathways thought to be involved in the pathogenesis of plexiform neurofibromas have been studied in phase 2 clinical trials. For example, Weiss and associates conducted a phase 2 trial of the mTOR inhibitor sirolimus in patients with progressive NF1-associated plexiform neurofibromas. They found that treatment with sirolimus was associated with a significantly prolonged time to progression (TTP) compared with placebo (median TTP 15.4 months vs 11.9 months, respectively, P = .001). However, sirolimus did not shrink the tumors.

The above-mentioned trials generally found that the rate of a decrease in tumor volume of 20% or more from baseline was low. Better responses were observed with the MEK inhibitor selumetinib in mouse models, which led to its evaluation in clinical trials. Selumetinib inhibits the MEK enzyme that is part of the RAS signaling pathway in cells, thus leading to inhibition of tumor growth. Dombi and associates conducted a phase 1 trial of selumetinib in 24 children with NF1 who had inoperable plexiform neurofibromas. The median patient age was 10.9 years, and the median tumor volume was 1205 mL. Selumetinib was administered orally at 20 to 30 mg/m2 on a continuous dosing schedule. The investigators found that the children were able to receive long-term treatment. The median number of cycles was 30. The maximum tolerated dosage was 25 mg/m2. A partial response (PR), defined as a decrease in tumor volume of 20% or more from baseline, was confirmed in 17 patients (71%). PRs were sustained for a median of 23 cycles. The most common toxicities were acneiform rash, gastrointestinal effects, and asymptomatic increase in creatine kinase.

On April 1, 2019, selumetinib was granted breakthrough therapy designation for NF1 plexiform neurofibromas. Selumetinib is specifically approved for children 3 years of age and older who have NF1 and symptomatic and/or progressive, inoperable plexiform neurofibromas. This decision was based on the results of the SPRINT trial conducted by Gross and associates. This was an open-label phase 2 trial of selumetinib treatment in children with NF1 and inoperable plexiform neurofibromas and one or more related morbidities. Selumetinib was given orally at a dosage of 25 mg/m2 twice daily on a continuous dosing schedule. Response to treatment was assessed by volumetric MRI analysis, with a PR defined as tumor volume decrease of 20% or more from baseline and by evaluating plexiform neurofibroma-related morbidities after every 4 cycles.

A total of 50 children (30 male) were enrolled in the study and had a median age of 10.2 years. The most common plexiform neurofibroma-related morbidities...
were disfigurement (n = 44), motor dysfunction (n = 33), and pain (n = 28). The median change in plexiform neurofibroma volume was -27.7%, with a PR (best response) in 36 patients (72%) and stable disease in 12 (24%). Two patients (4%) had no restaging. Of the 36 patients with PR, 22 continued to have a PR for one or more years. Parent-reported and child-reported pain intensity and pain interference scores were significantly improved (P < .01). Strength and range of motion of affected muscle groups/joints were also significantly improved (P < .01). The most common toxicities associated with selumetinib were nausea and vomiting, diarrhea, asymptomatic elevation in creatine kinase, acneiform rash, and paronychia.13 The dosage of selumetinib was reduced in 12 patients; treatment was discontinued in 5 of these patients. Another MEK inhibitor that has been studied in clinical trials is mirdametinib (PD-0325901). Weiss and colleagues conducted a phase 2 open-label study of this agent in adolescents and adults with NF1-related plexiform neurofibromas.14 The study enrolled 19 patients. Eight patients (42.1%) had a response. The therapy was well tolerated. The most common dose-limiting toxicity was acniform rash (16%). Five (26.3%) had grade 3 toxicities, primarily pain (21%).

At the 2019 annual meeting of the American Society of Clinical Oncology (ASCO), Romo and colleagues reported findings from 3 adults with NF1 and astrocytoma who were treated with the MEK inhibitor trametinib (2 mg/d); 2 received it as initial therapy. They found 2 partial radiographic responses to treatment. All of the patients had acniform rash, and one had transient transaminitis that required temporary discontinuation and subsequent dose reduction.

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF). Most vestibular schwannomas express VEGF.15 Bevacizumab has been shown to slow the growth of vestibular schwannomas in patients with NF2 and has been shown to improve hearing in a subset of patients.17-23 Studies are also evaluating the efficacy of combining targeted therapies. Angus and colleagues, for example, reported that co-targeting mTORC1/2 and EPH RTK/SFK may have a role in treating NF2-deficient meningiomas.24 Zhao and colleagues found encouraging results with the combination of cMET inhibition and radiation therapy in NF2.25

In this expert interview below, Jian Campian, MD, PhD, provides her insights into the emerging therapies for NF.

Q: Could you briefly review the similarities and differences between the types of neurofibromatosis?
DR CAMPION: Neurofibromatosis has at least 3 distinct classifications.1,26 The most common one is neurofibromatosis type 1 (NF1). The next is neurofibromatosis type 2 (NF2), and the third, and the least common, is schwannomatosis. They share some similarities. All 3 are characterized by peripheral nerve sheath tumors, such as neurofibromas in NF1 and schwannomas in NF2. However, they are very different. Each has a distinct genetic etiology, and they differ in terms of diagnostic criteria, monitoring, and treatment.

NF1 affects one out of 3,000 individuals worldwide.1,26 It occurs in both children and adults. With this pro-tumor condition, patients tend to develop more tumors in the central nervous system (CNS), which can be cranial or in the periphery. Most are benign. The most common type of tumor is schwannoma, especially bilateral schwannoma, which is a hallmark of NF2. Other common CNS tumors are meningiomas and spinal ependymomas.

The third type of neurofibromatosis, schwannomatosis, is rare. It most often occurs in adults. Patients typically present with spinal and peripheral schwannomas.

Q: What do you consider to be the most promising therapeutic targets in neurofibromatosis?

“We now know that the molecular pathways in NF1 and NF2 contain numerous potential targets for therapy.”

-Jian L. Campian, MD, PhD
DR CAMPIAN: We now know that the molecular pathways in NF1 and NF2 contain numerous potential targets for therapy. We know that NF1 deregulates the NF1 protein neurofibromin. The RAS pathway stimulates cell growth. When NF1 is mutated, that activates RAS and increases cell proliferation and induces tumor growth. The RAS pathway transmits growth-promoting signals through a cascade of other proteins. The downstream effectors in this molecular pathway, such as MEK, AKT, and mTOR, can be targeted. MEK inhibitors are available, and mTOR inhibitors and other agents have been approved for renal cell carcinoma, and these may also be useful in NF1 and NF2. In fact, MEK inhibitors and mTOR inhibitors are in multiple clinical trials.

In NF2 tumors, the tumor suppressor gene that results in the protein Merlin [Moesin-ezrin-radixin-like protein], can control cell growth through different signaling pathways. These pathways including MEK, mTOR, ErbB2, Src, FAC, and Rac1 can all be targeted. The most studied targets are ErbB2 and mTOR.

Q: Based on the results of the phase 2 SPRINT trial, the MEK inhibitor selumetinib has been granted breakthrough therapy designation for children 3 years of age and older who have NF1 and symptomatic and/or progressive, inoperable plexiform neurofibromas.13

How do you select patients for this therapy?

DR CAMPIAN: This is exciting because the treatment of inoperable plexiform neurofibromas is challenging. The condition causes a lot of comorbidity and pain, and there was no effective medical therapy until MEK inhibitors were developed. A small phase one study using the MEK inhibitor selumetinib showed a very impressive 70% PR.11 Although this was a small study, the PR is meaningful. The patients also had symptom relief, with improved pain relief. Since then, a larger phase 2 study has confirmed that response rate.13 The study showed tumor shrinkage, and patients had a decreased pain score and improved mobility, with responses lasting longer than 6 months. I think this is very good news for us and for patients.

The study was done for children and young adults, ages 2 to 18, and resulted in approval of selumetinib for patients who have progressive, inoperable plexiform neurofibromatosis. This therapy is being used off label and in clinical trials for adults as well. Several clinical trials are ongoing in adults with NF1 with progressive, inoperable plexiform neurofibroma. Dose reductions are often used. The drug is relatively well tolerated, but we do see a significant percentage of patients with skin toxicity. There is some gastrointestinal toxicity, which is usually manageable.

In light of the concerns about drug tolerability, what advice can you give clinicians about how to monitor and manage the skin rash that may occur in patients being treated with MEK inhibitors? When would you consider a treatment break?

DR CAMPIAN: In my experience, rash is common, occurring in more than 50% of patients, and it may be even more common in adults than in children. The rash is acriform and can be severe. Early recognition and treatment are the keys to management. We check the skin at least monthly.

Sometimes I ask patients to send pictures of their rash every 2 weeks if they are not coming in every month. I had a patient develop a rash after being on the drug for less than 10 days. If a local treatment such as a topical corticosteroid does not control the rash, then oral tetracycline may be indicated. I first monitor and provide local treatment, and if there is no improvement, I consider dose reduction. In children, the reduction is from 25 to 20 mg. For adults, we try to do a 20% dose reduction if there is no improvement with local treatment after a month or two. We also refer patients early on to a dermatologist.

After dose reduction, patients should be reevaluated every month, with the potential for multiple dose reductions. The patient should be maintained on the drug, but if the rash worsens, a treatment break can be considered. Normally we do a treatment break every 2 weeks and reevaluate the skin lesions. Most of the time, we can restart after 1 to 2 months. Treatment can last for a few years.

In most cases, rash is manageable. But if treatment is delayed, smaller rashes can become bigger and damage the skin, which can then develop into cellulitis. At that time, it is difficult to manage the rash, and treatment will need to be stopped.

Q: What role do you expect other targeted therapies such as the mTOR inhibitors to have in NF2?

DR CAMPIAN: Multiple mTOR inhibitors have been studied in NF2, the most common one being everolimus.12 Most of the studies so far are negative, but they are small—for instance, no response in 9 or 10 patients, 5 patients with stable disease, and no tumor shrinkage observed. Another way to interpret the data is that some patients may have delayed tumor growth. I think a larger study is looking at time to progression. However, a zero response is still questionable. These are not benign drugs. There are adverse effects (AEs). So I would not treat patients off-label with an mTOR inhibitor unless they are part of a clinical trial.

Q: Recent studies suggest that bevacizumab can prevent tumor growth, help preserve hearing, and improve quality of life in patients with vestibular schwannomas.17-23

Recent studies suggest that bevacizumab can prevent tumor growth, help preserve hearing, and improve quality of life in patients with vestibular schwannomas.17-23
What role do you see bevacizumab having in the future? Any concerns, caveats, or nuances that are important to mention?

**DR CAMPIAN:** We use bevacizumab often, and I think it will have an important role in the future. Bevacizumab is useful in the treatment of NF2, especially in patients with progressive vestibular schwannoma with hearing loss. Multiple studies have shown that it has activity, with tumor reduction, hearing improvement, and improvement in quality of life.\(^3\)\(^1\)\(^2\)

In general, bevacizumab is safe and easy to give. It does have AEs, including a black box warning about bowel perforation. Multiple studies have shown clinical benefit, especially in hearing preservation and improvement. We have also seen tumor reduction, which is more profound in adults than in children.

An important finding is that using a higher dose of bevacizumab (10 mg/kg every 2 weeks) is not more effective than the standard dose (7.5 mg/kg every 3 weeks).\(^13\) This is a meaningful finding because the risk of AEs such as hypertension, proteinuria, and kidney dysfunction, is smaller with the lower dose. So if we can give the lower dose and keep patients on treatment longer, they should have a better quality of life.

One concern is the cost. Bevacizumab is expensive. The patients still need to keep coming in every 3 to 4 weeks, which can cause problems for younger patients. After 6 months, maintenance therapy can be given, but patients still need to be monitored for AEs.

Patients also need to have a hearing test periodically. At a certain point, patients can have a treatment break, which can help reduce toxicity and improve quality of life. Treatment can always be restarted when necessary.

**Q:** When would you consider combining therapies that target different pathways?

**DR CAMPIAN:** More studies are needed to determine the role of combining different targeted therapies in the treatment of neurofibromatosis. Based on personal experience, I think bevacizumab may be an easy drug to use in combination with other medications. For example, we might be able to combine it with an mTOR inhibitor. They do not have overlapping toxicities. But I would be cautious. I need to see the data. The use of bevacizumab in combination with other targeted therapies needs further study. We do not know how much more benefit can be added when bevacizumab is combined with something else. At this time, I am more comfortable using single-agent bevacizumab. Right now, I would only use combination therapy as part of a clinical trial.

**Q:** What advice would you offer to clinicians about how to decide when to treat conservatively vs aggressively? What are the key factors they should consider?

**DR CAMPIAN:** Most patients with NF1 and NF2 are young, and now they live longer, so I tend to be more conservative. I treat the symptoms, and if there are no symptoms, I watch. I try to avoid anything aggressive. We even try to avoid MRI if possible. We do not want to expose them to radiation too often. Whether you treat conservatively or aggressively depends on the specific condition. Conditions that are low grade or relatively benign take a long time to change, so you can be more conservative. You can hold off treatment until it is really needed. Occasionally, a patient with NF1 will have high-grade glioma or high-grade sarcoma, so you have to give treatment early and aggressively. We use radiation only for aggressive tumors, such as high-grade glioma or high-grade sarcoma.

**FIVE KEY REFERENCES**


For full reference list, visit cancernetwork.com/neurofibromatosis
The Relationship Between Checkpoint Inhibitors and the Gut Microbiome and Its Application in Prostate Cancer

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ABSTRACT: Indications for checkpoint inhibitors (CPIs) are growing rapidly within the field of oncology; however, they continue to have heterogeneous outcomes in different cancers. Other than mismatch repair deficiency, there are no consistent tests to determine a tumor’s susceptibility. By exploring factors beyond the cancer cell, researchers have learned that the efficacy of CPIs may be governed by a myriad of variable host factors, including the tumor microenvironment (TME) and gut microbiome (GMB). The GMB serves as one of the primary organs of immune defense and has well-established local and systemic effects on the host immune system. Recent investigations suggest that the GMB also affects the TME. This review article discusses the concepts of a TME and a GMB and their effects on responses to CPIs. It also reviews recent research investigating these 3 topics, and how it can be applied to using CPIs in prostate cancer. By highlighting this important pathophysiologic process, we hope to provide insight into a possible explanation for differences in interindividual response to CPIs, discuss a potential method for transferring treatment efficacy between patients, and propose a method for expanding the use of CPIs to prostate cancer.

Introduction
As a disease, cancer remains one of the most complex pathologic processes in the body. Although unregulated cell division is a hallmark of the disease, it is well understood that there are a vast number of factors that contribute to the pathophysiology of cancer. These factors include, but are not limited to, sex, genetics, nutrition, macroenvironment, microenvironment, comorbidities, and immune-mediated host processes. Investigating these factors is paramount to creating a thorough understanding of cancer, and it also provides a potential opportunity for new therapeutic interventions. The relationship between systemic immunity, the tumor microenvironment (TME), and the gut microbiome (GMB) is an emerging topic of research in oncology—especially as it applies to outcomes with immunotherapy.¹⁻⁴ Within the last decade, checkpoint inhibitors (CPIs) gained approval for use in over 10 different solid tumor cancers and classical Hodgkin lymphoma.⁵ Despite the increased utilization of this class of medications, there remains a large spectrum of response between individual patients.⁶ The GMB contributes to systemic immunity and recent investigations point toward a significant interaction between CPIs and the GMB.⁷ A greater understanding of this interaction may allow for an explanation of the interindividual variability in response to CPIs and novel targets to improve immunotherapy outcomes. This review aims to outline current understandings of the TME, GMB, and CPIs, and review recent research investigating the relationship between these entities. Of particular interest is applying this relationship to the field of prostate cancer, as the efficacy of CPIs has largely evaded this field—suggesting the need for a novel approach.

TME
Although tumors may initially arise from abnormal cellular division, as the tumor progresses, a TME develops that drives its interactions with the host.⁸ This TME is composed of cancerous cells, vasculature, stroma, inflammatory cells, and a myriad of signaling factors.⁹ The microenvironment serves as the growth scaffold for the tumor, allowing it to manipulate its surroundings in a way that promotes tumor proliferation. Host immune cells, including tumor-infl-
trating lymphocytes (TILs), may recognize antigens from cancerous cells as foreign and invade the TME in an attempt to provide defense through activation of cytotoxic T-cell lymphocytes (CTLs); however, tumors can evade host immunity through a myriad of pathways. This process is known as tumor escape and it is centered on suppressing or manipulating invading immune cells in a way that prevents immune-mediated tumor regression. Escape mechanisms include alterations of malignant cells to reduce immunogenicity, alteration of immune-mediated signaling to promote the release of inhibitory cytokines or reactive oxygen species, upregulation of host anti-inflammatory pathways, and the formation of a physical barrier of macrophages that prevent CTL-associated tumor infiltration. Additionally, this chronic inflammatory state can lead to T-cell exhaustion, further dampening the immune system response to tumors. On the contrary, tumors that have more immune activity, both within the core and at the periphery, seem to have a higher degree of immune-mediated tumor regression and response to CPIs. Essentially, the TME is a dynamic, elegant system that mandates a nuanced understanding to identify potential treatment options.

CPIs

T cells can receive a co-inhibitory signal from the tumor cell, interfering with T-cell activation and tumor cell death. These co-inhibitory signals are collectively termed checkpoints. Checkpoints are found on T cells, antigen-presenting cells (APCs), macrophages, and cancerous cells and provide a physiologic role in regulating T-cell activity—preventing auto-immunity and excessive tissue damage during pathologic states. Cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death protein 1 (PD-1) are 2 particular checkpoints that play a pivotal role in immune evasion and have demonstrated clinical efficacy. During T-cell activation, APCs process foreign antigens and present them on major histocompatibility complexes that interact with T-cell receptors. T-cell activation is enhanced by the costimulatory receptor CD28, expressed on T cells, interacting with CD80/86 on APCs. CTLA4 is found on T-cells and attenuates T-cell activation by competing with CD28 for CD80/86 ligands, reducing the costimulatory signal and inducing multiple intracellular signaling pathways that decrease T-cell activity. This process occurs, primarily, within secondary lymphoid organs. During inflammatory states, such as cancer, CTLA4 expression increases in an attempt to avoid excessive inflammation, thereby reducing antitumor immunity.

While CTLA4 acts at the APC and T-cell interface, PD-1 on T cells interacts with programmed cell death ligand-1 (PD-L1) on cancer cells in peripheral tissue. Therefore, PD-1/PD-L1 activity is primarily within the TME, where malignant cells express PD-L1 binding ligands and TILs have high PD-1 expression. Once bound, PD-1 ligands are thought to influence multiple signaling pathways that ultimately lead to reduced T-cell activity.

There are 2 identified mechanisms for increased PD-L1 expression within TMEs—innate and adaptive immune resistance. Innate immune resistance refers to genetic alterations within malignant cells that leads to increased PD-L1 expression, whereas adaptive immune resistance refers to increased PD-L1 expression in response to inflammatory factors. By manipulating overexpression of these checkpoints, tumors are able to avoid immune-mediated attacks, promoting cellular immortality.

CPIs are monoclonal antibodies that bind checkpoint receptors or ligands, and inhibit interaction with the endogenous protein allowing for a more effective, host-mediated immune response to cancer. Examples of CPIs used in clinical practice include ipilimumab (a CTLA4 antibody); nivolumab, pembrolizumab, and cemiplimab (PD-1 inhibitors); and avelumab, atezolizumab, and durvalumab (PD-L1 inhibitors). Initially approved for use in melanoma, CPIs are now approved for use in more than 10 solid tumors and classical Hodgkin lymphoma. As with other treatments, there is significant variability in efficacy among patients. This variability is attributed to multiple causes including poor antigenicity of a tumor, tumor-specific immunosuppression, and aberrant or exhausted host immune system function. Recently, an understanding of the GMB as a factor in host immunity led to investigations on its role in immunotherapy.

GMB

The human GMB is a complex, living entity that starts developing at birth and continues to develop throughout adulthood. Through a longitudinal process that is influenced by environment, diet, genetics, sex, and multiple other factors, the microbiome matures to contain over 100 trillion microorganisms with a high degree of variability between individuals, and it continues to evolve as one ages. Initially, the purported contributions of the GMB were limited to the metabolism and absorption of nutrients and defense against pathogenic bacteria. Understanding of the GMB is now expanding, with studies showing that it plays a key role in the development of gut-associated lymphoid tissue (GALT), regulation of inflammation, and overall host immunity. This first came to light when mice raised in germ-free environments displayed incomplete GALT—with follow-up studies showing that gut microbes provided necessary stimulatory signals for GALT maturation. Furthermore, studies showing that mice from germ-free environments had reduced regulatory T cells (involved in reducing immune activity) and T helper cells (pro-inflammatory cells), provide a basis for the role of the GMB in immune system homeostasis. In addition to local gut immunomodulation, there is evidence to suggest that the GMB affects systemic immune function, with immune regulatory proteins derived from gut microbes found in distant organs. The effect this immune regulation process has on autoimmune conditions such as inflammatory bowel disease is well studied; however, recent studies suggest that the GMB also plays a role in cancer.
**Gut Microbiome in Cancer**

Studies thus far indicate that the GMB has both oncogenic and tumor suppressive actions. The International Agency for Research on Cancer identifies several carcinogenic microbes that are associated with oncogenesis—typically through signaling pathways that promote direct double-stranded DNA damage, increased reactive oxygen species, β-catenin pathway modulation, and amplification of nuclear factor kappa-light-chain-enhancer of activated B cells signaling. This interaction may be driven by interplay between an oncogenic microbe and commensal gut bacteria. In a study of mice infected with *H. pylori* only, they had delayed development of gastric cancer compared with mice harboring both gut bacteria and *H. pylori*.39

In contrast, there is substantial work showing that the microbiome may promote anti-tumor effects as well. One general protective measure that the GMB provides is competition that selects against carcinogenic pathogens, reducing the ability for these pathogens to populate a host.39 Much of this selection is determined by the predominant species within the GMB. Additionally, metabolism of certain host nutrients by microbes may protect against tumorigenesis. In particular, the byproducts of fiber, which are processed by distal gut bacteria, may protect against cancer.27 Donohoe et al reared mice in a gnotobiotic (ie, specific known microbials) population that varied in the presence of a butyrate-producing gut microbe.40 The 3 conditions were: wild type, attenuated producers, and non-butyrate-producing microbes. These mice were fed a high-fiber or low-fiber diet. The mice were injected with carcinogenic azoxymethane and dextran sodium sulfate to induce the formation of colorectal carcinoma. Among the high-fiber diet population, mice reared with wild-type butyrate-producing microbes had less tumor burden, while those reared with attenuated and nonproducing bacteria had the highest tumor burden. Additionally, providing exogenous butyrate to mice reared with non-butyrate-producing bacteria led to a lower tumor burden than similar mice that were not given exogenous butyrate.40 Butyrate is thought to protect against cancer by altering gene expression and reducing inflammation. Colonocytes typically utilize butyrate as their primary metabolic source, however neoplastic colonocytes utilize glucose, allowing butyrate to accumulate within the nucleus of these neoplastic cells, where it can act as a histone deacetylase inhibitor, promoting cell apoptosis and halting cell cycle progression.41 Butyrate also appears to have protein-coupled signaling effects, promoting immunosuppressive regulatory T-cell recruitment and reducing inflammatory states that can led to cellular dysplasia.42 In addition to these locally protective mechanisms, the promotion of regulatory T cells by microbes may reduce the formation of extraintestinal tumors, suggesting a more systemic effect of gut microbes.43 Further studies showed that commensal bacteria affected the composition of the TME and, consequently, the response to chemotherapeutic drugs.2

Given the substantial evidence suggesting a relationship between host microbiome and immune system function, it is logical to posit a connection between the microbiome and immunotherapy response. This connection is supported by several murine models showing reduced tumor control in mice pretreated with broad-spectrum antibiotics prior to CPI initiation.14 To better understand this relationship, Sivan et al studied the response to CPI therapy in mice with melanoma from 2 different populations—Jackson Laboratory (JAX) and Taconic Farms (TAC)—with known different commensal bacteria.44 The mice from JAX had higher tumor-mediated T-cell responses, a higher volume of intratumoral CD8 T cells, and subsequently, less aggressive melanoma growth rate. Prophylactic transfer of JAX fecal material to TAC recipients resulted in delayed tumor growth, increased T-cell activity, and an increased intratumoral CD8 population compared with TAC recipients receiving a saline transplant or TAC fecal material. This observation suggests that variance among the 2 microbial populations conferred innate differences to tumor susceptibility. Next, TAC mice with melanoma received JAX fecal material alone, a monoclonal antibody to PD-L1 (mAb PD-L1), or a combination of the 2. Mice receiving a fecal transplant or antibody therapy alone had comparable increases in T-cell activity and intratumoral CD8 populations and decreases in tumor growth. However, combination recipients had a greater reduction in tumor growth and a higher increase in T-cell activity. Additionally, JAX mice receiving the mAb PD-L1 showed improved tumor control compared with TAC mice receiving the mAb PD-L1. When combined, these findings suggest a complex interplay between the GMB and CPIs that can lead to an aggregated response to therapy.

Analysis of the JAX fecal transplant/TAC recipients showed a significant increase in the *Bifidobacterium* population that corresponded with antitumor T-cell activity. TAC mice with melanoma were fed a mixed species *Bifidobacterium* preparation or a non-*Bifidobacterium*-containing preparation. Those receiving *Bifidobacterium* species showed increased *Bifidobacterium* within fecal matter, improved tumor control, and increased T-cell activity and intratumoral T-cell infiltration (Figure 1).45 Comparatively, CD8-depleted mice receiving *Bifidobacterium* or mice receiving a killed *Bifidobacterium* did not display therapeutic benefit, suggesting the necessities of inherent host immunity and live bacteria interaction. One possible explanation to account for improved tumor control in both JAX fecal transplant and *Bifidobacterium* recipient mice is the corresponding increase in dendritic cell activation and maturation. This, in turn, leads to improved function among CD8+ intratumoral T cells, allowing for more effective host antitumor immune function and increased efficacy of CPI immunotherapy.44 The relationship between host microbiome and CPIs appears to extend to CTLA4 antibody therapy, as investigated by Vêti-
mixed bacterial products, some of which those living in GF conditions were fed positional change, mice given a BSA and increased Bacteroides species in the small increased fecal population, and Clostridiales Burkholderiales species, an in- and antibody led to decreased fecal Bacteroi- biome. Overall, treatment with the CTLA4 plored the effect of CPIs on the host micro- and colon cancer. The researchers then ex- was also seen in mice with RET melanoma and TIL activity. This differential response also had less splenic CD4+ T-cell activation those that were treated with antibiotics (BSA) had a lower response to therapy. Mice living in GF conditions and antibiotics (JAX) did not. More- with reduced tumor progression, while conditions responded to the immunotherapy (GF) conditions. Mice raised in SPF con- against sarcoma in mice that were raised in microbiome depleted of CD8+ T-cell population, reduced tumor growth. (B) Mice with TAC microbiome inoculated with Bifidobacterium species inoculation in mice. (A) Mice with TAC microbiome PD-L1 monoclonal antibody therapy, Bifidoceterium species inoculation in mice. (A) Mice with TAC microbiome treated with PD-L1 monoclonal antibody had increased T-cell activity, intratumoral CD8+ cell population, reduced tumor growth. (B) Mice with TAC microbiome received fecal microbiome transplant from JAX mice and had increased T-cell activity, intratumoral CD8+ cell population, reduced tumor growth. (C) Mice with TAC microbiome received fecal microbiome transplant from JAX mice and treated with PD-L1 monoclonal antibody showed greater increase in T-cell activity, intratumoral CD8+ population and greater reduction in tumor growth compared to mice in A,B,D and E. (D) Mice with TAC microbiome inoculated with Bifidobacterium inoculation had increased T-cell activity, intratumoral CD8+ cell population, reduced tumor growth. (E) Mice with TAC microbiome depleted of CD8 cells did not have response when inoculated with Bifidobacterium.

zou et al.1 These researchers studied the activity of a CTLA4 monoclonal antibody against sarcoma in mice that were raised in specific pathogen-free (SPF) and germ-free (GF) conditions. Mice raised in SPF conditions responded to the immunotherapy with reduced tumor progression, while mice raised in GF conditions did not. Moreover, mice treated with broad-spectrum antibiotics (BSA) had a lower response to therapy. Mice living in GF conditions and those that were treated with antibiotics also had less splenic CD4+ T-cell activation and TIL activity. This differential response was also seen in mice with RET melanoma and colon cancer. The researchers then explored the effect of CPIs on the host microbiome. Overall, treatment with the CTLA4 antibody led to decreased fecal Bacteroidales and Burkholderiales species, an increased fecal Clostridiales population, and increased Bacteroides species in the small intestinal mucosa.

To evaluate the importance of this compositional change, mice given a BSA and those living in GF conditions were fed mixed bacterial products, some of which contained Bacteroides fragilis (Bf) and then treated with a CTLA4 antibody (Figure 2). In both groups, only those mice fed Bf-containing mixtures had an antitumor response to therapy, which correlated with an increased response in T-helper type 1 (Th1) cells within tumor-draining lymph nodes. The effect of these Th1 memory cells appears to hinge upon the associated microbe. Transfer of Bf-induced Th1 cells into mice given a BSA or those living in GF conditions led to tumor suppression with CPIs, whereas transfer of B. distasonis-in-duced Th1 cells into these mice did not lead to tumor control with CPI therapy. Lastly, investigators transferred Bacteroidales-containing fecal matter from human patients with melanoma following anti-CTLA4 therapy to mice raised in GF conditions, which resulted in an improved response to anti-CTLA4 therapy.1 This work by Vétizou et al suggests that both eradication of GMB species and selection of specific populations can alter the efficacy of immunotherapy. Furthermore, a treatment-responsive microbiome can be transferred to alter outcomes to immunotherapy.

Routy et al applied these findings to a retrospective analysis of 249 patients with non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), or urothelial cancer. Among these patients, 28% were prescribed antibiotics (beta-lactam +/- beta-lactamase inhibitor, macrolides, or fluoroquinololone) within 2 months before or 1 month after initiation of a PD-1 or PD-L1 antibody.4 In a combined analysis of patients with NSCLC and those with RCC, progression-free survival (PFS) and overall survival (OS) were significantly shorter in patients giv- en antibiotics—supporting the theory that the GMB affects immunotherapy response. Routy et al advanced the study by taking fecal material from 4 of the nonresponding and responding patients with NSCLC and transplanting the ma- terial into mice that were pretreated with antibiotics. These mice were then inocu-lated with sarcoma cells and given a PD-1 monoclonal antibody. Mice receiving a fecal transplant from responding patients showed a greater response to the CPI and increased CD4 cells within the TME.
The above findings offer exciting insight on what may be a new frontier for immunotherapy. Although some of the studies identified different microbes that conferred a therapeutic response, a notable similarity was the transference of a response through fecal transplant. Additionally, the observations that mice reared in GF environments derived less benefit from CPIs underscores the importance of commensal bacteria and, potentially, of microbial diversity. This is supported by observational data regarding CPIs and antibiotic use among patients with RCC or NSCLC. In patients with either cancer, antibiotic use 30 days prior to initiation of a CPI was associated with significant decreases in PFS and OS compared with those that did not receive antibiotic therapy. When the window for antibiotic use was extended to 60 days prior to CPI initiation, OS remained significantly lower in patients with NSCLC and there was a nonsignificant trend towards decreased OS in patients with RCC.45 These observations support a theory linking the GMB and CPI efficacy and highlight the importance of commensal gut bacteria.46

In a recent, novel prospective study, Gopalakrishnan et al investigated the murine-based findings of CPI response and fecal transplant described above in humans with metastatic melanoma.4 Patients with melanoma were treated with a PD-1 inhibitor and divided into responder and nonresponder categories based on Response Evaluation Criteria in Solid Tumors 6 months after treatment initiation. Responders had a significant difference in gut microbiome diversity and a higher population of the Ruminococcaceae family microbes, genus Faecalibacterium and order Clostridiales, whereas nonresponders had a higher population of the genus Bacteroidales. Further analysis of the TME showed that patients with gut microbes predominated by the Ruminococcaceae family, Faecalibacterium genus or Clostridiales order had higher populations of CD8 TILs and systemic circulating CD4 and CD8 cells, and preserved cytokine activity, whereas patients with a Bacteroidales-based GMB had more regulatory T cells and myeloid-derived suppressor cells, and reduced cytokine activity. Next, stool from responding and nonresponding patients after anti–PD-1 therapy was transplanted into mice from a GF environment with melanoma. Mice receiving a stool transplant from responding patients showed a reduction in tumor size and a greater response to anti–PD-1 therapy, and a shift in the GMB population with a higher Faecalibacterium abundance. There was also a change in the TME post transplant, with recipients given responder stool showing higher amounts of TILs and effector T cells, and recipients given non-responder stool having higher amounts of regulatory and suppressor cells.3

To date, the benefits of immune CPI therapy have not applied widely to treating patients with prostate cancer; however, the development of 2 different prostate cancer-specific vaccines suggests that prostate cancer is an immune-responsive malignancy.47 Notably, a phase III trial showing improved OS in patients with metastatic, castrate-resistant prostate cancer (mCRPC) given sipuleucel-T—an activated cancer vaccine—provides clinical evidence that manipulating T-cell activity may lead to an additional route for tumor control.48 Vaccine recipients had significant increases in both antibodies against prostate-derived proteins and T-cell proliferation with a subsequent increase in OS compared with placebo recipients.
Unfortunately, results from 2 phase III trials of CPIs in mCRPC have not shown improvement in survival.\textsuperscript{50} It remains unclear why prostate cancer is less responsive to CPIs. The relatively low prevalence of microsatellite instability likely factors into the reduced response rate;\textsuperscript{51} however, as seen in other cancerous processes, there may be a compositional difference in the GMB of patients with adenocarcinoma of the prostate, or at least in those patients that were studied. A single-center, case-controlled study comparing patients with benign prostatic hypertrophy to those with prostate adenocarcinoma showed significant differences in their GMB populations.\textsuperscript{51} In particular, those with benign prostate disease had a higher proportion of a \textit{Faecalibacterium} species that is known to be a high butyrate-producing species. Although the sample size was small, this study provides some evidence that the GMB is influenced by the systemic processes promoting prostate cancer or can influence the development of prostate cancer. Of note, in a phase III trial with ipilimumab, patients receiving the CPI had significantly increased PFS compared with those receiving placebo. A post hoc analysis showed that patients with favorable prostate cancer traits had significantly increased OS and PFS with ipilimumab compared with placebo within the subgroup.\textsuperscript{52} Additionally, case reports and early findings in a phase II trial showed positive responses among patients with metastatic prostate cancer treated with a CPI.\textsuperscript{53,55}

There are likely multiple factors that influenced the clinical findings in the studies above, and one such factor may be a difference in the microbial populations between the 2 groups. If this proves to be the case, then successful transfer of CPI efficacy between patients through fecal transplant could provide a promising option for surpassing barriers of CPI therapy in prostate cancer. Within the field of prostate cancer, it is also important to highlight the effects of sex hormones and androgen-deprivation therapy (ADT) on immunity and the GMB. It is suspected that part of the sex difference noted in autoimmunity between men and women may be due to the immune-stimulating effects of estrogens versus the anti-inflammatory effects of androgens.\textsuperscript{54} The effect that sex hormones have on GMB development is less clear; however, a small cross-sectional study of 30 men showed that patients with prostate cancer that received ADT had a significantly different GMB compared with men with prostate cancer not receiving ADT and men without prostate cancer. Interestingly, patients within this study that received ADT had a higher population of gut flora that were previously associated with improved response to CPIs.\textsuperscript{57} This will be an important factor to consider when investigating CPIs and the GMB in humans with prostate cancer.

Currently, there are 4 human trials investigating fecal transplants and CPIs in patients with advanced melanoma that are in the recruitment phase (NCT03817125, NCT03772899, NCT03341143, NCT03353402). There is one human trial of fecal transplant in mCRPC (NCT04116775). Success in these trials will provide a novel approach to navigating variable responses among CPIs and, hopefully, a method to expand the use of CPIs into a variety of different cancers.

**Conclusions**

As is often the case, this review brings about as many new questions as it tries to answer. The strongest conclusion one can draw from the material within is that cancer is a profoundly complex process that involves far more than cellular mutation. By expanding our understanding of the pathophysiology of cancer, we can continue to develop new targets to potentially treat cancer or improve the efficacy of established therapies. It can also be surmised that, although CPIs are meant to target a local structure, their efficacy is driven by a systemic pathway that includes their first point of contact in the gastrointestinal tract. This review also greatly underscores the pivotal importance of gut bacteria and supports current efforts to restrict antibiotic use only to those cases where there is a clear indication. Given the discrepancy among tumor suppressive microbes in the findings discussed above, further research is needed to clarify which microbes help protect against cancer, or if the composition of a treatment-specific GMB differs with each cancer subtype. Hopefully, this question will be clarified through current clinical trials involving CPIs and fecal transplants. The findings of these trials will be paramount to testing the hypothesis that treatment response can be transferred through fecal transplantation and provide a new pathway for circumventing the poor outcomes of treatment-refractory malignancies.

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PARP INHIBITORS AS FRONTLINE TREATMENT IN PATIENTS WITH OVARIAN CANCER

Kevin Wright

The time has come for maintenance treatment with poly(adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitors to become the standard of care in the frontline setting for patients with ovarian cancer. This message, backed by recent data from clinical trials, was at the forefront of the Society of Gynecologic Oncology’s 25th Annual Winter Meeting held February 6-8 in Aspen, CO.

“The rationale is that we may be curing more patients,” said Kathleen M. Moore, MD, the Jim and Christy Everest Endowed Chair in Cancer Research at the Stephenson Cancer Center in Oklahoma City during a presentation. “If patients are going to benefit from a PARP, they’re going to benefit most early on. We just need to identify those patients a little bit more accurately.”

Moore’s assertion is supported by results from 3 clinical trials—PAOLA-1, PRIMA, and VELIA—that were first released at the European Society for Medical Oncology Congress 2019.

In the phase III PAOLA-1 trial, frontline maintenance therapy with bevacizumab (Avastin) plus olaparib (Lynparza) as maintenance therapy showed an increase in median progression-free survival (PFS) compared with placebo (13.8 months vs 8.2 months, HR for disease progression or death, 0.62; 95% CI, 0.50 to 0.76; P <.001). Similar to the PAOLA-1 trial, patients with HRD tumors derived the greatest benefit, with an increase in median PFS of almost 12 months (21.9 months vs 10.4 months; HR, 0.43; 95% CI, 0.31 to 0.59; P <.001).

Positive findings for a third PARP inhibitor, veliparib, were demonstrated in the phase III VELIA trial, which measured the effectiveness of veliparib as a first-line treatment and maintenance therapy. The combination of veliparib, carboplatin, and paclitaxel followed by maintenance veliparib monotherapy extended median PFS by nearly 7 months compared with chemotherapy plus placebo followed by placebo maintenance (23.5 months vs 17.3 months; HR for disease progression or death, 0.68; 95% CI, 0.56 to 0.83; P <.001) in the overall population, while patients with BRCA mutations saw median PFS increase by more than a full year (34.7 months vs 22.0 months; HR, 0.44; 95% CI, 0.28 to 0.68; P <.001).

“What was really neat about the presentation of [data from] all 3 trials was the differences between them in terms of the patient populations [examined], the drug combinations evaluated, and the different drugs used,” said Angeles Alvarez Secord, MD, a gynecologic oncologist at the Duke Cancer Center. “We are able to synthesize this information to determine what the best option is for our patients.”

Secord, who moderated a case-based symposium entitled “Feed Your Brain—Digesting PAOLA, PRIMA, VELIA,” noted that when it comes to choosing the right PARP inhibitor, there is not necessarily 1 right answer. Instead, it is important to consider the different patient populations evaluated in each trial and the benefits of the agents in each subgroup, to aid in the decision-making process.

The use of PARP inhibitors does come with an increased risk of bone marrow and gastrointestinal toxicity, along with the risk of severe hematologic toxicity. Twelve percent of patients in the PRIMA trial and 20% of those enrolled in the olaparib arm of the PAOLA-1 trial discontinued therapy due to adverse events, with 70.9% of patients from PRIMA and 41% of patients from PAOLA-1 requiring a dose reduction.

The benefits far outweigh the risks, however, according to Moore. “What we know…at least when you consider fatigue, nausea, and vomiting is that time spent without toxicity far exceeds time spent with toxicity. The patients are telling us, at least from what we ask them, that [PARP inhibitors] are well tolerated.”

For references visit cancernetwork.com/WinterSGO2020
Thirty years ago, patients with multiple myeloma faced a poor prognosis, with 5-year survival rates of approximately 25%. With the development of immunotherapy and targeted agents, that number has now almost doubled.

**Q:** Multiple myeloma seems to be one of the fastest changing realms of cancer care. What would you say are the major trends in multiple myeloma treatment over the past year or so?

**DR. ANDERSON:** There has been very rapid progress, both in the targeted therapy and immune therapy areas. A targeted therapy, for example, such as venetoclax (Venclexta) is very effective in 11;14 translocation or high B-cell lymphoma 2 (BCL-2)-expressing myeloma. On the immune side, there are B-cell maturation antigen (BCMA)-directed immuno-toxins, bispecific T-cell engagers (BiTEs), and chimeric antigen receptor (CAR) T cells, all of which are looking very promising in clinical trials. So, rapid progress is being made in the targeted therapy area and with immune therapies.

**Q:** There is also a fair amount of clinical work going on with combinations, not just individual agents.

**DR. ANDERSON:** So, there is continued progress in combinations. Our progress to date has been related to developing new classes of drugs and then combining them based on preclinical rationale, suggesting that they are additive or synergistic. So, for example, in newly diagnosed patients, lenalidomide (Revlimid)/bortezomib (Velcade)/dexamethasone (RVd) were combined and are used broadly in patients with myeloma and achieve a very high rate of response and extent of response.

The monoclonal antibodies, daratumumab (Darzalex) and elotuzumab (Empliciti) (especially daratumumab), now have been added to RVd and at this [past] American Society of Hematology (ASH) [Annual Meeting and Exposition in December 2019], RVd/daratumumab or carfilzomib (Kyprolis)/lenalidomide (Revlimid)/dexamethasone (KRd)/daratumumab were shown to achieve … [an] even deeper or higher extent of response, including a high frequency of minimal residual disease (MRD)-negative responses. So, adding an antibody to RVd or KRd is increasing the extent of response.

**Q:** What studies that have yet to report results are folks in the research industry most excited about?

**DR. ANDERSON:** I think in terms of the combination approaches, the Intergroupe Francophone Myelome (IFM)/Dana-Farber Cancer Institute (DFCI) trial, which is RVd in newly diagnosed myeloma transplant candidates… as initial therapy, and then randomization… to… early high-dose melphalan (Alkeran) in stem cell transplant versus not. This trial has been going on since 2009 and is asking the question as to the added value of a stem cell transplant in the era of combination novel therapies. So that is one trial that we are really anticipating and excited about the results.

In the relapsed setting, new regimens are also based on combination approaches. At the ASH annual meeting, for example, carfilzomib (Kyprolis)/dexamethasone/daratumumab were compared with carfilzomib (Kyprolis)/dexamethasone, and the triplet was found to be superior in terms of treatment for relapsed myeloma. So, in newly diagnosed [patients] and [those who have] relapsed, novel combinations are showing more efficacy.
CD38 antibody called isatuximab which has some characteristics similar to daratumumab but...[it] is qualitatively different. A large randomized phase [III] trial of isatuximab with pomalidomide (Pomalyst)/dexamethasone versus pomalidomide/dexamethasone [alone] is fully enrolled and it is expected that the results of this trial will provide the framework for its FDA approval to treat relapsed myeloma. A second example would be the trials of 11;14 translocation myeloma or myeloma that expresses high levels of BCL-2.

A randomized study called the BELLINI trial has compared venetoclax/bortezomib (Velcade)/dexamethasone with bortezomib (Velcade)/dexamethasone and shown that the benefits are primarily in those patients who have the 11;14 translocation or express high levels of BCL-2, whereas other patients do not similarly benefit. Those would be among the most exciting short-term trials. I would also say that the excitement is in the immune trials,...in 3 areas. There is the BCMA immunotoxin from GlaxoSmithKline and clinical trials of this immunotoxin are showing activity in relapsed multiple myeloma with significant prolongation of progression-free survival that should provide the benefit for its FDA approval.

There are now many BiTEs. Early data presented at the [recent] ASH [meeting] showed that once the correct dose was defined, significant responses in terms of high rates of response and high rates of MRD negativity were achieved. And thirdly, the clinical trials of CAR T-cell [therapy] are numerous and very promising. I think a summary in myeloma would be that the responses are in far-advanced myeloma and extremely deep. Often, MRD-negative complete responses are achieved in spite of multiple prior therapy. The safety of [CART T-cell therapy] is being improved, [as a] decreased [incidence] of serious cytokine release syndrome (CRS) [has] been observed. What remains as an obstacle is the durability, as progression-free survival on average is still around 18 months.

**Q:** Of the CAR T-cell therapy trials, which is furthest along? Is this something we would expect to see become a standard of care—at least in sort of heavily pretreated myeloma—in the near future?

**DR. ANDERSON:** I think that the furthest along in the CAR T-cell [therapy] area are the bb2121 CAR T-cell approaches. The response rates are very high in spite of multiple lines of prior therapy and I would anticipate that [bb2121] would be approved later in 2020 or early in 2021. Multiple other trials are trying to, if you will, improve upon the durability and efficacy of CAR T-cell therapy. So, for example, the bb2121 concept is [manufacturing] CAR T cells in the presence of a phosphoinositide-3 kinase inhibitor to select for early lineage memory CAR T cells. Early data suggest that you can detect memory CAR T cells in patients after treatment.

There are experiments utilizing combinations of CD4- and CD8-positive CAR T cells. There are CAR T cells that have been modified so they bind to BCMA in 2 different domains, the so-called bivalent CAR T cells. The initial experience was in China and very encouraging, showing that fewer CAR T cells are needed and high rates of response and extent of response were observed. Now in America, the same bivalent BCMA vector is used, and [results from] the CARTITUDE-1 trial [were] reported at the [recent ASH meeting]. Very high rates of response, and extent of response, including MRD negativity were observed, but the follow-up is short and the durability of those responses remains to be seen.

**Q:** You talked about the incidence of CRS going down. Was that particularly high in the initial trials of CAR T-cell therapy? And what they have been doing to get it down?

**DR. ANDERSON:** Well, I think the severe CRS was observed primarily in the earliest studies. And subsequent, there has been [a] marked increase in [the] understanding and...recognition of CRS, and...in its treatment—such that [the] tocilizumab (Actemra) antibody directed at interleukin-6 is used often and early and can in large part aggregate severe CRS.

**Q:** Is there hope that eventually CAR T-cell therapy might be a replacement for traditional transplantation?

**DR. ANDERSON:** Yes, I think there is. As with our other novel drug or immune approaches, CAR T-cell [therapy] is now being first tested in far advanced patients with relapsed/refractory disease. Having established efficacy and safety in that setting, [CAR T cells] are now being tested earlier in the disease course. For example, in patients who have high-risk, genetically high-risk multiple myeloma, such as [those with a 17p deletion], CAR T cells are being utilized at the time of first relapse..., so relatively early in the disease course.

**Q:** Is there work underway to move the use of CAR T-cell therapy earlier in the process as frontline treatment or at least in the less heavily pretreated patients?

**DR. ANDERSON:** Yes, there is. As with our other novel drug or immune approaches, CAR T-cell [therapy] is now being first tested in far advanced patients with relapsed/refractory disease. Having established efficacy and safety in that setting, [CAR T cells] are now being tested earlier in the disease course. For example, in patients who have high-risk, genetically high-risk multiple myeloma, such as [those with a 17p deletion], CAR T cells are being utilized at the time of first relapse..., so relatively early in the disease course.
immune effects from a BCMA antibody which include antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. It also delivers an auristatin immunotoxin as a second mechanism of myeloma killing. The second or next class of drugs are called BiTEs, and they...have 2 antibody-binding domains. They bind on the one hand to BCMA-positive multiple myeloma cells and on the other to CD3 on the surface of T immune cells, thereby bringing the immune cells in proximity to the myeloma cells. As in leukemia and lymphoma, early data in myeloma suggest that you can have [greater] potency, more selectivity, and perhaps a better therapeutic index by localizing the immune response in the microenvironment of the tumor and potentially avoid more systemic side effects.

I think people understand how [CAR T-cell therapy] works, but I will just mention [that] the T cells are harvested from patients with myeloma, transfected usually with a lentiviral vector that allows for their binding to BCMA-positive myeloma cells, [which] activates their T-cell receptor, and usually has a costimulatory molecule (4-1BB or CD28). These transfected BCMA-targeting autologous T cells, which are activated...[and] then expanded ex vivo or in the laboratory with CD3/CD28 beads into large numbers. These autologous cells are then transfused back to patients, as I like to say, [to] their own immune army. And, as I mentioned already, very impressive extent and frequency of responses are observed.

Q: What is driving these new trials? Is it a better understanding of the underlying biology of the myeloma?

DR. ANDERSON: I think it is a combination [of things]. Certainly, the single agents and combination therapies are being informed by preclinical science, both in the laboratory and in animal models, which suggest cytotoxicity directed at myeloma cells that can be enhanced or...synergistic effects when used in combination. There are also observations at the bedside that are then brought back to the laboratory, back to the bench, and result in further experimentation and improvement in some strategies that can go back to the clinic. So, it is [that] bed-to-bench-to-bedside iteration that leads to improved therapies or improved combination therapies and improved efficacy.

Q: What are the big things we have learned about the biology of multiple myeloma in the past couple of years?

DR. ANDERSON: Well, we have known for many years that myeloma evolves from monoclonal gammopathy of undetermined significance (MGUS) to a stage called smoldering multiple myeloma and then to active multiple myeloma disease. Traditionally, we have only treated myeloma when complications develop, such as hypercalcemia, renal disease, anemia, or bone disease. Starting in 2016, because we have very effective therapies for myeloma that are well tolerated, we have now redefined smoldering multiple myeloma and treat some of those affected patients before they develop [hypercalcemia], kidney [disease], anemia, or bone disease. In particular, even patients who do not have those end-organ sequelae are treated if they have more than 60% plasma cells,...bone disease on sensitive imaging, or...a kappa lambda ratio more than 100-fold abnormal. In these patients, we hope by treating early we can prevent or delay the development of those complications. That is a major clinical advance.

In terms of the biology of the progression from MGUS to smoldering myeloma to multiple myeloma, recent studies have characterized the genetic progression of disease and shown that the majority of changes genetically are already present at the MGUS stage. Patients who progress rapidly to myeloma are those who have expansion of an abnormal genetic clone that was already there at time of diagnosis. Those patients who take a longer time to progress have what we call clonal evolution where there is genetic, if you will, changes that occur in the myeloma clone that ultimately correlate with progression.

The major point here is that since the majority of genetic changes are present very early, many laboratories and investigators have turned their attention to the bone marrow microenvironment. Changes in the bone marrow milieu,...accessory cells in the bone marrow and the patient’s immune cells in the bone marrow,...actually correlate or are associated with progression of disease. In other words, if the majority of genetic changes are already there very early, the progression may very likely be due to changes in the patient’s bone marrow microenvironment, the accessory cells there, and especially the patient’s autologous immune system.

Q: You talked about specific mutations appearing to make particular treatments work more effectively. How many patients with multiple myeloma right now have a mutation that would drive treatment? And what efforts are underway to sort...
of segment people a little better to see what is going to work for whom?

**DR.ANDERSON:** There has been significant progress in terms of the genetic profiling of myeloma for use at [the] time of diagnosis and for prognosis. We have progressed from fluorescent in situ hybridization to gene sequencing of patients’ multiple myeloma cells. To date,… the only precision medicine in multiple myeloma is venetoclax alone or together with a proteasome inhibitor in patients who have 11;14 translocation or high BCL-2 expression. That population ranges somewhere between 30% and 40% of patients [with myeloma]. I and others have sequenced large numbers of patients with myeloma…to subset them, and they are based on bulk RNA characterization. There are at least 11 subgroups of multiple myeloma based on DNA sequencing. There are large numbers of mutations, some of which appear to be driver mutations.

For example, RAS or KRAS are the most commonly mutated genes in myeloma, and there have been early attempts to block the RAS/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase signaling pathway using MEK inhibitors or extracellular signal-regulated kinases inhibitors. These treatments have achieved responses that were only transient. Combination targeted therapies are now being employed. Clinical trials are being done, such as the MyDRUG (Myeloma–Developing Regimens Using Genomics) umbrella trial, to try to treat patients with relapsed myeloma with precision medicine.

I will mention that in this trial, patients’ myeloma, when it relapses, is being sequenced. These patients are then being treated with an active regimen of the proteasome inhibitor, ixazomib (Ninlaro), and the immunomodulatory drug, pomalidomide, to which is added a targeted therapy based upon the mutations that are identified. The…MyDRUG umbrella trial will define whether the targeted therapy actually depletes the mutated myeloma clone. And, if it does, this will be a hypothesis or a new lead to be tested further in subsequent clinical trials.

But, in summary, myeloma is extremely heterogeneous right at diagnosis. There is continual ongoing DNA damage and genomic evolution as the disease progresses. And, as of today, the only real true precision medicine in myeloma would be venetoclax-containing regimens in the 11;14 translocation or high BCL-2-expressing myeloma subset.

**Q:** Which investigations have you been actively involved with?

**DR.ANDERSON:** Our center has been involved in the preclinical evaluation and clinical trial evaluation of all of [these] advances. And we have been blessed in multiple myeloma to have 26 FDA approvals [to date] which have incorporated novel agents, and our center has been actively involved in the preclinical and clinical development of 22 of those new advances.

**Q:** Of all the clinical trials that you have been involved with, are there 3 or 4 that you would consider to be your “greatest hits”?

**DR.ANDERSON:** One is the trials of proteasome inhibitors, in particular bortezomib (Velcade) in the early 2000s, that achieved remarkable responses in far advanced relapsed/refractory myeloma, ultimately leading to FDA approval. We similarly participated in the preclinical and clinical development of lenalidomide, which…was FDA approved, first in relapsed myeloma and then [as part of] combination [therapy].

So, we did clinical trials…of the combination of lenalidomide (Revlimid) with bortezomib (Velcade) and dexamethasone based on preclinical studies, and this RVd regimen achieved high response rates and extent of response and is now used all over the world as initial therapy in myeloma.

The most important trial I think that is not yet mature is the DFCI/FJM trial, which is…RVd given to newly diagnosed transplant candidates, with…randomization to high-dose melphalan and stem cell transplantation or not, in each case followed by lenalidomide maintenance. This is a landmark trial in myeloma as it will define the utility of high-dose melphalan and stem cell transplantation in the era of novel combination targeted agents.

**Q:** Which investigational accomplishments from your career are you most proud of?

**DR.ANDERSON:** I think that when I began studying multiple myeloma back in the 1970s, the survival of patients was only a few months. And then starting in 1980, I extended my interest to a laboratory interest in multiple myeloma which involves studying not only the myeloma cell but also the microenvironment. The advances came in the 1980s, primarily…high-dose melphalan and autologous stem cell transplantation. The bisphosphonates came [into use] in the early 1990s to avoid the terrible bony complications of myeloma.

But to get to your question, the most exciting accomplishments or progress that I have been associated with has to do with the advances since the late 1980s—novel drug classes that target both the tumor and the microenvironment. And these drugs…are the immunomodulatory drugs, the proteasome inhibitors, [and] monoclonal antibodies. And these advances, these classes of agents used sometimes alone, but much more commonly in scientifically informed combinations, have transformed…outcome[s] in myeloma.

At the present time, for example, novel combination agents are used to treat newly diagnosed myeloma and achieve responses in the overwhelming majority of patients. These combinations of 3 and now 4 agents are so active that we have clinical trials examining whether high-dose melphalan and stem cell transplantation adds [any] value. And novel agents such as lenalidomide and others have been used as maintenance…to transform myeloma into a chronic illness in many cases.

I am most proud of the role that our group and our very large laboratory and clinical effort has played in these advances in drugs targeting the tumor and the microenvironment and in particular, in the transformation of myeloma treatment. It is said that patients’ survival [has] improved at least 3- to 4-fold. That is a conservative estimate because many patients on maintenance therapy truly do have myeloma as a chronic illness and grow old and die of something else.
Hepatocellular Carcinoma Recurrence After Liver Transplantation

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A 64-year-old white woman with hepatitis C virus (HCV) infection-related well-compensated cirrhosis (Child-Pugh score, B7; Model for End-stage Liver Disease, 12 points) was diagnosed with hepatocellular carcinoma (HCC) within the Milan criteria (bilobar disease, 2 nodules, largest diameter of 13 mm) (Figure 1). The patient’s performance status was optimal, without ascites and no associated diseases. She was cataloged as stage A according to the Barcelona Clinic Liver Cancer staging system and received an orthotopic liver transplant (OLT).

Serum alpha-fetoprotein (AFP) level at diagnosis was 16.6 IU/mL (19.6 ng/mL). The patient received 2 cycles of doxorubicin-loaded drug-eluting beads transarterial chemoembolization (DEB-TACE) with 75 to 150 micron particles as bridging therapy. The right lobe was initially treated followed by a second session in the left lobe. Both sessions were performed within a 3-month period. A computed tomography (CT) scan after the first procedure showed a complete tumor response (with modified response evaluation criteria in solid tumors [mRECIST] criteria) while a radiologic evaluation after the second session was not possible as the patient was transplanted less than a month after the procedure. No surgical or medical complications were reported and the patient recovered satisfactorily and was discharged on day 12 post surgery.

Explant liver histology revealed a signifi-
Table: Different selection criteria for liver transplantation.1

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>Milan</td>
<td>Single tumor ≤ 5 cm or multiple tumors ≤ 3 nodules ≤ 3 cm in size without vascular invasion</td>
</tr>
<tr>
<td>UCSF</td>
<td>Single nodule ≤ 6.5 cm or 2-3 nodules ≤ 4.5 cm and total tumor diameter ≤ 8 cm</td>
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<tr>
<td>Up to 7</td>
<td>Having the number of 7 as the sum of the size of the largest tumor and the number of tumors</td>
</tr>
<tr>
<td>TTV + AFP</td>
<td>TTV &lt; 115 cm3 and AFP &lt; 400 ng/ml</td>
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<tr>
<td>AFP-French model</td>
<td>Points system based on tumor size, number, and AFP cutoff levels at 100 ng/ml and 1000 ng/ml</td>
</tr>
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AFP indicates alpha-fetoprotein; TTV, total tumor volume; UCSF, University of California San Francisco.

Discussion

OLT is the best curative treatment for HCC1 within the Milan criteria as it achieves complete tumor excision and resolution of the underlying pro-oncogenic cirrhosis.2 Patients transplanted based on the Milan criteria have a posttransplant survival time similar to that of those transplanted for non-oncologic reasons.3

In patients within the Milan criteria, bridging therapies such as TACE or ablation are advisable. As bridging treatments, their main goal is to prevent transplant list drop-off, especially when a waiting time greater than 3 months is expected.4

Other more permissive criteria have also been developed because the Milan criteria can be considered too restrictive (Table).1 In patients outside conventional criteria, a good response to TACE (downstaging treatment) has been associated with a posttransplant survival time comparable to that of patients within the criteria.1,5 This effect is likely because responding tumors have a less aggressive biology.6

Even with a liver transplant, in candidates who strictly fit imaging criteria, up to 60% are incorrectly staged when explants are histologically analyzed.7 Unfortunately, a worrisome high rate (upwards of 30% and 50%) of radiologic/pathologic discrepancies, both overstaging and understaging, have been reported in the literature.8,9

The first case of recurrent HCC after transplant was reported in 199510; thereafter, several prevention strategies were. These strategies rely on the identification of risk factors for recurrent HCC and can be divided into 2 main groups. Pretransplant factors (not considering donor- and graft-related risk factors) include tumor burden, AFP values, and composite inflammatory markers (such as a neutrophil-to-lymphocyte ratio >5).11 Posttransplant risk factors include mostly tumor characteristics at explant pathology: poorly differentiated tumors, vascular invasion, tumor burden, and satellite lesions.12,14

Recently, gene signatures are also being highly considered as predictive factors of recurrence.15

Overall, there are no well-established surveillance protocols; however, follow-up at close intervals in the first 2 to 3 years is a widely accepted practice and it should not be abandoned after the first few years. Several scores (eg, Risk Estimation of Tumor Recurrence After Transplant score) can help in stratifying the risk of recurrence and designing a personalized follow-up program for each patient.16

Despite all the well-known risk factors, the HCC recurrence rate ranges from 10% to 20%, with a median time to recurrence of 14 months after transplant and a post recurrence median survival of 12.2 months.17,18 Seventy percent of recurrence cases are diagnosed within the first 2 years of follow-up and most (72.9%) of these are extrahepatic.20

Recent HCC should be categorized as early or late-onset (ie, within or after 2 years from transplantation), as this is considered the most important factor for long-term survival.21 Early recurrence carries a poor prognosis and is probably the result of pre-existing or undetected tumor cells at transplantation.22,23 Conversely, late recurrence is associated with a better prognosis.19 Late engrafing of HCC cells
that remained latent is a possible explanation for this phenomena. Some investigators suggest that neo-oncogenesis could be responsible for late hepatic recurrences, especially in patients with untreated viral infections and recurrent cirrhosis. However, with current antiviral therapies this is a less likely scenario. Aside from an early recurrence, the most significant adverse factors for survival are not being amenable to curative-intent treatments and an AFP level greater than 100 ng/mL at the time of recurrence.

In our patient, both hepatic and adrenal recurrences were late onset and diagnosed simultaneously. This synchronism can be explained by the theory previously exposed of late-engrafting tumoral cells. The circulating clones may find the liver’s environment more favorable to engraft in than extrahepatic ones. This tropism can explain the predominant hepatic disease. However, an alternative hypothesis is that the adrenal recurrence was consequence of an undetected pretransplant metastasis with subsequent liver involvement. Nevertheless, an earlier diagnosis of recurrence would favor this hypothesis.

Once a diagnosis is established, a therapeutic decision should be made. Extrapolation of the data from case series and trials of non-transplanted patients with HCC frequently cannot be applied to this particular population largely due to the presence of immunosuppression and several comorbidities. This is the main reason why transplanted patients are an orphan population for clinical trials investigating mainly systemic treatments.

Currently, there are no established consensus guidelines addressing the management of HCC recurrence after OLT. Therapeutic decisions should involve a multidisciplinary team.

Treatment options can be divided into 3 groups: (1) potentially curative interventions (surgery/ablation); (2) locoregional treatments (especially transarterial); and (3) systemic therapies. Each one is not mutually exclusive, and most of the time, a combination of all 3 may be employed depending on the clinical scenario.

**Surgery and Ablation**

Resection of recurrent HCC should be considered the first-line approach. It provides the longest median survival (42 ± 24.45 months) compared with other treatment modalities, and it is suitable in patients with isolated hepatic or extrahepatic metastases. However, its good outcome is probably due to selection bias influenced by the fact that ideal candidates have a good performance status, optimal liver function, and a favorable location for resection.

Surgical morbidity and mortality does not appear to be increased in post OLT patients. Technical factors, such as the presence of peritoneal adhesions in patients with multiple previous abdominal surgeries, should always be taken into account. Unfortunately, only 10% to 30% of patients with recurrent HCC can be treated with resection or ablation.

**Transarterial Therapies**

TACE has been reported as a first-line treatment for HCC recurrence by several investigators, with a median survival of 11.2 ± 8.81 months. Multinodular disease and an unfavorable location for resection/ablation are the 2 key factors to be considered when selecting patients as TACE candidates.

Regarding the different embolization techniques, there are no comparative studies that provide information on superiority, with conventional TACE the most common technique. However, technical difficulties may be present because of post-surgical arterial anatomic changes due to stenosis, loops, or kinks. Concerns about symptomatic biliary ischemia secondary to poor arterial collaterality may be present, especially with lobar embolizations. In spite of this, higher complication rates have not been reported in transplanted patients. Other vascular procedures, such as selective internal radioembolization therapy with yttrium-90, have been reported in the literature with favorable results.
Key Points

- Recurrent HCC after OLT management is challenging and notoriously difficult.
- High oncologic-risk patient identification and close follow-up are essential.
- Recurrences diagnosed within the first 2 years after OLT can be classified as early-onset and are associated with poor prognosis.
- Surgical resection should be the first curative attempt when it is technically feasible.
- TACE in patients who have undergone OLT appears to be effective and safe.
- Sorafenib can be used as systemic therapy in cases with multi-organ recurrence; newer therapies are emerging.
- The benefit of immunosuppression with an mTOR inhibitor has not been established.
- In the posttransplant setting, a combination treatment approach is warranted.

Systemic Therapy

HCC is a chemotherapy-resistant tumor. In 2008, sorafenib was approved as a first-line treatment for advanced stage HCC. The effectiveness of this tyrosine kinase inhibitor in HCC recurrence after OLT has not been tested in randomized clinical trials. Only case series have reported the use of this drug as a first-line therapy and regorafenib as a second-line therapy.

A study from Italy reported better outcomes in patients with recurrent HCC after liver transplantation given sorafenib than in those given best supportive care (median patient survival from recurrence: 21.3 months vs 11.8 months; hazard ratio, 5.2; \( p = 0.009 \)). Similar results have been published, with stable disease the most frequent response obtained. Nevertheless, some data suggest an increased intolerance to sorafenib, especially in combination with mTOR inhibitors, leading to dose reduction or discontinuation.

The recent introductions of other tyrosine kinase inhibitors (lenvatinib in the first line and cabozantinib in the second and third line) and monoclonal antibodies (ramucirumab in the second line) into the therapeutic armamentaria will likely be adopted soon in the transplant setting (excluded in registration trials) in real life series, as previously done for sorafenib and regorafenib.

On the other hand, several safety issues still significantly impede the use of immunotherapy (atezolizumab plus bevacizumab in the first line) in patients who have undergone transplants, even when promising preliminary results from the IMbrave150 clinical trial have been announced (ClinicalTrials.gov identifier: NCT03434379). This is because of the unpredictable risk of graft rejection once the immune system is reactivated.

Immunosuppression and HCC Recurrence

Immunosuppression is believed to significantly contribute to HCC recurrence in transplant recipients. Therefore, it is highly recommended to gradually wean patients off immunosuppression to improve the immune system’s ability to detect and eliminate HCC cells while maintaining enough immunosuppression to minimize the risk of graft rejection.

In patients with HCC recurrence, it has been proposed to switch the immunosuppression regimen to mTOR inhibitors. This is because sirolimus has shown a potential antineoplastic effect on HCC cells in vitro and in vivo. Clinically, the use of sirolimus as a prevention strategy for HCC recurrence in transplant recipients was explored by the SiLVER study. This phase III randomized clinical trial compared sirolimus-containing versus mTOR inhibitor-free immunosuppression in patients who underwent liver transplantation for HCC. The results did not suggest any significant differences in overall recurrence rate or survival in the five years after OLT, surprisingly even in high-risk patients. An initial concern about mTOR inhibitor safety was present because phase II trials prompted a black box warning regarding an increased incidence of hepatic artery early thrombosis post OLT, but this was not confirmed in further studies.

Patient Outcome

Our patient can be categorized as having a late recurrence of HCC. She was approached with a combination of locoregional treatments (as she presented with predominantly unresectable liver disease) and systemic treatment because of intrahepatic spread. Two cycles of doxorubicin-loaded DEB-TACE were performed within a 2-month interval; the super-selective left TACE was technically challenging because of a postsurgical loop in the hepatic artery, making microcatheter navigation difficult. A complete response (per mRECIST criteria) in all liver nodules was achieved. Sorafenib was started (and reduce to 400 mg daily because of adverse events) and the last follow-up CT scan (6 months after recurrence) showed stable adrenal disease and no further sites of recurrence. At 4 years and 4 months following OLT, the patient’s performance status and liver functions are optimal. Although there is a good response to combined treatment with the radiologic assessment, AFP levels are increasing. The patient will continue sorafenib; TACE will be reconsidered in the case of intrahepatic disease. The current immunosuppression regime scheme is CNI based; a shift to an mTOR inhibitor will be considered depending on the patient’s tolerance to combination treatment (sorafenib plus mTOR inhibitor).

For full reference list, visit cancernetwork.com/HCC_Quandary
Although accumulating data continue to show immunotherapy as a major step forward in the treatment of patients with non–small cell lung cancer (NSCLC), questions regarding optimal sequencing and treatment duration still remain. At the 17th Annual Winter Lung Cancer Conference®, hosted by Physicians’ Education Resource®, LLC, presentations from Karen Kelly, MD and Gilberto de Lima Lopes, MD, looked for answers to address these issues.

Treatment Initiation
While the use of immune checkpoint inhibitors, as a monotherapy and in combination with chemotherapy, has demonstrated benefits for patients with NSCLC, the key to unlocking the full therapeutic potential for these treatments, said Kelly, an associate director for clinical research at the University of California Davis Comprehensive Cancer Center, lies in the timing of treatment initiation.1 “For a majority of our patients who do not have oncogenic-driven cancers, there is now overwhelming and compelling data for the role of immune checkpoint inhibitors, either with chemotherapy or as monotherapy in the first-line setting,” acknowledged Kelly.2

She noted 2 relevant trials that studied concurrent versus sequential immunotherapy—KEYNOTE-189 (NCT02578680), which examined platinum chemotherapy plus pembrolizumab (Keytruda), and KEYNOTE-407 (NCT02775435), which looked at carboplatin plus paclitaxel or nab-paclitaxel (Abraxane) chemotherapy with or without pembrolizumab.3,4 Combination therapy with pembrolizumab showed superior outcomes over placebo in both trials, with an overall survival (OS) rate at 12 months of 69.2% vs 49.4% (hazard ratio (HR), 0.49; 95% CI, 0.38-0.64; P <.001) in KEYNOTE-189, and a median OS of 15.9 versus 11.3 months (HR for death, 0.64; 95% CI, 0.49-0.85; P <.001) in KEYNOTE-407.

Patients in the placebo arms of KEYNOTE-189 (n = 206) and KEYNOTE-407 (n = 281) crossed over to receive pembrolizumab after disease progression at rates of 41% and 32%, respectively.3,4 Survival data for those patients were inferior to that of those who received concurrent therapy, noted Kelly. “We have learned a lot in...recent years about the association of chemotherapy with immunotherapy and the tumor microenvironment,” said Kelly during her presentation. “The dogma we held, that chemotherapy was 100% immunosuppressive, we now know is false. While [chemotherapy] can be immunosuppressive, it can also be immunostimulatory.”

A third trial, the currently enrolling phase III INSIGNIA study (NCT03793179), aims to specifically address the sequencing debate. INSIGNIA will randomize patients to 1 of 3 arms: (1) frontline pembrolizumab followed by chemotherapy in the second line; (2) frontline pembrolizumab followed by pembrolizumab plus chemotherapy in the second line; or (3) the control arm of induction therapy with combination chemotherapy and pembrolizumab with maintenance pembrolizumab and pemetrexed.5

Finding the Finish Line
For patients with metastatic NSCLC, disease progression and toxicity have been 2 of the commonly used benchmarks to determine cutoff targets for treatment with programmed cell death protein 1(PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. However, the solution for handling those patients who tolerate treatment and do not experience progression is not that obvious, according to de Lima Lopes.6

de Lima Lopes, an associate professor of clinical medicine and associate director for global oncology at Sylvester Comprehensive Cancer Center, University of Miami Health System, noted that cumulative data from the randomized trials that have been conducted so far suggest that those patients who have been treated with PD-1/PD-L1 inhibitors for 1 year should continue treatment until disease progression, unacceptable toxicity, or the 2-year mark is reached.

“What we have seen in the clinical trials is that we have either continued immunotherapy until disease progression or toxicity,” said de Lima Lopes. “In the case of [trials conducted with] pembrolizumab, we have stopped at 2 years.”

In the phase IIIb/IV CheckMate 153
Eighty-seven patients in the discontinuation arm had a response or stable disease at the time of randomization. Forty-three (49%) patients had disease progression after discontinuation, with 34 of those patients (79%) subsequently retreated with nivolumab. The median duration between progression and retreatment was 0.6 months (range, 0.1-4.9) and the median duration of retreatment was 3.8 months (range, 0.1-17.5).

“These [data] answer the question, at least for now, that 1 year [with nivolumab] is probably not enough,” de Lima Lopes said. “Would I stop at 1 year? Only if there is good reason.”

Long-term follow-up data from the KEYNOTE-10 trial (NCT01905657) showed that patients who completed 2 years of pembrolizumab had a durable response with manageable adverse events. “Importantly, among patients who stopped [treatment with pembrolizumab] and then progressed, 14 patients did get a second course of pembrolizumab and of those patients, 43% had a partial response and 36% had stable disease; so, we do salvage some patients if they have been on immunotherapy for 2 years.”

Ultimately, de Lima Lopes acknowledged that the decision to continue or discontinue treatment is made on an individual patient-by-patient basis. “Usually what happens is I will talk to a patient who is approaching 2 years [on immunotherapy] if they still have a continued response or stable disease,” de Lima Lopes said. “One patient may say, ‘You tell me what to do, doc.’ But typically, we have a short discussion with the data I have just shown you and about half of my patients elect to continue [therapy] and half want to stop.”

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**Pneumocystis jirovecii** Pneumonia in Patients With Metastatic Prostate Cancer on Corticosteroids for Malignant Spinal Cord Compression: Two Case Reports and a Guideline Review

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**ABSTRACT:** *Pneumocystis jirovecii*, formerly known as *Pneumocystis carinii*, is an atypical fungal pathogen best known for causing *Pneumocystis jirovecii* pneumonia (PCP). The epidemiology of PCP is changing such that patients without HIV infection now comprise the largest subset of individuals diagnosed with PCP. While those with hematologic malignancies and organ transplants are at greatest risk for non-HIV-related PCP, this review will focus on PCP in patients with solid tumors. They are at risk for PCP due to their chemotherapy regimens and use of steroids in the management of various complications of treatment, and possibly because of the immunosuppressive effect of the cancer itself. In particular, patients with solid tumors being treated for metastatic spinal cord compression are at great risk for PCP. Patients with solid tumors and PCP face greater mortality than those with HIV infection. Multiple reviews have attempted to describe the ideal regimen of corticosteroids for metastatic spinal cord compression, but there is little consensus. We present 2 cases of patients with metastatic spinal cord compression due to prostate cancer undergoing radiation therapy and treatment with corticosteroids. These cases highlight the difficulties in predicting the length of corticosteroid therapy and the dangers that patients face without appropriate prophylaxis. This article will also provide a review of the current guidelines for PCP prophylaxis in patients undergoing treatment for metastatic spinal cord compression. We recommend empiric treatment with trimethoprim-sulfamethoxazole or dapsone in those patients with a sulfa allergy in all patients with solid tumors when any high-dose steroids are started for the treatment of metastatic spinal cord compression. Further research is needed to assess the epidemiology of PCP in patients with solid tumors and additional trials are necessary to refine PCP prophylaxis.

**Introduction**

*Pneumocystis jirovecii*, formerly known as *Pneumocystis carinii*, is an atypical fungal pathogen best known for causing *Pneumocystis jirovecii* pneumonia (PCP), the most common opportunistic infection in people with HIV infection. However, the epidemiology of PCP is changing, such that individuals without HIV infection now comprise the largest subset of patients diagnosed with PCP in resource-rich countries. Among those without HIV infection who are at greatest risk for PCP include patients with hematologic malignancies, hematopoietic stem cell transplant recipients, individuals with solid tumors, and those with various rheumatologic conditions on immunosuppressive therapy. These patients are at high risk for PCP not only due to chemotherapy, but also due to the complications of novel immunotherapies and cancer complications that require the use of high-dose glucocorticoids. There has been plentiful research on the risk of PCP in patients with hematologic malignancies and recipients of stem cell transplants. This review focuses on PCP in patients with solid tumors, an under-examined population.

Individuals with solid tumors are a unique population of patients at risk for PCP due to chemotherapy regimens and the use of high-dose glucocorticoids in treatment. The incidence of PCP in individuals with solid malignancies,
compared with other risk factors, is increasing. Sepkowitz notes that 47% of patients without HIV infection diagnosed with PCP had underlying malignancies, compared with an incidence of 3.6% described in a previous review. Patients with solid tumors, compared with those with hematologic malignancies, face higher rates of death from PCP, have higher rates of mechanical ventilation, and are more often treated in the intensive care unit. It is well documented that patients with PCP without HIV infection have death rates greater than 30% when compared with patients with HIV infection and PCP (who have a mortality rate of about 4%).

Patients with solid tumors receive glucocorticoids for the treatment of complications of metastatic disease including bowel obstructions, spinal cord compression, vasogenic edema in the brain, and bone pain. Metastatic spinal cord compression occurs in 5% to 10% of patients with cancer. Patients with breast, prostate, and lung cancers make up approximately 60% of all metastatic spinal cord compression cases. Treatment of metastatic spinal cord compression is comprised of glucocorticoids followed by radiation therapy or surgical decompression to avoid irreversible neurologic deficits associated with significant morbidity and mortality.

In a recent review, Kumar and colleagues sought to determine the effect of glucocorticoid administration before definitive therapy on patient outcomes and establish the glucocorticoid-dosing regimen associated with the best patient outcomes. Based on a case series totaling 504 patients, glucocorticoid administration resulted in improved patient outcomes if administered at the time of diagnosis. The glucocorticoid regimen that balanced patient outcomes with adverse effects was a 10-mg intravenous bolus of dexamethasone followed by oral administration of 16 mg twice daily for 7 to 14 days. The investigators of this study acknowledged the paucity of high quality data available for glucocorticoid administration for metastatic spinal cord compression, as only 6 studies met criteria for the review. Additionally, the investigators commented extensively on the use of proton pump inhibitors to prevent adverse events related to gastric bleeding and perforation but there was no mention of PCP prophylaxis.

A second review on metastatic spinal cord compression focused specifically on the use of glucocorticoids. This review of seven studies determined that glucocorticoids were beneficial for the treatment of metastatic spinal cord compression, but that individuals undergoing high-dose glucocorticoid therapy had a much higher rate of adverse events including infection. This information is validated in a more recent review article.

Patients receiving prolonged corticosteroids are at increased risk for PCP. In a study of patients without HIV infection diagnosed with PCP, over 90% had undergone therapy with glucocorticoids prior to PCP diagnosis. The average daily steroid dose was 30 mg of prednisone, but 25% of patients had been on 16 mg of prednisone daily. The average length of steroid treatment prior to PCP diagnosis was 12 weeks; however, 25% of patients developed PCP after 8 weeks or less. We present 2 cases that highlight the development of PCP in patients with prostate cancer undergoing treatment for metastatic spinal cord compression.

**Case 1**

A 75-year-old male presented with metastatic hormone-sensitive prostate cancer. He underwent treatment with leuprolide, abiraterone acetate, and prednisone 5 mg twice daily for 1.5 years until his cancer became castrate resistant. He was subsequently started on enzalutamide, and abiraterone acetate and prednisone were discontinued. Six months later, he developed back pain and weakness in his upper extremities. Magnetic resonance imaging (MRI) of the thoracic spine was performed, revealing a metastatic tumor circumferentially involving the spinal cord from thoracic vertebrae 3 to 5. He was started on 8 mg dexamethasone twice daily and referred to radiation oncology for definitive treatment. He was maintained on this steroid regimen throughout his radiation therapy. During the course of radiation therapy, he developed some left eye irritation for which he was prescribed ofloxacin drops. He also developed a dry cough initially thought to be radiation pneumonitis. He was maintained on 8 mg dexamethasone twice daily (>100 mg prednisone equivalent/day) for a total of 49 days, at which point he was tapered to 4 mg twice daily. Three days into the steroid taper, he was febrile (temperature up to 102°F), hypotensive with a new oxygen requirement, and had diarrhea. He was admitted to the hospital and found to have norovirus gastroenteritis. Additionally, a direct fluorescent antibody test was positive for *Pneumocystis*. 

**Figure 1** Case 1: Coronal and axial computed tomography scans of the chest after administration of contrast demonstrate bilateral ground-glass opacities with associated septal thickening, the absence of pleural effusion, and no hilar adenopathy.
jirovecii. He also had elevated lactate dehydrogenase and (1,3)-beta-D glucan levels. A computed tomography (CT) scan of the chest demonstrated diffuse bilateral ground-glass opacities (Figure 1). Despite maximum medical treatment, the patient’s respiratory status continued to decline and he was ultimately transitioned to comfort care, succumbing to PCP and its subsequent complications. During hospitalization, it was discovered that he had herpes zoster virus keratitis in his left eye; thus, his cough and eye irritation were in retrospect the first signs of his compromised immune status.

Case 2
A 76-year-old male with a history of prostate cancer treated with radical prostatectomy presented years later with dysphagia, hoarseness, facial droop, and tongue deviation. Brain MRI revealed metastatic disease with a large skull base mass extending from the left occipital bone to the left hypoglossal canal and jugular foramen. The mass also involved cervical vertebrae 1. Given his neurologic symptoms, the patient was started on 8 mg dexamethasone twice daily and underwent evaluation by radiation oncology for palliative radiation. He was also started on bicalutamide and leuprolide for metastatic prostate cancer. At the time of discharge, he was tapered from 8 mg dexamethasone twice daily to 4 mg dexamethasone twice daily and received follow-up in the outpatient setting with radiation therapy for the metastases in the base of his skull. During this time, he was maintained on dexamethasone 4 mg twice daily (>50 mg prednisone equivalent/day) for a total of 34 days until radiation therapy was complete. While tapering dexamethasone at a daily dose of 2 mg, the patient experienced sudden onset lethargy and weakness. On arrival to the emergency department, he was found to be in acute hypoxic respiratory failure and was admitted to the medical intensive care unit for workup. A CT scan of the chest revealed diffuse bilateral ground-glass opacities and multiple sub-segmental pulmonary emboli (Figure 2). He was initially treated with therapeutic anticoagulation; however, given the lack of improvement in his respiratory status, he underwent bronchoscopy with bronchoalveolar lavage (BAL). The BAL fluid tested positive for Pneumocystis jiroveci. The patient was treated with high-dose prednisone and pentamidine and was discharged with improvement in his respiratory status.

Discussion
Both cases demonstrate the consequence of patients developing PCP after receiving high-dose dexamethasone and radiation therapy for metastatic spinal cord compression. While the second patient recovered from PCP, the first passed away from this preventable infection. These cases highlight 2 issues in the management of patients with solid tumors and PCP. The first is the need for clinicians to maintain a heightened awareness of the possibility of PCP in patients receiving high-dose, prolonged steroids. The second is the need to routinely assess whether PCP prophylaxis is warranted in a patient’s clinical course, medications, and imaging should be done. Imaging can often be nonspecific with perihilar and mid-to-apical predominant ground-glass opacities on radiography and CT. When determining whether a pulmonary infiltrate is PCP versus radiation pneumonitis, it is important to recall that radiation pneumonitis is a more geographic finding with confluent ground-glass opacities that are confined to the path of radiation. For PCP, pneumatoceles without pleural effusion and lymphadenopathy can be seen in 30% of cases.

Given the complexity of their disease, patients with cancer are often managed by multiple specialties. Multiple organizations have commented on appropriate glucocorticoid therapy for metastatic spinal cord compression and PCP prophylaxis, as listed in Table 1. The American Society of Clinical Oncology (ASCO), Infectious Diseases Society of America, and American Thoracic Society are the only professional organizations that provide clear guidelines on PCP prophylaxis for patients with cancer. All groups recommend prophylaxis for these patients when they will be receiving prolonged high-dose steroids (>20 mg prednisone equivalents for 1 month or more), based on previous epidemiologic research. Notably, ASCO recommends prophylaxis when an patient’s risk of PCP is greater than 3.5%. Predicting the risk of PCP in a patient...
TABLE 1  Current Guidelines From Major Specialty Groups on Glucocorticoids and PCP Prophylaxis in Patients With Cancer

<table>
<thead>
<tr>
<th>Organization</th>
<th>Date of Guideline</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Radiology</td>
<td>July 2015</td>
<td>For all 5 clinical variants, prompt steroid therapy is recommended; no comment is provided on PCP prophylaxis.32</td>
</tr>
<tr>
<td>American Society for Radiation Oncology</td>
<td>2018</td>
<td>Does not comment on the use of steroids for bone metastases.23</td>
</tr>
<tr>
<td>American Society of Clinical Oncology and Infectious Diseases Society of America</td>
<td>September 2018</td>
<td>PCP prophylaxis is recommended for patients receiving chemotherapy regimens that are associated with a &gt;3.5% risk for pneumonia as a result of this organism (eg, those with ≥20 mg prednisone equivalents daily for ≥1 month or on the basis of purine analog usage).29</td>
</tr>
<tr>
<td>American Thoracic Society</td>
<td>2006</td>
<td>PCP prophylaxis is recommended with TMP-SMX, but no comment is given regarding which patients with solid organ malignancies should receive it.23</td>
</tr>
<tr>
<td>American Thoracic Society</td>
<td>May 2010</td>
<td>Consider prophylaxis with TMP-SMX when prednisone dose &gt;20 mg/day for &gt;1 month, especially if the patient has associated T-cell defects, or is receiving other cytotoxic drugs or anti-TNF agents. Some experts recommend monitoring CD4 counts in patients without AIDS, again using the threshold of 200 cells/microliter for determining the need for prophylaxis.26</td>
</tr>
<tr>
<td>Congress of Neurological Surgeons</td>
<td>2005</td>
<td>Recommends use of steroid therapy in patients with metastatic spinal cord compression but does not provide any recommendations regarding PCP prophylaxis.22</td>
</tr>
</tbody>
</table>

PCP indicates Pneumocystis jirovecii pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole; TNF, tumor necrosis factor.

with cancer may prove difficult, thus discouraging providers from prescribing prophylaxis if they are unable to quantify the risk. Additionally, it can be difficult to predict exactly how long a patient will be receiving glucocorticoid therapy.31 One issue with the management of metastatic spinal cord compression is that patients are often managed by multiple specialties and the handoff between services could represent a time when treatment duration is inadvertently prolonged.

Given the lack of rigorous data concerning PCP prophylaxis in patients with solid malignancies undergoing treatment for metastatic spinal cord compression, we recommend starting empiric prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) to prevent a possibly life-threatening infection (Table 2). As mentioned previously, among patients undergoing treatment for PCP, those with solid malignancies often have worse outcomes in terms of mortality compared with those with HIV infection.13,14 For this reason, prophylaxis initiation at the onset of steroid therapy is of the utmost importance. There are few risks in starting PCP prophylaxis at the time of steroid initiation. TMP-SMX is fairly well tolerated and is very effective in preventing PCP. The reported rate of discontinuation of TMP-SMX when used for PCP prophylaxis is about 3%. Most patients with cancer who require high-dose steroids will likely be on treatment for longer than 1 month. Therefore, it may be in the patient’s best interest to initiate PCP prophylaxis, similar to gastrointestinal prophylaxis, at the start of corticosteroid treatment. The biggest concern with starting TMP-SMX in patients with solid tumors is an increased risk of myelosuppression due to the medication. However, if the risk of myelosuppression is high, it could be minimized with the use of atovaquone instead of TMP-SMX.

The 2 cases above highlight the difficulty in predicting a priori the duration of steroid therapy when treating patients with solid tumors and with malignant spinal cord compression. In case 1, the patient was continued on high-dose steroids longer than expected due to suspicion of radiation-induced pneumonitis. In case 2, the patient underwent a longer course of radiation than initially expected. Interestingly, neither of these 2 patients had risk factors for PCP other than their steroid use. Since research has demonstrated that metastatic disease in itself can be a risk factor for immunosuppression,28,30 this raises the question of whether metastatic disease is also a risk factor itself for immunosuppression with regards to PCP.

Future research specifically on the epidemiology of PCP in patients with solid malignancies would be useful to characterize which tumor types warrant prophylaxis. This research would also provide insight into what biomarkers could be used to predict which patients are at risk and need prophylaxis. For example, CD4 count is used in patients with HIV infection to guide PCP prophylaxis. Some research has been done concerning the use of CD4 count to guide PCP prophylaxis in patients without HIV infection. In these patients, there is an association between CD4 counts less than 300 cells/microliter and the incidence of PCP.11

The exact duration of PCP prophylaxis remains an area of research. The National Comprehensive Cancer Network...
immunosuppressive chemotherapies, of malignant disease manifestations, cord compression. Given the complexity use due to treatment of malignant spinal PCP in patients with prolonged steroid of symptoms is a concern.28 Slower tapering may be recommended if days until a physiologic dose is reached. reductions by 2.5 to 5 mg every 3 to 7 Typical recommendations suggest dose and immune-mediated complications of contemporary immunotherapies that all require long-term glucocorticoid use, the development of PCP actually affects a much broader population of patients with cancer. Strategies such as the routine use of PCP prophylaxis at the initiation of high-dose steroids, close monitoring for PCP symptoms, and early identification of PCP in patients receiving high-dose or prolonged steroids are paramount.

Conclusions PCP continues to be a pervasive opportunistic infection that affects patients with solid tumors. This review provides a detailed account of the varied reasons why patients with solid tumors and metastatic spinal cord compression are at increased risk of PCP and provides a thorough examination of the literature available on ideal treatment regimens. Additionally, through 2 case reports, the diagnostic evaluation of patients with solid tumors is examined. Finally, the recommendations for PCP prophylaxis from multiple subspecialty organizations are examined. We recommend that all patients with solid tumors being initiated on high-dose steroids for any reason warrant PCP prophylaxis.■

**TABLE 2 Preferred Regimens for PCP Prophylaxis**

<table>
<thead>
<tr>
<th>First-line PCP prophylaxis regimen</th>
<th>Second-line PCP prophylaxis for patients with sulfa allergies, severe renal impairment, history of systemic lupus erythematosus, or concern for myelosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trimethoprim-sulfamethoxazole (160 mg/800 mg) orally 3 times weekly</td>
<td>• Dapsone 50 mg orally twice daily or 100 mg orally once daily</td>
</tr>
<tr>
<td>• Trimethoprim-sulfamethoxazole (80 mg/400 mg) orally once daily</td>
<td>• Atovaquone 1500 mg orally once daily</td>
</tr>
<tr>
<td></td>
<td>• Pentamidine 300 mg inhaled monthly</td>
</tr>
<tr>
<td></td>
<td>• Pentamidine injection, 4 mg/kg once daily for 21 days</td>
</tr>
</tbody>
</table>

PCP indicates *Pneumocystis jiroveci* pneumonia.

guidelines recommend continuing PCP prophylaxis until at least the completion of steroid therapy. There are various recommendations for tapering steroid therapy. Steroid taper regimens are generally based upon dose and duration of corticosteroid treatment. Concerns for steroid withdrawal are related to suppression of the hypothalamic–pituitary–adrenal axis, which can result in symptoms of adrenal insufficiency during steroid tapering. In addition to symptoms of adrenal insufficiency, tapering steroids could also result in the potential for disease flare-exacerbating symptoms of bowel obstruction and brain metastases, among others. Typical recommendations suggest dose reductions by 2.5 to 5 mg every 3 to 7 days until a physiologic dose is reached. Slower tapering may be recommended if the risk of disease relapse or recurrence of symptoms is a concern.28

In this review, we presented 2 cases of PCP in patients with prolonged steroid use due to treatment of malignant spinal cord compression. Given the complexity of malignant disease manifestations, immunsuppressive chemotherapies, and immune-mediated complications of contemporary immunotherapies that all require long-term glucocorticoid use, the development of PCP actually affects a much broader population of patients with cancer. Strategies such as the routine use of PCP prophylaxis at the initiation of high-dose steroids, close monitoring for PCP symptoms, and early identification of PCP in patients receiving high-dose or prolonged steroids are paramount.

For full reference list, visit cancernetwork.com/PCP-Pneumonia

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CONTINUING MEDICAL EDUCATION

RECOGNIZING AND TREATING VTE IN PATIENTS WITH CANCER
Bridging Guideline-Based Recommendations with Real-World Evidence

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Recognize the prevalence, morbidity, and mortality rates, as well as risk factors, associated with development of VTE in patients with cancer
- Apply recent evidence-based guideline recommendations for the prevention and treatment of cancer-associated VTE into clinical practice
- Identify strategies for the prevention and treatment of VTE in patients with cancer, including the reduction of risk of recurrence after initial treatment
- Implement individualized anticoagulation regimens for prevention and treatment of VTE in patients with cancer that are based on the unique needs and characteristics of each patient

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Recognizing and Treating Venous Thromboembolism in Patients With Cancer

As advancements in cancer treatments continue to improve outcomes and survival times for patients, the risks of disease- or treatment-related complications, such as venous thromboembolism (VTE), increase as patients live longer on chronic therapy. VTE, comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is a life-threatening condition associated with active cancer. \(^1\) The annual incidence of VTE in patients with cancer ranges from 0.5% to 20%, and it is the second leading cause of death in this population. \(^2,3\) In addition, patients with cancer who experience VTE have substantially higher inpatient mortality than those without a VTE, and a greater risk of death in the presence of metastatic disease than patients with localized disease. \(^4\) In an investigational study evaluating incidence of VTE and patient outcomes, investigators reported that the relative risk of developing symptomatic VTE was 20 times greater in patients with metastatic melanoma, 9 times higher in patients with bladder cancer, and 5- to 6-fold higher in those with metastatic breast or uterine cancers. \(^1\) In general, patients with cancer also find themselves at greater risk of recurrent VTE and bleeding episodes. \(^4\)

Although incidence in the general population is predicted to remain unchanged, the incidence in patients with cancer is predicted to increase in the future due in part to patients having more treatments, hospitalizations, and extensive disease. \(^4\) Table 1 below describes individual, cancer-specific, and treatment-related risk factors associated with VTE occurrence. \(^4,6,7\) Surgery, common in abdominal and thoracic cancers, may play a role in the increased incidence of VTE reported in this group. Additionally, the use of central venous catheters (CVCs), novel anticancer treatments, and antiangiogenic drugs augments risk in patients with later-stage disease. These patients are at an even higher risk of VTE during times of hospitalization and while actively receiving cancer treatment. \(^4\)

Although the relationship between cancer and subsequent VTE episodes has been extensively established, studies have also demonstrated a possible correlation with unprovoked VTE and the subsequent development of cancer. In a prospective study conducted by Prandoni et al, investigators evaluated and followed for 2 years patients with a documented, symptomatic DVT. \(^8\) Patients (N = 250) were stratified by the type of VTE episode experienced: idiopathic thrombosis, secondary thrombosis, or recurrent idiopathic thrombosis. The results demonstrated a statistically significant association of VTE with subsequent overt cancer, with a cumulative frequency of 17.1% in patients who had a recurrent VTE within 1 year of patients experiencing VTE.

### TABLE 1 Risk Factors Associated With VTE Occurrence.\(^4,6,7\)

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th>Cancer-Related Factors</th>
<th>Treatment-Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Site of origin: pancreas, uterus, lung, stomach, kidney, primary brain tumor</td>
<td>Major surgery: pelvis and abdomen</td>
</tr>
<tr>
<td>Comorbid conditions: renal failure, respiratory failure, heart disease, obesity, infection, hypertension</td>
<td>Time since diagnosis (first 3 to 6 months)</td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>Previous episodes of VTE</td>
<td>Stage: advanced/metastatic</td>
<td>Immune modulatory treatment</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Histology: NSCLC: adenocarcinoma &gt; SCC; high-grade tumors &gt; low-grade tumors</td>
<td>Antiangiogenic agents (VEGF tyrosine kinase inhibitors)</td>
</tr>
<tr>
<td>Possibly: gender, ethnicity</td>
<td></td>
<td>Cisplatin-containing regimens</td>
</tr>
</tbody>
</table>

NSCLC indicates non–small cell lung cancer; SCC, squamous cell carcinoma; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism.
with documented idiopathic DVT, 5 of 153 were found to have overt cancer at the time of VTE diagnosis, and 11 of 145 were diagnosed at the time of follow-up (mean, 79.8 weeks). A total of 35 patients experienced a recurrent VTE, 6 of whom subsequently developed overt cancer. In a meta-analysis conducted by Van Es et al, 1 in 20 patients had been diagnosed with cancer within 12 months of VTE diagnosis, further supporting the association between primary VTE episodes and subsequent cancer development. The study authors suggested many patients with unprovoked VTEs may already have cancer, just very early stages and undetectable at the time of diagnosis of VTE.

Despite increased awareness of the incidence and severity of VTEs among patients with cancer, specific unmet needs for treating this complication remain. In a gap analysis based on interviews with 44 experts in the field and review of guidelines and seminal articles on the topic, 3 main areas of unmet needs were identified: the need for improved VTE risk-assessment tools for primary prophylaxis; the need for broader choice and longer duration of therapeutic anticoagulation; and the need to understand the role of direct oral anticoagulants (DOACs) in VTE prophylaxis and treatment.

These 3 areas of focus have attracted much attention, and multiple ongoing studies seek to provide data to fill such critical gaps.

### Assessing VTE Risk in Patients With Cancer

In order to assess the risk of VTE in patients with cancer, it is important to understand the underlying mechanisms that cause such an episode. According to the Virchow’s triad, 3 essential mechanistic categories leading to VTE exist: stasis of blood flow; vascular injury; and hypercoagulability. Stasis, or abnormal blood flow, can be caused by direct compression from the tumor or cancer cells or from hyperviscosity. Vascular injury may occur due to tumor invasion, the presence of cytokines, or external factors (eg, CVC and choice of chemotherapy treatment). Hypercoagulability is caused by direct or indirect activation of plasmatic coagulation and platelets, likely via several mechanisms. Direct activation includes the expression of mediators, such as tissue factor, podoplanin, and protein disulfide isomerase on cancer cells. Indirect mechanisms of hypercoagulability include the release of cancer-derived factors that stimulate neutrophils to release neutrophil extracellular traps, which exacerbates clot formation by activating and entrapping platelets.

The most popular predictive scoring system used for VTE risk is the Khorana score (Table 2). This tool considers an array of patient-specific and cancer-specific factors, scored from 1 to 7 points, to classify a patient’s risk for developing a VTE. Patients with a score of 0 are categorized as low risk; those with a score of 1 to 2 as intermediate risk; and those scoring ≥3 as high risk. Stomach and pancreas are categorized as very high risk regarding site of cancer; lung, gynecologic, bladder, and testicular sites are considered high risk. This risk-assessment model was designed to be used on patients receiving chemotherapy in the ambulatory setting. Currently, the Khorana scoring system is being used as a stratification factor for ambulatory patients with cancer in primary thromboprophylaxis studies.

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk</td>
<td>2</td>
</tr>
<tr>
<td>High risk</td>
<td>1</td>
</tr>
<tr>
<td>Pretreatment platelet count ≥350 x 10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL or use of hematopoietic growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Pretreatment leukocyte count &gt;11 x 10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>BMI ≥35 kg/m^2</td>
<td>1</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

Additional scoring systems include the Ottawa scoring for recurrent VTE, the Vienna score and COMPASS-CAT for prediction of first event, and the Wells criteria to predict an acute event. The Ottawa score evaluates type of cancer, disease stage, gender, and history of thrombosis. It aims to predict the risk of VTE recurrence for the first 6 months of treatment with anticoagulants. Unfortunately, data from this scoring system yield modest accuracy and low sensitivity, and its use has not been standardized.

The Vienna scoring system uses the predictors from the Khorana score and two additional biomarkers: sP-selectin and D-dimer. In the Vienna Cancer and Thrombosis study (CATS), prediction scores performed modestly in predicting VTE in patients with cancer, although some utility was found in differentiating between high-risk and low-risk patients. Further improvements and additional studies are required before consideration for introduction into clinical practice.
having an acute DVT. This scoring technique is yet to be validated in observational studies.

The Wells criteria assess the risk of a symptomatic patient having an acute DVT. This tool is not to be used as a diagnostic criterion, but as an algorithm to decide next diagnostic steps, whether that be determination of D-dimer levels or an ultrasound doppler. Based on the criteria listed in Table 3, a score of <1 is indicative of low probability; a score of 1 to 2, moderate probability; and >2, high probability of a DVT as assessed by imaging ultrasound. This scoring system has additive predictive value when combined with D-dimer. A low Wells score and a negative D-dimer allow patients to forgo additional screening. The Wells group has also shown that clinical probability can be combined with D-dimer testing in the diagnostic strategy for suspected recurrent DVT. D-dimer as a predictive value, however, has shortcomings; its value appears to be greater in younger patients, and it is frequently elevated at baseline in patients with cancer. This scoring method has also been tested in PE and is currently used as a diagnostic guide in emergency care settings. Wells criteria do not account for important PE-related factors, such as cigarette smoking, chronic obstructive pulmonary disease, and hypertension.

Predictors for bleeding are different from predictors for VTE. In a study conducted by Khorana et al, patients with 6 tumors known as high risk for VTE were evaluated: lung, pancreas, gastrointestinal (GI) system, colorectal, bladder, and ovarian. Bladder cancer (OR, 4.09; 95% CI, 3.58-4.68; P <.0001) and gastric cancer (OR, 2.16; 95% CI, 1.77-2.65; P <.0001) were at highest risk for bleeding. Cetuximab, an agent used frequently in head and neck cancer and colorectal cancer (OR, 1.47; 95% CI, 1.15-1.87; P <.05), and erythropoietin (OR, 1.60; 95% CI, 1.48-1.74; P <.0001) were also shown to be significantly increased factors for VTE occurrence.

Guideline-Based Approaches to Managing VTE in Patients With Cancer
The treatment and prevention of VTE in cancer are complex. Treatment of VTE varies depending on cancer type, stage, and treatment selection, as well as a variety of host factors. Conversations between patients and providers are necessary to establish treatment goals, patient administration preference, treatment tolerance, and cost restrictions, if any.

Treatment Management of Bleeding and VTE Recurrence
There have been multiple advances in anticoagulation treatment in the form of novel agents available with alternative mechanisms of action; however, implementation of these agents may not be as clear in patients with active cancer due to the lack of available data for this population. The current standard of care for patients with VTE and active cancer has been low molecular weight heparin (LMWH), with drugs such as dalteparin and enoxaparin. This consensus was derived from data reported in the CLOT study, which compared the safety and efficacy of dalteparin with the vitamin K antagonists (VKA), warfarin or acenocoumarol. A total of 676 patients with active cancer were randomized to receive dalteparin 200 IU/kg subcutaneous (SQ) daily for a month, followed by 150 IU/kg SQ daily for 5 months or a VKA with a target international normalized ratio of 2.5 for a total 6 months, with an initial 5 to 7 days of bridging with dalteparin. Primary outcome measures included recurrent VTE, and secondary outcome measures consisted of any bleeding event, major bleeding, and death. Recurrent VTEs were reported in 7.0% of patients in the dalteparin group compared with 15% of patients randomized to a VKA (HR, 0.48; 95% CI, 0.30-0.77; P = .002). There were no differences in the rates of major bleeding (6% vs 5%; P = .27) or death (39% vs 41%; P = .53) between the dalteparin and VKA groups, respectively. In a post hoc analysis that stratified patients from the CLOT trial into high-risk (defined as having metastatic disease or recent exposure to chemotherapy) and low-risk groups, patients in the high-risk group realized a clinical benefit with LMWH over a VKA for the prevention of recurrent VTE without increasing the risk of bleeding, whereas patients in the low-risk group experienced no difference in benefit between LMWH and a VKA.

The non-vitamin K antagonist DOACs have gained much attention due to ease of administration compared with LMWH and lack of close monitoring required with warfarin. DOACs include: factor
### TABLE 4  Phase III Trials for Treatment and Prevention of Cancer-Related VTEs.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total Patients (N)</th>
<th>Intervention</th>
<th>Population</th>
<th>Major Bleeding (%)</th>
<th>Recurrent VTE (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment of VTE in Patients With Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CLOT20</td>
<td>676</td>
<td>Dalteparin vs VKA for 6 months</td>
<td>Active cancer</td>
<td>6% vs 5%</td>
<td>7% vs 15%</td>
<td>39% vs 41%</td>
</tr>
<tr>
<td>RE-COVER I &amp; II (NCT00291330 &amp; NCT00680186)26</td>
<td>2568</td>
<td>Dabigatran vs warfarin for 6 months</td>
<td>221 with active cancer</td>
<td>3.8% vs 3.0%</td>
<td>3.5% vs 4.7%</td>
<td>NR</td>
</tr>
<tr>
<td>EINSTEIN-DVT/PE (NCT00440193 &amp; NCT00439777)25</td>
<td>655</td>
<td>Rivaroxaban vs enoxaparin /warfarin for 6 months</td>
<td>430 with active cancer</td>
<td>2% vs 5%</td>
<td>5% vs 7%</td>
<td>NR</td>
</tr>
<tr>
<td>AMPLIFY (NCT00643201)27</td>
<td>5365</td>
<td>Apixaban vs enoxaparin/ warfarin or 6 months</td>
<td>169 (3.1%) with active cancer</td>
<td>0.5% vs 2.8%</td>
<td>1.1% vs 6.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Hokusai (NCT02073682)30</td>
<td>1046</td>
<td>LMWH followed by edoxaban vs dalteparin for 12 months</td>
<td>Active cancer</td>
<td>6.9% vs 4.0%</td>
<td>12.8%, 6.9% vs 11.3%</td>
<td>39.5% vs 36.6%</td>
</tr>
<tr>
<td>SELECT-D (ISRCTN86712308)31</td>
<td>406</td>
<td>Rivaroxaban vs dalteparin for 6 months</td>
<td>Active cancer; exclusions: esophageal and gastroesophageal cancer</td>
<td>6% vs 4%</td>
<td>4% vs 11%</td>
<td>6 months OS: 75% vs 70%</td>
</tr>
<tr>
<td>ADAM VTE (NCT02585713)32</td>
<td>300</td>
<td>Apixaban vs dalteparin for 6 months</td>
<td>Active cancer; included brain metastases</td>
<td>0% vs 1.4%</td>
<td>0.7% vs 6.3%</td>
<td>16% vs 11%</td>
</tr>
<tr>
<td>CANVAS (NCT02744092)32</td>
<td>940 (estimated)</td>
<td>Physician’s choice: rivaroxaban, apixaban, edoxaban, dabigatran, or LMWH VKA for 6 months</td>
<td>Active cancer; exclusions: acute leukemia, stem cell recipients, or planned recipient</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Secondary Prophylaxis to Prevent Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CARAVAGGIO (NCT03045406)34</td>
<td>1168</td>
<td>Apixaban vs dalteparin for 6 months</td>
<td>Active cancer</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>CASTA-DIVA (NCT02746185)35</td>
<td>160</td>
<td>Rivaroxaban vs dalteparin for 3 months</td>
<td>Active cancer</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>CONKO-011 (NCT02583191)36</td>
<td>450</td>
<td>Rivaroxaban vs LMWH for 6 months</td>
<td>Active cancer</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>COSIMO (NCT02742623)37</td>
<td>528</td>
<td>Rivaroxaban for 6 months</td>
<td>Active cancer</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NCT0324012039</td>
<td>99 (estimated)</td>
<td>Dabigatran vs tinzaparin for 24 months</td>
<td>Active cancer</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; LMWH, low molecular weight heparin; NR, not reported; OS, overall survival; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.
**PE with rivaroxaban**

The treatment of DVT and PE with rivaroxaban 15 mg orally twice daily for 21 days, followed by 20 mg orally daily thereafter, and enoxaparin bridged to warfarin therapy. A subgroup analysis stratified patients by active cancer diagnosis, a history of cancer, and no cancer. For the 430 patients with active cancer enrolled in this study, recurrent episodes of VTE occurred in 5% of patients treated with rivaroxaban and in 7% of patients treated with LMWH and warfarin. Similar rates of major bleeding were observed in the rivaroxaban arm and the enoxaparin followed by warfarin arm (2% vs 5%). Rivaroxaban was found to be noninferior to warfarin in both trials, prompting FDA approval of the drug for the treatment of both DVT and PE. Additionally, the EINSTEIN EXT and EINSTEIN CHOICE trials provided enough evidence for the approval of two doses of rivaroxaban (10 mg daily and 20 mg daily) for extended secondary prevention.

The phase 3 AMPLIFY trial (NCT00643201) reported data reflecting noninferiority of apixaban compared with enoxaparin bridged to warfarin therapy for the treatment of acute VTE. In a subgroup analysis of this population, 169 patients (3.1%) had active cancer at baseline, and 365 patients (6.8%) had a previous history of cancer with no active disease at the time of evaluation. Recurrent VTE occurred in 3.7% and 6.4% of patients who received apixaban and enoxaparin followed by warfarin therapy, respectively. Major bleeding occurred less in the apixaban arm (2.3%) compared with the enoxaparin-containing arm (5.0%). Larger studies evaluating treatment of VTE with apixaban in the presence of active cancer are currently underway.

The phase 3 Hokusai VTE Cancer trial (NCT02073682) was a noninferiority study designed to compare the efficacy and safety of oral edoxaban versus SQ dalteparin for at least 6 months of treatment. Patients were randomized to receive at least 5 days of treatment with LMWH, followed by edoxaban 60 mg daily (30 mg for patients with creatinine clearance [CrCl] 30–50 mL/min, body weight <60 kg, or concomitant treatment with P-glycoprotein inhibitors) or dalteparin 200 IU/kg SQ once daily for 30 days and then followed by 150 IU/kg daily thereafter. Patients with basal-skin cancer and squamous-cell skin cancer were excluded from this trial. With a total of 1050 patients, 67 of 522 (12.8%) in the edoxaban group had a recurrent VTE, compared with 71 of 524 (13.5%) in the dalteparin group. Major bleeding was significantly increased in the edoxaban group (6.9% vs 4%; HR, 1.77; 95% CI, 1.01–5.6; P = .04). This increase occurred mostly in patients with GI cancer: 12.7% who received edoxaban experienced major bleeding, compared with 7.9% in patients receiving dalteparin (HR, 0.43; 95% CI, 0.19–0.99). Risk of clinically relevant non-major bleeding was higher for those receiving rivaroxaban compared with patients receiving dalteparin (6% vs 4%; HR, 1.83; 95% CI, 0.68–4.96). Patients with esophageal or gastroesophageal cancer were excluded from enrollment after an interim safety analysis revealed a non-significant but modest increase in major bleeding.

The phase 3 ADAM VTE trial (NCT02585713) assessed whether apixaban is associated with lower rates of bleeding versus dalteparin in patients with active cancer and acute VTE. A total of 300 patients were randomized 1:1 to receive either apixaban 10 mg orally twice daily for 7 days followed by 5 mg twice daily or dalteparin 200 IU/kg SQ daily for 1 month followed by 150 IU/kg daily for months 2 to 6. Median treatment duration was 12 months. The primary endpoint was the occurrence of major bleeding and a composite of minor bleeding and non-major bleeding. A total of 152 patients were enrolled, and 147 were evaluable. The primary endpoint occurred in 26 patients (17%) in the apixaban group and 32 patients (21%) in the dalteparin group (HR, 0.73; 95% CI, 0.46–1.16; P = .16). The occurrence of major bleeding was lower in the apixaban group (6% vs 11%; HR, 0.52; 95% CI, 0.23–1.16; P = .10).

**CME**

Xa inhibitors rivaroxaban, edoxaban, and apixaban; and the direct thrombin inhibitor (factor IIa) dabigatran. The first approval of a DOAC was dabigatran in 2010, followed shortly thereafter by rivaroxaban in 2011. The first time Xa inhibitors were approved; however, primary studies in VTE treatment did not include large numbers of patients with active cancer receiving chemotherapy. Several phase 3 trials are listed in Table 4 and described below.

The phase 3 RE-COVER I and II trials (NCT00291330 and NCT00680186) compared the efficacy and safety of dabigatran and warfarin in patients with acute VTE. Recurrent VTE was documented in 2.3% of patients in the dabigatran group and 2.2% of patients receiving warfarin. Major, clinically relevant nonmajor, and any bleeding were observed less often in the dabigatran group compared with patients in the warfarin group. Results for the subgroup of 50 patients (3.9%) with documented active cancer were consistent with data from participants without cancer.

The open-label, phase 3 EINSTEIN-DVT/PE trials (NCT00440193 and NCT00439777) evaluated the treatment of DVT and PE with rivaroxaban 15 mg...
duration was 5.78 months for patients on apixaban and 5.65 months for patients on dalteparin. No patients in the apixaban arm (n = 145) and 2 patients in the dalteparin arm (n = 142; 1.4%) experienced bleeding at 6 months (95% CI, not estimable; \( P = .138 \)). Recurrent VTE occurred in 1 patient in the apixaban group and 9 patients in the dalteparin group (HR, 0.099; 95% CI, 0.013-0.780; \( P = .0281 \)). This study met its primary outcome of reduced major bleeding; however, major bleeding was much lower than expected in both treatment arms. This may be due to the study population’s lower prevalence of GI-related cancers, although they were not explicitly excluded.

The interventional CANVAS trial (NCT02744092) is designed to compare DOACs with LMWH alone or LMWH with transition to warfarin for 6 months of therapy in patients with cancer. This study will evaluate rivaroxaban, apixaban, edoxaban, and dabigatran; VKA warfarin; and LMWHs dalteparin and enoxaparin. The primary outcome measure is VTE recurrence, and secondary outcome measures include major bleeding, participant-reported health-related quality of life, and burden of anticoagulation treatment, as well as mortality. This trial is actively recruiting participants, with an estimated end date of August 2020.

There are a number of ongoing trials with apixaban, rivaroxaban, and dabigatran for treatment of cancer-related VTE. The phase 3 CARAVAG-GIO study (NCT03045406) is a prospective, randomized trial comparing apixaban with dalteparin in patients with cancer and an active VTE. A total of 1168 patients, stratified by active cancer versus cancer history and symptomatic versus incidental VTE, will receive apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily, or dalteparin 200 IU/kg SQ daily for 1 month, followed by 150 IU/kg SQ daily. Treatment duration is 6 months. Patients with basal-cell skin carcinoma, squamous-cell carcinoma, primary brain tumors, intracerebral metastasis, or acute leukemia are excluded from this study. Primary outcome measures include recurrent VTE and major bleeding. Secondary endpoints include symptomatic recurrent VTE, quality of life, clinically relevant nonmajor bleeding, and treatment discontinuation.

The phase 3 CASTA-DIVA trial (NCT02746185) is a non-inferiority trial to assess the efficacy of rivaroxaban with dalteparin for a treatment duration of 3 months in patients with active cancer and a newly diagnosed acute VTE. A total of 450 participants will be randomized to receive either rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily for 3 months compared with LMWH options, enoxaparin 1 mg/kg SQ twice daily, tinzaparin 175 IU/kg SQ once daily, or dalteparin 200 IU/kg SQ once daily. Primary outcome measures include patient-reported treatment satisfaction. Secondary outcome measures include VTE rates in a 3-month period, compliance, overall mortality at 3 and 6 months, and rate of clinically relevant bleeding.

The observational COSIMO study (NCT02742623) is designed to evaluate patient-reported outcomes while receiving rivaroxaban with a duration of follow-up for 6 months. A total of 505 patients currently have been enrolled to assess primary outcome treatment satisfaction burden score with the Anti-Clot treatment scale (ACTS). Secondary outcome measures include patient-reported quality of life, changes of ACTS scores over time, and type and number of bleeding events. Preliminary published results from the 2019 American Society of Hematology annual meeting demonstrated similar rates of VTE incidence and bleeding episodes compared with other DOACs studied in patients with active cancer.

An ongoing interventional trial (NCT03240120) is a single-arm study evaluating the effectiveness and safety of dabigatran for the treatment of malignancy-associated VTE. The primary endpoint is number of patients with symptomatic VTE, and secondary outcome measures will include mortality, major bleeding, and clinically relevant non-major bleeding. This study is currently recruiting participants.

Several guidelines are available to help support informed treatment decisions. American Society of Clinical Oncology (ASCO) guidelines list LMWH, unfractionated heparin (UFH), fondaparinux, or rivaroxaban as first-line options for treatment of VTE in patients with cancer. LMWH is preferred over UFH if parenteral anticoagulation is chosen, unless there is significant renal impairment. More recently, edoxaban was added to the list of recommended options, with caution in those who are at risk of bleeding, such as patients with GI or genitourinary cancer.
once daily for 2 to 6 months; and combination therapy with enoxaparin 1 mg/kg SQ every 12 hours or dalteparin 20 units/kg SC daily and edoxaban 60 mg orally daily beginning after completion of at least 5 days of parenteral anticoagulation. Treatment should be continued for at least 6 months. The International Society on Thrombosis and Haemostasis (ISTH) guideline statement recommends individualized treatment regimens determined by the patient and oncology team. These guidelines suggest specific DOACs (those that have data on cancer patients) for patients with an acute VTE, a low risk for bleeding, and no drug-drug interactions with their current chemotherapy regimen; and LMWH for cancer patients with acute VTE and at high risk for bleeding, which may include, but are not limited to, patients with GI and genitourinary cancers, nephrectomy, and GI abnormalities, such as colitis, gastritis, and esophagitis. The International Initiative on Thrombosis and Cancer (ITAC) guidelines list the following as grade 1b regimens: 1) LMWH for those with CrCl ≥30 mL/min; and 2) rivaroxaban and edoxaban for patients with low risk of bleeding and CrCl ≥30 mL/min. UFH is recommended when LMWH or oral anticoagulants are contraindicated.

Although treatment regimens have been steadily examined to determine best outcomes, specifics on duration of treatment of VTE in patients with cancer remains unanswered. Most studies examining VTE have a treatment duration of 3 to 6 months, and there are not much data beyond 6 months. The Hokusai trial had a treatment period of 12 months; however, median therapy duration was 6 months, and major bleeding was not reported beyond the initial 6 months. In clinical practice, the decision to continue prophylaxis beyond 6 months typically depends on a patient’s cancer status as well as selection of chemotherapy with thrombogenic potential. Factors such as severity of initial VTE, type of cancer, quality of life considerations, and patient preference should also be assessed. The adopted consensus by multiple guidelines is to continue anticoagulation while cancer remains active in a patient. The primary prevention of VTE requires an in-depth analysis of a patient’s individual risk/benefit with prophylaxis. Factors such as cancer type and stage should be evaluated, as well as current chemotherapy treatment. Presently, there are several ongoing trials assessing the use of primary prophylaxis in patients with cancer, particularly with DOACs. Results from two phase 3 trials, CASSINI and AVERT, have provided evidence supporting the prophylactic use of DOACs rivaroxaban and apixaban, respectively (Table 5).

### TABLE 5 Efficacy End Points from the Phase III CASSINI and AVERT Trials

<table>
<thead>
<tr>
<th></th>
<th>CASSINI</th>
<th>AVERT</th>
</tr>
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<tbody>
<tr>
<td>Clinicaltrials.gov identification</td>
<td>NCT02555878</td>
<td>NCT02048865</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Rivaroxaban 10 mg once daily</td>
<td>Apixaban 2.5 mg twice daily</td>
</tr>
<tr>
<td>No. of patients enrolled</td>
<td>841</td>
<td>563</td>
</tr>
<tr>
<td>Duration</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Median treatment duration</td>
<td>4.3 months</td>
<td>5.2 months</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Khorana score ≥2</td>
<td>Khorana score ≥2</td>
</tr>
<tr>
<td>Types of cancer</td>
<td>Solid tumors, lymphomas</td>
<td>Solid tumors, lymphomas, myelomas, primary brain tumors</td>
</tr>
<tr>
<td>Primary events</td>
<td>Symptomatic, screening-detected, incidental</td>
<td>Symptomatic, incidental</td>
</tr>
<tr>
<td>Reduction in primary end point</td>
<td>NNT VTE = 35; on-treatment, 26</td>
<td>NNT VTE = 17; on treatment, 16</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>NNH = 101</td>
<td>NNH = 59; on-treatment, 100</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban vs placebo</td>
<td>Apixaban vs placebo</td>
</tr>
<tr>
<td>VTE occurrence (%)</td>
<td>2.60 vs 6.41</td>
<td>4.2 vs 10.2</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>1.98 vs 0.99</td>
<td>3.5 vs 1.8</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding (%)</td>
<td>2.72 vs 1.98</td>
<td>7.3 vs 5.5</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>20.0 vs 23.8</td>
<td>12.2 vs 9.8</td>
</tr>
</tbody>
</table>

NNH indicates number needed to harm; NNT, number needed to treat; VTE, venous thromboembolism.

**Primary Prophylaxis of VTE**

The primary prevention of VTE requires an in-depth analysis of a patient’s individual risk/benefit with prophylaxis. Factors such as cancer type and stage should be evaluated, as well as current chemotherapy treatment. Presently, there are several ongoing trials assessing the use of primary prophylaxis in patients with cancer, particularly with DOACs. Results from two phase 3 trials, CASSINI and AVERT, have provided evidence supporting the prophylactic use of DOACs rivaroxaban and apixaban, respectively (Table 5). These trials have complementary findings; however, it is important to address the differences in study design and analyses. For instance, the AVERT trial included patients with myeloma and brain tumors, while the CAS-
The CASINI trial did not. The CASINI trial did, however, enroll more participants with higher early mortality rates, such as patients with pancreas cancer. The AVERT trial had no screening at baseline, while the CASSINI trial did; thus, removing these patients and reducing the number of events during the study.

Data have recently been released from the phase 2 MYELAXAT trial (NCT02066454). A total of 104 patients with multiple myeloma (89.4% in relapse) received apixaban 2.5 mg twice daily for 6 months for primary prevention of VTE and were followed for 7 months. Patients were treated for their myeloma with either melphalan/prednisone/thalidomide (MPT) (first-line setting) or lenalidomide/dexamethasone (relapsed setting). Primary outcome measures include incidence of VTE and rate of clinically relevant nonmajor bleeding. Secondary outcomes evaluate incidence of VTE complications stratified by active myeloma or relapse, incidence of cardiovascular events, and safety. With a median duration of 168 days, 2 VTE events (both in relapsed patients) and 11 bleeding events (similar between both relapsed and first-line patients) were observed. Primary prophylaxis of VTE appears safe and tolerable in patients with cancer and will require validation with larger studies.

Patients who undergo major cancer surgery are at an even higher risk of developing at VTE. This is further exacerbated if the patient has characteristics considered to be high risk for developing a VTE, such as lack of mobility or presence of metastatic disease. Per the ASCO guidelines, patients undergoing major cancer surgery should receive anticoagulation prophylaxis before surgery and after surgery for at least 7 to 10 days. This duration is extended to up to 4 weeks in patients undergoing major open or laparoscopic abdominal or pelvic surgery who have high-risk factors, such immobility, obesity, or prior VTE. ASCO recommends either UFH or LMWH unless contraindicated. Combined pharmacologic and mechanical prophylaxis may be utilized, but it is not recommended that mechanical VTE prophylaxis be used alone as prevention.

Notably, both ASCO and ITAC have responded to the mounting evidence to recommend primary prophylaxis in select patients with active cancer in their respective guidelines. The most recent update from ASCO guidelines recommends that patients with low bleeding risk may be offered primary prophylaxis with apixaban, rivaroxaban, or LMWH. This applies to select high-risk patients being managed in the outpatient setting. Additionally, ITAC published updated guidelines recommending LMWH for locally advanced or metastatic pancreatic cancer (1b), and rivaroxaban or apixaban for patients with a low risk of bleeding and intermediate to high risk of VTE (Khorana score ≥2) (1b).

Summary

Advances in cancer therapies now available for patients have improved outcomes, but long-term treatment has become more complicated to manage as patients increase in age and the use of novel agents expands. Understanding a patient’s risk of experiencing a VTE recurrence after an initial clot or bleeding event is imperative in identifying populations at increased risk and in preventing similar episodes or a serious VTE complication. Risk status should be individualized to a patient’s cancer type and drug therapy, which can help physicians tailor a patient’s treatment plan as well as supportive care measures to treat and prevent cancer-related VTE. The strategic combination of targeting cancer while preventing life-threatening adverse events will enable patients with cancer to live longer and have a better quality of life.
A diagnosis of prostate cancer was life-changing news for over 170,000 people per year.

Cutting edge treatments that are noninvasive so he can enjoy a life-changing trip around the world.

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All human cells maintain a redox balance between reactive oxygen species (ROS) and antioxidants, such as NQO1, to resist oxidative stress.1,2 The optimal redox balance differs between cells and determines their specific “redox signature,” which can have downstream effects on potent oncogenic signaling pathways, including STAT3.1,3,4

Research suggests that a subset of cancer cells, including some cancer stem cells, possess a distinct redox signature that may make them susceptible to approaches that generate cytotoxic levels of ROS.3,4 These cells signal to other cells in the tumor microenvironment and promote the phosphorylation of STAT3. The presence of phosphorylated STAT3 in a tumor may indicate this redox signature and favorability to ROS-generating intervention.3

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