Inhibition of PARP blocks repair of DNA single-strand breaks (SSBs), resulting in DNA double-strand breaks (DSBs), which are lethal in DNA DSB repair–defective cancer cells, such as are found in patients with germline BRCA mutations.
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What led you to examine sex differences in the tolerability of immunotherapy?

**DR. DUMA:** Most research projects start at the bedside. During my time on the inpatient oncology service, I observed several patients with grade 3 immune-related adverse events admitted to the hospital. After several weeks, we noticed most of the patients were women receiving immune checkpoint inhibitors.

While this sample was skewed towards severe adverse events in a tertiary center, we decided to investigate if our observation was the same in the outpatient setting.[1]

Among patients at the Mayo Clinic Rochester who received anti–PD-1 immune checkpoint immunotherapy for metastatic melanoma, you found that premenopausal women had a higher rate of immune-related adverse events (IRAEs) leading to treatment discontinuation than postmenopausal women, and that both groups of women had higher rates than men, correct?

**DR. DUMA:** Yes, despite a small sample size (30 premenopausal women), we observed that premenopausal women had higher rates of IRAEs and were more likely to discontinue their anti–PD-1 agent due to toxicity (irrespective of the clinical benefit they had obtained from the treatment).

These differences were observed when comparing [premenopausal patients] with postmenopausal women and men with metastatic melanoma.

The differences were limited to lower-grade (grade 1 and 2) IRAEs, correct?

**DR. DUMA:** We did not observe differences in IRAEs higher than grade 3, meaning most of the difference came from grade 2 adverse events. One of the challenges while conducting studies like ours is that grade 1 adverse events are often under-documented. We hope to continue our work in this area and conduct a large prospective study where data regarding adverse events of all grades will be well documented and later analyzed.

Did the site of metastasis affect IRAE risk?

**DR. DUMA:** Previous observations suggested that patients with liver metastases were more likely to develop IRAEs. In our cohort, we did not find a correlation between liver, lung, or brain metastases and risk of developing IRAEs. We are planning to conduct further analysis regarding the association of primary tumor location and IRAEs.
Were there trends for specific types of IRAEs?

**DR. DUMA:** When analyzing IRAEs in subcategories (by organ involvement), we observed that women were more likely to develop endocrinopathies such as hypothyroidism, adrenal insufficiency, etc. In the general population, women are more likely to develop hypothyroidism during their lifetime compared to men.

Might sex hormones be a factor there?

**DR. DUMA:** Perhaps sex as a biologic variable plays an important role in the development of IRAEs and in the differences between the sexes in this area. Further studies are necessary to understand the etiology of these mechanisms and the role of sex hormones in the development of IRAEs.

Were there demographic or clinical variables in addition to patient sex that affected IRAE risk?

**DR. DUMA:** We conducted a multivariable analysis to try to identify other risk factors for the development of IRAEs. We did not observe any significant association besides sex. Included in the analysis were specific tumor characteristics and mutations; history of prior radiation, chemotherapy, or colony-stimulating agents; and comorbidity indexes. None of these were statistically significant.

How did IRAEs affect patient outcomes?

**DR. DUMA:** We failed to observe a meaningful difference in progression-free survival between the women with IRAEs and those without, but this could have been in part due to our small sample size in the premenopausal group.

On the other hand, we captured a trend towards better progression-free survival in men who developed IRAEs, suggesting an association between immune system “hyperactivation” and response to therapy. We are collecting more data from our sites in Florida and Arizona with the hope of increasing our sample size. This project has been an enterprise-wide effort.

What implications do your team’s findings have for the use of immune checkpoint blockade regimens in women?

**DR. DUMA:** At this time, we believe we need further studies to better understand our observations, but these findings bring attention to a very important issue: women are biologically different and may require closer monitoring while receiving treatment with anti–PD-1 therapy for metastatic melanoma. As more trials utilizing anti–PD-1 agents are opening every day, we hope that the data regarding adverse events will be reported by sex and that larger studies can be conducted with the existing data.

How should your findings affect monitoring for immune checkpoint inhibition–associated IRAEs?

**DR. DUMA:** The treatment landscape of multiple malignancies has changed with the introduction of immune checkpoint inhibitors. Clinical practices should adapt to these changes. Our questions regarding adverse events are shifting away from the traditional nausea, vomiting, etc to the new—rash, joint pain, and cough, for example.

ASCO recently released guidelines for the treatment of IRAEs; we invite everyone to review them. Consistent practices would allow our patients to receive the best care independent of whether they are treated at a tertiary center or in a community practice.

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Sharing Serious News With Cancer Patients: Strategies That Can Help

Patricia A. Parker, PhD¹, Smita C. Banerjee, PhD²

ABSTRACT: Sharing serious news is a key communication task that occurs frequently throughout the trajectory of caring for a cancer patient. When sharing serious news, it is important to consider many factors, including those related to patient diversity, such as cultural and family background; language barriers; socioeconomic factors; and health literacy. Importantly, the way in which serious news is discussed significantly affects many outcomes and aspects of patient care. Sharing serious news is not an innate skill but can be effectively taught and learned.

A common definition of bad news is "any news that seriously and adversely affects the patient's view of his or her future."[1] Whether news is "bad" cannot be determined a priori, but is dependent on an individual's subjective evaluation.[2] This is a key point because it distinguishes bad news from other types of more emotionally neutral information about cancer given to patients, such as information about chemotherapy. At the same time, practitioners should be cautioned that what they might think is good news to one patient ("I'm glad this tumor can be removed") might be perceived as much more troubling to another ("This is terrible…I just can't handle another surgery"). Thus, it is important to elicit the patient's expectations and understanding of the medical situation as part of the "bad news" discussion.

We prefer to use the term "sharing serious news" rather than "breaking bad news" because it more accurately reflects both the interactive nature of the communication and the fact that it may be a process rather than a discrete, one-time event. Sharing serious news is a complex communication task and involves a verbal component (giving the news), as well as recognizing and responding to the patient's emotions, involving the patient in decision making, and finding ways to frame "hope" and provide support.[3] Ideally, sharing serious news is a dynamic interaction between the clinician and the patient in which not only is information transmitted to the patient, but the patient, in reacting to this information, provides cues to the clinician regarding his or her attitudes, goals, needs, and concerns. This process requires that the clinician continually adapt to a variety of patient, system, cultural, and other factors.[4,5] Importantly, sharing serious news is the gateway to many aspects of patient care, such as discussing a treatment plan, engaging in shared decision making, obtaining informed consent, and involving the family in the patient's care.

What is important to patients when being told serious news?

Studies across a variety of cancer populations have shown that cancer patients desire information about the status of their disease.[6,7] This is true even in countries where, traditionally, bad news (especially a dire prognosis) has been withheld from patients. For example, in a UK study, Jenkins et al.[6] found that 98% of patients wanted to be informed of their diagnosis and 87% wanted all possible information, both good and bad. It is important to note, however, that not all patients are interested in obtaining complete information. Thus, an important first step may be to ask patients about their information preferences.

In several studies, patients have been asked how they would like to be given bad news. For example, Parker et al asked 351 patients with a variety of different cancers at different stages about their communication preferences when given bad news of an initial cancer diagnosis or disease recurrence.[8] The highest-rated elements included the following physician behaviors:

• Being up to date on the latest research on the patient's cancer.
• Informing the patient about the best treatment options and taking time to answer all patient questions.
• Being honest about the severity of the condition.
• Using simple and clear language, giving the news directly, and giving full attention to the patient.

Differences in patient preferences were based on sex, age, and level of education, underlining the importance of tailoring the conduct of the discussion to the individual patient. In this study, cancer type did not predict patients' preferences.

Why is it challenging for clinicians to share serious news? What are the barriers?

Due to the increase in cancer survival, not only must information regarding the state of the disease and its response to a multitude of treatments over time be communicated effectively to the patient, but adverse information related to side effects and complications of the illness and the treatment must be discussed as well. Sharing serious news is typically not perceived as a skill that can be learned, but is...
seen rather as an innate ability.[9,10] Oncologists are rarely trained in techniques for sharing serious news.[11,12] Additionally, physicians often experience negative emotions, such as anxiety and fear of being blamed, when they must tell their patients that treatment has not worked.[13,14] Consequently, there is a danger that they may react to patient emotion by offering false hope or premature reassurance, or that they may omit important information from the disclosure.[15]

Patient diversity, including differences in cultural and family background, language, socioeconomic status, and health literacy, can also make sharing serious news more difficult.[16-18] In a meta-synthesis of more than 40 qualitative studies of breaking bad news, researchers identified several factors that affected these discussions. Among the important factors were the characteristics of the family and cultural considerations.[5]

As described previously, cultural background greatly influences many aspects of the communication process. Although some cross-cultural descriptive studies have been conducted, especially on views about disclosure of the diagnosis,[19,20] relatively little is known about the specific influence of culture on the interaction between patients and their healthcare practitioners. The ways in which cultural variables might affect the information that patients want, their preferred and assumed participatory style, and other aspects of the interaction warrant further study.

There are many ways in which effective communication skills can help clinicians when sharing serious news with patients and their families. Effective communication can provide structure for the consultation, enhance the relationship between patients and their families, and may make consultations more efficient.

How the Way Clinicians Communicate Can Impact Patients and Other Key Outcomes

There is a growing body of empirical research examining the associations between aspects of communication and patient outcomes. Effective communication helps establish a working relationship between the practitioner and the patient and plays an important role in the diagnosis and treatment of medical illnesses, including cancer.[21] According to a recent review of physician-patient communication, the three main goals of effective communication are:

• To create a good interpersonal relationship.
• To facilitate exchange of information.
• To include patients in decision making.[22]

Consistently across the literature, practitioner-patient communication has been identified as one of the most essential facets of patient care.[23] Research has shown that aspects of the practitioner-patient interaction impact patient outcomes, including satisfaction, distress, knowledge, and adherence.[24-27] For example, studies have found that empathic communication is associated with improved satisfaction and decreased distress among patients.[25-30] These findings emphasize the benefits of effective communication between practitioners and their patients and that training practitioners in communication skills may improve their communication with their patients.

However, in discussing benefits of effective practitioner-patient communication, it is also important to highlight what constitutes ineffective communication. In a qualitative study of negative feedback from patients about physicians, 38 cases of complaints were analyzed and coded.[31] Results indicated that ineffective communication involved these verbal/nonverbal physician behaviors:

• Inadequate information provided to the patient.
• Poor quality of information (ie, no rationale given, inadequate explanations).
• Lack of empathy and lack of respect.
• Poor nonverbal behaviors (ie, lack of eye contact, negative facial expressions, problems with volume/tone of voice).
• Poor verbal behaviors (ie, not listening, patients not given a chance to ask questions, inappropriate choice of words).

The deleterious patient outcomes when serious news is shared in an ineffective manner include increased distress and suffering, failure to thrive, nonadherence, and dissatisfaction with medical care.[25,32,33] Since poor communication has also been found to be associated with medical malpractice suits, this is another important reason to strive to communicate serious news as effectively as possible.[34,35]

Specific Guidelines and Recommendations for Sharing Serious News

Studies have shown that the majority of physicians do not have a consistent plan or strategy when they share serious news with their patients. For example, Baile et al.[11] found that among a sample of physicians attending an annual meeting of the American Society of Clinical Oncology, 22% reported that they did not have a consistent approach to the task of breaking bad news to patients, and 51.9% reported that they had several techniques or tactics but did not have an overall plan. Determining what patients believe to be important in the interaction may help refine the current guidelines and yield specific evidence-based recommendations that can help with this challenging task.[3]

Guidelines provide a useful roadmap for key steps or issues to focus on when sharing serious news. However, as with any other complex skill, sharing serious news is best learned through practice. One protocol or method for disclosing serious news is represented by SPIKES,[3] a six-step approach that comprises:

• Setting up the interview (choosing the right location, establishing rapport).
• Understanding the patient’s perception of the medical situation.
• Asking the patient permission to explain, or getting an invitation.
• Addressing emotions that might occur during bad news disclosure.
• Strategizing a treatment plan and summarizing the plan for the patient and family.

SPIKES is a useful approach because it is short, easily understandable, and focuses on specific skills that can be practiced. Moreover, it
Table. Sharing Serious News: Conveying Threatening Information in a Way That Promotes Understanding, Recall, Support for the Patient’s Emotional Response, and a Sense of Ongoing Support

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Skills</th>
<th>Process Tasks</th>
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<tbody>
<tr>
<td>1. Set agenda</td>
<td>• Declare your agenda items</td>
<td>• Make introductions</td>
</tr>
<tr>
<td></td>
<td>• Invite agenda items</td>
<td>• Invite patient appropriately</td>
</tr>
<tr>
<td></td>
<td>• Negotiate agenda</td>
<td>• Sit at eye level</td>
</tr>
<tr>
<td></td>
<td>• Take stock</td>
<td>• Great patient appropriately</td>
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<tr>
<td>2. Tailor the consultation to the patient’s needs</td>
<td>• Check understanding</td>
<td>• Avoid interruptions</td>
</tr>
<tr>
<td></td>
<td>• Check preferences for information</td>
<td>• Invite appropriate third party</td>
</tr>
<tr>
<td>3. Provide information in such a way that it will be understood and recalled</td>
<td>• Preview information</td>
<td>• Avoid jargon</td>
</tr>
<tr>
<td></td>
<td>• Invite questions</td>
<td>• Respond to all questions</td>
</tr>
<tr>
<td></td>
<td>• Check understanding</td>
<td>• Draw diagrams</td>
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<td></td>
<td>• Summarize</td>
<td>• Categorize</td>
</tr>
<tr>
<td>4. Respond empathically to emotion</td>
<td>• Encourage expression of feelings</td>
<td>• Write information down</td>
</tr>
<tr>
<td></td>
<td>• Acknowledge</td>
<td>• Provide hope and reassurance</td>
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<td></td>
<td>• Normalize</td>
<td>• Offer tissues</td>
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<td></td>
<td>• Validate</td>
<td>• Provide literature</td>
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<tr>
<td></td>
<td>• Ask open questions</td>
<td>• Provide website addresses</td>
</tr>
<tr>
<td>5. Check readiness to discuss management options, including palliative care</td>
<td>• Take stock</td>
<td>• Address palliative needs</td>
</tr>
<tr>
<td></td>
<td>• Preview information</td>
<td>• Write information down</td>
</tr>
<tr>
<td>6. Close the consultation</td>
<td>• Check understanding</td>
<td>• Offer to help tell others or respond to their questions</td>
</tr>
<tr>
<td></td>
<td>• Invite questions</td>
<td>• Make introductions</td>
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<td>• Summarize</td>
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<td></td>
<td>• Review next steps</td>
<td>• Offer website addresses</td>
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<tr>
<td></td>
<td>• Review next steps</td>
<td>• Address palliative needs</td>
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</table>

One model for sharing serious news is described in the program Oncotalk, in which oncology fellows are given a didactic lesson in how to give bad news and then afforded practice with standardized patient interviews.[37] Compared with the standardized patient interviews before the workshops, post-workshop interviews showed that participants displayed significantly more skills in breaking bad news.[37]

The Communication Skills Training and Research Program (Comskil) at Memorial Sloan Kettering Cancer Center was created to train providers in communication skills to support the patient throughout the cancer disease trajectory.[38] The Comskil program includes a module on sharing serious news; the module has an overarching goal, which is achieved through a set of broad strategies.[39] These strategies are in turn achieved through communication skills and process tasks.[39]

The goal of this module is to convey threatening information in a way that promotes understanding, recall, support for the patient’s emotional response, and a sense of ongoing support. In order to accomplish this goal, six strategies are recommended (Table). Strategy 1 focuses on setting the agenda so that the clinician and the patient share goals for the meeting. Skills that allow the clinician to do this include declaring the agenda, inviting the patient to submit agenda items, and negotiating the agenda (if appropriate). Strategy 2 involves tailoring the consultation to the patient’s needs. By checking patient understanding and exploring patient preferences for information, the clinician elicits how much (or how little) the patient knows about his or her disease and learns how to best provide relevant information. Strategy 3 focuses on providing information in such a way that it will be understood and recalled. Using the information gathered from the patient in Strategy 2, the clinician can modify the consultation to provide the most relevant information while previewing information, inviting patient questions, checking understanding, and summarizing. For Strategy 4, empathically responding to the patient’s emotion or experience allows the clinician to check how the patient is doing emotionally and respond appropriately. The skills required for this strategy include acknowledging, validating, normalizing, and encouraging expression of feelings, as well as praising patient efforts. Strategy 5 involves checking readiness to discuss management options, including palliative needs. This involves the skill of taking stock, which allows the clinician to review the prior
discussion and then seek the patient’s permission to move on. Then, the clinician recaps the main details that were just conveyed to the patient, and provides a review statement about what was just said in order to summarize the information. The last strategy (Strategy 6)—closing the conversation—focuses on checking patient understanding, inviting patient questions, summarizing information, and reviewing next steps. These six strategies, along with their respective skills and process tasks, are summarized in the Table.

Although there are some subtle differences between the various approaches recommended for sharing serious news, there are also many common elements. For example, each of these strategies recommends giving the news in an appropriate setting (quiet place, with uninterrupted time), assessing the patient’s understanding of his or her illness, providing information that the patient wants, allowing the patient to express emotions and responding appropriately, summarizing the information provided, and developing a plan for the next step(s). Additional research is needed to further empirically support the impact of these techniques.

Summary and Future Directions
Sharing serious news is stressful for the patient, the family, and the doctor. Learning to give bad news is a complex skill that involves major communication tasks such as establishing rapport, obtaining information from the patient, providing information in understandable language without jargon, dealing with patient emotions, and providing a treatment plan to guide the patient through cancer therapy.[40] Communicating in ways in which patients’ information needs are met and in which they feel emotionally supported increases their feelings of trust, hope, and sense of being respected as a person, and it promotes their willingness to be a partner with their doctor to achieve the best outcome possible. The argument may be made that there has been little research done to show the efficacy of these methods in regard to patient outcomes. While this may be true, communication skills in general have been shown to have a significant impact on outcomes. Nonetheless, this is an area in which research could and should be expanded.

One should also be aware that most recommendations for how to deliver bad news are based on “best practices” and derive from patient preferences for receiving information. Communication skills training has been shown to be effective in enhancing oncologists’ skills and competencies in sharing serious news. However, very few oncology training programs provide opportunities for fellows to learn skills related to sharing serious news with patients and their families.[12] One of the core competencies outlined by the Accreditation Council for Graduate Medical Education is interpersonal skills and communication. This has increased awareness of and emphasis on approaches to ensure that oncology residents and fellows receive adequate training in how to share serious news and carry out other important communication tasks. In addition, an increased emphasis on patient satisfaction and the patient experience in healthcare has highlighted the importance of practitioner-patient communication. Additional educational and research efforts should be directed at evaluating training efforts, as well as identifying other factors that influence how serious news is shared and received.

KEY POINTS
- Sharing serious news is a complex communication task that occurs many times during the course of caring for a cancer patient.
- Although challenging, sharing serious news in a compassionate and clear way can enhance the clinician-patient relationship, as well as other important patient and clinician outcomes.
- Communication skills are not innate, and experience alone does not improve these skills; however, there are many strategies and recommendations that can be employed to enhance these skills.

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REFERENCES
A 30-year-old Caucasian man presented with a left-lower-extremity posterior thigh area skin lesion. The lesion had started as a rash 3 months prior, and in time turned into an ulcerated open wound with some nodularity in and around it (A). Initial treatments with topical measures, oral antibiotics, and wound care consolidation did not help. There was no history of fevers, chills, night sweats, or weight loss. Physical examination revealed no organomegaly or lymphadenopathy. A biopsy of the skin lesion revealed extensive involvement of skin and subcutaneous tissue by sheets of large atypical cells (B), including C-shaped and multinucleated cells (C) with strong positivity for CD30, CD2, CD45, granzyme B (D), and EMA (epithelial membrane antigen). Immunoperoxidase stains were negative for CD20, PAX5, ALK, pan-keratin, S100, MART-1, CD34, and P63.

Based on the images shown, what is your diagnosis?

A. Angioimmunoblastic lymphoma  
B. Cutaneous B-cell lymphoma  
C. Peripheral T-cell lymphoma  
D. Anaplastic large T-cell lymphoma

To find the answer to the above quiz, scan the QR code or go to cancernetwork.com. Visit the website for additional “Test Your Image IQ” quizzes—a new quiz appears every week!
HOW AN EXPERT APPROACHES IT

Using PARP Inhibitors in Advanced Ovarian Cancer
Roisin E. O’Cearbhaill, MD

ABSTRACT: Poly(ADP-ribose) polymerase (PARP) proteins are used by cells in several DNA repair processes. PARP inhibition can result in preferential death of cancer cells when another mechanism for repairing DNA is defective. Two PARP inhibitors, olaparib and rucaparib, have been approved by the US Food and Drug Administration (FDA) for the treatment of recurrent, BRCA-associated ovarian cancer. More recently, these two and a third PARP inhibitor, niraparib, were approved by the FDA as maintenance therapy following platinum-based chemotherapy for recurrent ovarian cancer. This has caused a paradigm shift in disease management and a challenge for clinicians, who must decide how best to use these agents in individualized treatment. The oral formulation is attractive to patients, but adverse effects such as nausea and fatigue can impact quality of life. As clinicians become comfortable selecting PARP inhibitors and managing associated toxicities, future steps will be to investigate how to safely administer them in combination with other therapies.

Inhibition of poly(ADP-ribose) polymerase (PARP) proteins, which cells use in a variety of DNA damage repair mechanisms, is a promising therapy for ovarian cancer.[1] Because ovarian cancer cells often have pre-existing defects in DNA damage repair pathways,[2] the inhibition of PARP can result in preferential death of cancer cells when another mechanism for repairing DNA is defective. This is called synthetic lethality. The concept of synthetic lethality is that cell death occurs when two separate mechanisms for repair of defective DNA are present in a cell and both are incapacitated. (If only one DNA repair mechanism is defective, then the cell can remain viable.) For example, synthetic lethality occurs when ovarian cancer cells with a BRCA mutation are exposed to a PARP inhibitor. The mutation causes defective repair of breaks in double-stranded DNA and the drug prevents repair of breaks in single-stranded DNA. Thus the cancer cells that have BRCA mutations die while cells with a functioning BRCA gene remain unaffected.[1,2]

Two PARP inhibitors, olaparib and rucaparib, received US Food and Drug Administration (FDA) approval in 2014 and 2016, respectively, for the treatment of BRCA-associated ovarian cancer.[3-6] Since 2017, three PARP inhibitors—niraparib, olaparib, and rucaparib—have received FDA approval in the recurrent setting as maintenance therapy following platinum-based therapy.[7-11] The approval of three PARP inhibitors in rapid succession has resulted in a paradigm shift in the management of recurrent ovarian cancer. However, these choices present a challenge for clinicians, who now struggle with the selection of PARP inhibitors for individual patients, as well as with how to best incorporate these agents into existing treatment strategies.

How PARP Inhibitors Are Used in Recurrent Ovarian Cancer

Treatment of recurrent, BRCA-associated ovarian cancer

PARP inhibitors were initially studied in ovarian cancers with germline BRCA mutations. In December 2014, olaparib was the first PARP inhibitor to receive US and European regulatory approval in ovarian cancer.[3-5] It was approved for women with recurrent ovarian cancer who had a deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation, and who had received at least three prior lines of chemotherapy. Olaparib capsules are being phased out, and it is now available as tablets (300 mg twice daily; 4 tablets per day).

Rucaparib was studied in ovarian cancers with germline BRCA mutations and in patients whose tumors demonstrated homologous recombination deficiency (HRD) resulting from alterations in crucial DNA repair genes in the tumor shown to convey sensitivity to PARP inhibition. Consequently, the December 2016 FDA approval for rucaparib permitted....
KEY POINTS

- Olaparib is indicated for:
  1) treatment of recurrent ovarian cancer in patients with germline BRCA mutations after ≥ 3 prior lines of chemotherapy; 2) as post-platinum maintenance therapy for platinum-sensitive recurrences that responded to platinum-based chemotherapy, regardless of BRCA or homologous recombination deficiency (HRD) status.

- Rucaparib is indicated for: treatment of recurrent BRCA-mutated ovarian cancer (either germline or somatic mutation) after ≥ 2 prior lines of chemotherapy.

- Niraparib is indicated for: post-platinum maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer who responded to platinum-based chemotherapy, regardless of BRCA or HRD status. Niraparib must be started within 8 weeks of the last platinum dose.

its use for somatic (tumor) and/or germline BRCA1/2 mutations in patients with ovarian cancer who had received at least two prior lines of chemotherapy.[6] Rucaparib is available as tablets (600 mg twice daily; 4 tablets per day).

Maintenance following platinum-based chemotherapy for recurrent epithelial ovarian cancer
In March 2017, FDA approval of niraparib extended the role of PARP inhibition beyond BRCA-associated ovarian cancers.[7] Niraparib was approved as a post-platinum maintenance therapy in patients with recurrent epithelial ovarian cancer who had responded to their most recent platinum-based therapy. It is available as capsules (300 mg once daily; 3 capsules per day). It was recommended that patients start niraparib maintenance within 8 weeks of the last dose of platinum. Olaparib and rucaparib were approved by the FDA in August 2017 and April 2018, respectively, in a similar maintenance setting for women with recurrent epithelial ovarian cancer who are exhibiting a complete or partial response to platinum-based therapy, but without the 8-week-window stipulation.[8-11]

Impressive progression-free survival (PFS) results (up to a 15.5-month PFS benefit) were seen for all three agents in patients with germline BRCA mutations, and to a lesser degree in those with somatic BRCA mutations.[7-11] In patients with neither germline nor somatic BRCA mutations, the incremental approximate PFS advantage (median, 3-4 months) was comparable to that seen with maintenance bevacizumab.[7-9,11-13]

When selecting maintenance therapy for patients with non-BRCA-associated ovarian cancers, it is important not only to consider the toxicity profile of the agent but also to be cognizant that PARP inhibitors are restricted to patients with platinum-sensitive disease in that setting.[7-11] Also, future investigations may lead clinicians to consider using a PARP inhibitor as maintenance therapy for patients with mutations in other DNA damage response genes, such as ATM, RAD51, BRIP1, and PALB2.[1,2]

PARP Inhibitor Selection and Management of Toxicity
Patients like the oral formulation of PARP inhibitors, reporting that it promotes a greater sense of autonomy than intravenous (IV) administration.[3-11,14] However, the daily dosing schedule means that even low-grade symptoms, such as nausea and fatigue, can be particularly troublesome and affect quality of life. It is essential to counsel patients about how to proactively manage such side effects, and to alert them that dose modifications or dose interruptions may be required. Dose interruption and instigation of prophylactic supportive medications may permit resumption at the same dose level once the toxicity has resolved to baseline. However, more severe toxicities may necessitate a dose reduction on resumption of the PARP inhibitor, in addition to supportive measures. Rarely, discontinuation of the PARP inhibitor may be indicated.[3-11,14]

Gastrointestinal symptoms
Simple measures such as taking a PARP inhibitor with food or immediately prior to going to bed may help with gastrointestinal side effects. Patients should be counseled about managing nausea and vomiting, and antiemetics should be prescribed at the outset of treatment. It can be helpful to take prophyllactic antiemetics 30 to 60 minutes prior to the PARP inhibitor, especially in the initial weeks of therapy. Frequent re-evaluation of antiemetic control is important so that the treatment regimen can be revised accordingly.[14]

In patients prone to constipation, low-dose olanzapine (2.5-5.0 mg) can be used as an alternative to ondansetron but may cause sedation. Fosaprepitant should be avoided in patients taking olaparib, since inhibition of CYP3A may increase olaparib plasma concentrations.[3] Lorazepam may be helpful for anticipatory nausea. In the case of rucaparib, the gastrointestinal side effects are often most pronounced in the first weeks of therapy and can be mitigated by starting the PARP inhibitor at a lower dose—300 mg instead of 600 mg—twice daily for the first 3 to 4 weeks, and then increasing it up to the full 600-mg dose if tolerated.[6]

If a dose of a PARP inhibitor is missed or vomited, an additional dose should not be taken.

Consultation with a nutritionist may be beneficial for management of gastrointestinal side effects. Often patients may tolerate smaller, frequent snacks more readily than larger meals; avoidance of trigger foods can also be helpful. Patients who experience diarrhea should be counseled regarding increasing fluid intake and modifying what they eat, using the bananas, rice, apples, and toast (BRAT) diet. Other etiologies of diarrhea, such as infection or progression of disease, should be ruled out. Pharmacologic interventions include antimotility agents, such as loperamide. Dietary modifications in conjunction with education regarding mouth and dental care may help patients who experience stomatitis or dysgeusia. Proton pump inhibitors may be required for dyspepsia. A referral to a gastroenterologist for possible endoscopy should be considered if symptoms persist despite dose interruption and use of supportive medications.[14]
Fatigue
Fatigue is a common side effect and is reported with all three PARP inhibitors.[3-11,14] When a patient receiving a PARP inhibitor complains of fatigue, it is important to rule out other contributing factors, such as disease-related fatigue, depression, insomnia, and anemia, as well as sedation from concomitant medications. Patients should be advised to self-monitor fatigue levels and be encouraged to remain active and to exercise as tolerated. Consultation with a physical therapist or rehabilitation specialist may be helpful. Psychosocial interventions, including counseling, mind-body therapies, and even simple techniques such as massage and education regarding sleep hygiene may also help. Early involvement by palliative care specialists for additional support may be appropriate. Pharmacologic interventions, including treatment of underlying pain, depression, or insomnia, as well as consideration of methylphenidate, a psychostimulant, may improve energy levels. A red blood cell (RBC) transfusion may be required for symptomatic anemia, but it is also important to proactively investigate and treat any underlying vitamin and/or iron deficiencies.[14] Brief interruptions in dosing may be sufficient to address fatigue and may allow resumption of the PARP inhibitor at the same dose level. However, a dose reduction may be warranted if the fatigue is still intolerable despite these interventions.

Myelosuppression
Anemia and leukopenia are common adverse events with all three PARP inhibitors.[3-11] Before initiating PARP inhibitor maintenance therapy, it is medically appropriate to permit a patient to recover from hematologic toxicity caused by previous chemotherapy. It is important to note, however, that it is recommended that niraparib be started within 8 weeks of completion of the prior platinum-based chemotherapy.[7] RBC transfusions may be required to treat symptomatic anemia, and iron, folic acid, and vitamin B₁₂ supplements may be clinically indicated. Erythropoiesis-stimulating agents are not recommended. Withrucaparib and olaparib, complete blood cell counts (CBCs) should be checked monthly, with consideration given to checking every 2 weeks during the first 4 to 6 weeks of therapy. With niraparib, there is also a risk of profound thrombocytopenia, notably in the first 4 to 6 weeks of therapy, necessitating weekly CBCs. Premeditatively reducing the starting dose of niraparib from 300 mg to 200 mg daily during the first 4 to 6 weeks can be considered in patients with baseline myelosuppression and/or who weigh less than 77 kg (170 lbs). In the event of a precipitous drop in platelet count, even more frequent CBC monitoring is warranted, and weekly checks should be continued for at least 4 weeks after any dose change. Niraparib may thus not be the ideal choice for patients who are at increased risk of bleeding, such as those taking long-acting anticoagulants; patients who fall frequently; or those who have a comorbidity that increases the risk of complications in the setting of thrombocytopenia. Bleeding precautions should be carefully reviewed with patients receiving niraparib, including education about signs of thrombocytopenia, such as epistaxis, bleeding of gums, petechiae, melena, and hematuria. If they notice any of these, they should be instructed to hold niraparib and seek immediate medical evaluation and a same-day CBC check.[7] In patients with significant myelosuppression, dose reduction is required once the toxicity has resolved to grade 1.

Elevation of creatinine
Olaparib and rucaparib can be associated with increases in serum creatinine due to their effect on the multidrug and toxin extrusion transporters.[3-6,9-11] This often occurs early, and levels may not increase further. Ruling out other causes, such as hydrenephrosis or nephrotoxins, is essential. Dose reductions in olaparib are recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).[3-5,8-10] For rucaparib, dose reductions are recommended for patients with creatinine clearance < 30 mL/min. A 24-hour creatinine clearance may help determine whether renal function is compromised.

Elevations of transaminase levels
Rucaparib is often associated with a rise in transaminase levels; this usually occurs within the first 4 months of therapy and is not indicative of liver dysfunction.[6,11] The transaminase increases are not associated with hyperbilirubinemia and generally resolve over time. In 11% of patients, grade 3/4 elevations in liver enzymes are seen. In a patient who already has a large burden of liver disease, it may be challenging to determine if a rise in transaminase levels is due to the PARP inhibitor or progression of disease in the liver. Hy’s law can be used to assess for drug-induced liver injury. In any patient who meets Hy’s criteria for drug-induced liver injury (ie, alanine aminotransferase or aspartate aminotransferase > 3× the upper limit of normal [ULN] with concomitant bilirubin > 2× ULN, without alkaline phosphatase elevations or another clear reason for the elevations), immediate discontinuation of the drug is warranted.

KEY POINTS continued
- All three poly(ADP-ribose) polymerase (PARP) inhibitors cause fatigue, myelosuppression, and gastrointestinal side effects. Toxicity can be mitigated by preemptive patient education, prescription of prophylactic supportive medications, and careful patient selection.
- Niraparib is associated with significant thrombocytopenia, especially in the first 4 to 6 weeks of treatment. Olaparib and rucaparib may cause a rise in the serum creatinine level, thought to be due to their effect on the multidrug and toxin extrusion transporter in the kidney. Rucaparib may cause clinically insignificant transient elevations in liver transaminase levels.
Patients receiving rucaparib should be counseled to avoid hepatotoxins, including alcohol, and to discuss all supplements with the treating physician.

**Nasopharyngitis**

All PARP inhibitors, and especially olaparib, have been reported to cause nasopharyngitis.[3-11] Use of a humidifier at night and a decongestant or throat lozenges as required can be recommended to patients; they should also be counseled to avoid trauma to their nasal passageways.

**Hypertension and palpitations**

Hypertension and palpitations are commonly seen with niraparib due to an off-target effect of the drug on norepinephrine, dopamine, and serotonin transporters.[7] Patients should monitor their blood pressure at home, especially during the first month of treatment, and a plan should be made to initiate/adjust antihypertensives if needed. Heart rate and blood pressure should be monitored monthly in the clinic. Patients with preexisting cardiovascular disorders should be closely monitored.

**Rare but serious toxicities**

**Myelodysplastic syndrome (MDS).** Estimates indicate that 0.5% to 2.0% of patients treated with PARP inhibitors will go on to develop MDS or acute myeloid leukemia (AML). When trying to determine patients’ risk of future MDS or AML, it is important to consider prior exposure to alkylating agents such as cyclophosphamide, which they may have received for a prior breast cancer.[3-11] Prior exposure to platinum, as well as topoisomerase II inhibitors (such as etoposide) and anthracyclines (liposomal doxorubicin, or for breast cancer, doxorubicin) may also incrementally increase the risk of future hematologic malignancies. Patients with prolonged myelosuppression, or in whom there is a concern for MDS or AML, should be referred promptly to a hematologist for further evaluation, including bone marrow analysis and cytogenetic studies. MDS/AML may develop years later, so patients should have long-term follow-up.

**Pneumonitis.** Although dyspnea may be a sign of anemia, it is important to consider the rare possibility of pneumonitis (< 1% incidence) in patients who present with worsening dyspnea, cough, or fever, or associated suspicious radiographic changes.[3-11]

**Other Factors to Consider When Selecting a PARP Inhibitor**

**Oral administration**

All three PARP inhibitors are administered orally. [3-11] This is in contrast to IV delivery of most other cytotoxic agents used in the treatment of recurrent ovarian cancer. An oral agent may not be advisable for a patient with a recent history of small bowel obstruction and/or extensive peritoneal disease or preexisting refractory nausea, because of the likelihood of impaired drug absorption. A large burden of disease, and in particular use of PARP inhibitors late in the disease course, may be associated with reduced response rates. Olaparib, which previously required 16 capsules per day, was switched to a more manageable dosing regimen of 4 tablets per day.[3-5,10] Now being phased out, the capsules are not interchangeable with tablets. Rucaparib is administered as 2 capsules twice daily.[6,11] Niraparib’s once-daily dose is convenient and may be best taken at night to decrease nausea during the day.[7]

**Cost**

PARP inhibitors are frequently only available through specialty pharmacies. Clinicians may need to complete additional paperwork for insurance authorization, which may result in a delay in starting the drug. Even patients with good insurance coverage may discover that their coverage for outpatient oral medications is limited. The cost of PARP inhibitors is as high as $16,000 per month; thus, even a 10% to 20% copay may be a significant out-of-pocket expense. Many larger specialty pharmacies may be able to advise patients about financial assistance programs that can help them mitigate these costs.[15]

**Drug and food interactions**

It is important to consider potential interactions of PARP inhibitors with concomitant medications. Olaparib is metabolized by CYP3A, so patients should avoid strong or moderate inhibitors or inducers of this enzyme. If coadministration with a strong CYP3A inhibitor cannot be avoided, then the dose should be reduced from 300 mg to 100 mg twice daily. Similarly, patients should be advised to avoid grapefruit, Seville oranges, and the juices of these fruits, which contain furocoumarins, since they may inhibit intestinal CYP3A4 and therefore interfere with metabolism of olaparib. Absorption of olaparib may be slower when
taken with a high-fat meal, but this does not appear to decrease efficacy.[3-5] Rucaparib is predominantly metabolized via CYP2D6 and minor pathways, including CYP1A2 and CYP3A4, and may increase systemic levels of substrates of these enzymes that could result in toxicity.[6] Niraparib is not significantly metabolized by the cytochrome enzymes.[7]

**Future Directions**

As clinicians become comfortable with selecting PARP inhibitors and managing associated toxicities, the next challenge will be to safely and effectively administer these agents in combination with other therapeutic strategies. Current clinical trials are assessing combination approaches, such as PARP inhibition with immune-based strategies and/or other targeted agents, in an effort to overcome mechanisms of resistance to PARP inhibitors. In the recurrent, platinum-sensitive setting, a combination of olaparib and the antivascular agent cediranib is being investigated as an alternative to platinum-based chemotherapy (NRG GY004; ClinicalTrials.gov identifier: NCT02446600). Ongoing trials may soon help establish that PARP inhibitors can be used as part of primary therapy (veliparib: Gynecologic Oncology Group [GOG] 3015 [ClinicalTrials.gov identifier: NCT02470585]) or in the front-line maintenance setting (niraparib: PRIMA/GOG 3012 [ClinicalTrials.gov identifier: NCT02655016]; olaparib: SOLO-1 trial for patients with germline BRCA mutations [ClinicalTrials.gov identifier: NCT01844986]). While these combinations will add to the formidable array of choices with which patients and their clinicians already must contend, they will also allow clinicians to provide more effective treatments, more closely tailored to the individual needs of each patient.

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From the publishers of ONCOLOGY
Acute Kidney Injury in Patients With Cancer

Mark A. Perazella, MD1,2, Mitchell H. Rosner, MD3

ABSTRACT: Acute kidney injury (AKI) is a common complication in cancer patients and occurs in up to 30% of patients during their disease course. Multiple myeloma, leukemia/lymphoma, renal cell carcinoma, and hematopoietic stem cell transplantation are commonly associated with the development of AKI. Drugs used to treat various malignancies are also a common and notable cause of AKI in this population. Nephrology consultation is important to ensure proper and rapid diagnosis, as well as appropriate therapy and follow-up. In particular, knowledge of the nephrotoxicity of the various anticancer regimens employed is critical. This is a rapidly evolving area that requires continuous updating as new drugs are released into clinical practice and nephrotoxicity is observed.

Epidemiology of AKI in Patients With Cancer

Large population-based studies have supported the conclusion that acute kidney injury (AKI) is common in patients with cancer.[1,2] Depending upon the definition of AKI, the incidence rate varies, but in one study that used a cutoff of > 50% increase in serum creatinine level to define AKI, the rate of AKI was 17.5% within 1 year of cancer diagnosis.[2] Cancers with the highest risk of AKI include renal cell carcinoma (RCC), hepatocellular carcinoma, multiple myeloma, lymphoma, and leukemia.

Common Malignancies and Scenarios Associated With AKI

Multiple myeloma

AKI is common in patients with multiple myeloma (up to 50% will have an elevated serum creatinine level at diagnosis), can be secondary to pathology involving the glomeruli and/or tubules, and can be either directly associated with the production of a paraprotein or unrelated to the paraprotein (Figure 1).[3-5] AKI that is unrelated to paraprotein production is often secondary to volume depletion, hypercalcemia, or tumor lysis syndrome, and typically occurs early in the course of disease for myeloma patients.[6,7] Treatment centers on intravenous hydration and control of electrolyte and metabolic derangements, followed by myeloma-specific therapy. More specific to myeloma is AKI secondary to either a κ or λ paraprotein (Figure 1).[6,7] Depending upon the physicochemical properties of the paraprotein, protein deposition in the glomeruli can lead to glomerulonephritis of various histologic subtypes, typically associated with high-grade albuminuria (> 2 g/d).[8-10] These various paraprotein-related glomerular diseases require kidney biopsy for accurate diagnosis and appropriate therapeutic decision making. Treatment of these forms of glomerulonephritis centers on effective control of myeloma with chemotherapy.

A more common form of AKI associated with myeloma is light chain (LC) cast nephropathy, which refers to tubular injury and intratubular cast formation due to the overproduction and filtration of pathogenic LCs.[11,12] LC nephropathy represents the most common kidney manifestation of myeloma.[5] LCs associate with uromodulin, which is a normal secretory product of the loop of Henle,[13-15] forming intratubular casts that can obstruct urinary flow, as well as incite an inflammatory reaction leading to AKI. Intratubular cast formation is increased by volume depletion, metabolic acidosis, and use of loop diuretics and nonsteroidal anti-inflammatory drugs, as well as by iodinated radiopaque agents.[16,17]

In addition, LCs are endocytosed by proximal tubular cells, in which they are resistant to protease degradation and can cause proximal tubular injury manifested by Fanconi syndrome with or without AKI.[18,19] Treatment of LC nephropathy is multifaceted and includes cessation of nephrotoxic
medications; correction of acid-base and electrolyte disorders, including hypercalcemia; and institution of bortezomib-based antmyeloma therapy in combination with corticosteroids.[20-22] Treatment with bortezomib has the advantage of not requiring dosage adjustments in AKI patients.[23] In patients with a glomerular filtration rate (GFR) < 30 mL/min/1.73 m², a bortezomib-based triplet therapy regimen resulted in a renal response rate of 72%, with dialysis discontinuation in 57%.[22]

One way to increase the removal of nephrotoxic free LCs is by the addition of plasmapheresis or hemodialysis with a "high-cutoff" membrane, which allows for the removal of larger-molecular-weight proteins (up to 50 kilodaltons). The goal is to rapidly decrease free light chain (FLC) levels, as one study demonstrated that a 60% reduction in FLC levels by day 21 after diagnosis is associated with kidney recovery in 80% of cases.[24] Treatment of LC nephropathy with plasmapheresis remains controversial and is not applicable in patients receiving modern-day bortezomib-based therapy.[25]

Two clinical trials that were recently reported—MYRE and EuLITE—used extracorporeal therapy in addition to bortezomib-based therapy in patients presenting with newly diagnosed myeloma and a need for acute dialysis.[26,27] The MYRE study randomized 98 patients to either standard high-flux hemodialysis (HF-HD) or to high-cutoff hemodialysis (HCO-HD). There was no difference in the primary endpoint of dialysis independence at 3 months between the HF-HD and HCO-HD groups (33% vs 43%, respectively;
AKI IN CANCER PATIENTS

Table 1. Acute Kidney Injury (AKI) in Patients With Leukemia or Lymphoma

<table>
<thead>
<tr>
<th>Cancer-Related AKI</th>
<th>Therapy-Related AKI</th>
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<tr>
<td>Tumor infiltration of the kidneys (more common with lymphoma)</td>
<td>Therapy-related nephrotoxicity (including thrombotic microangiopathy, acute tubular injury, tubulointerstitial nephritis, intratubular obstruction, and glomerulonephritis)</td>
</tr>
<tr>
<td>Retroperitoneal lymphadenopathy leading to urinary tract obstruction</td>
<td>Tumor lysis syndrome with acute uric acid nephropathy and/or acute nephrocalcinosis</td>
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<tr>
<td>Hypercalcaemia-related prerenal kidney injury</td>
<td>Nausea, vomiting, and diarrhea associated with prerenal azotemia</td>
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<tr>
<td>Various paraneoplastic glomerular disorders</td>
<td>Sepsis-associated kidney injury</td>
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<tr>
<td>Lysosyuria with acute tubular injury associated with AMoL or CMML (rare)</td>
<td>Nephrotoxicity (acute tubular injury and acute tubulointerstitial nephritis) from other common medications (NSAIDs, ACE inhibitors, ARBs, diuretics, antimicrobial agents)</td>
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<tr>
<td>Acute tubulointerstitial nephritis associated with hemophagocytic disease (rare)</td>
<td>Contrast-associated kidney injury</td>
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<tr>
<td>Disseminated intravascular coagulation (rare)</td>
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ACE = angiotensin-converting enzyme; AMoL = acute monocytic leukemia; ARB = angiotensin receptor blocker; CMML = chronic myelomonocytic leukemia; NSAIDs = nonsteroidal anti-inflammatory drugs.

At 6 months, more patients in the HCO-HD arm than the control group were independent of dialysis (60% vs 38%, respectively; $P = .03$). However, the difference at 6 months was tempered by concern that the renal response to bortezomib in the HF-HD group was less than had been seen in other studies, suggesting that this population may have been atypical.[26] The EuLiTE study randomized 90 patients in a manner similar to that of the MYRE study—to either HF-HD or HCO-HD in addition to bortezomib-based chemotherapy. However, the dialysis regimens in the EuLiTE study were significantly different from those used in the MYRE study, making comparisons difficult. At 3 months, there was no difference in kidney recovery between the HF-HD and HCO-HD groups (55.8% vs 51.6%, respectively; $P = $ not significant). Given that both studies were small and had equivocal results, the routine use of HCO-HD cannot be recommended.[27]

Lymphoma and leukemia

Patients with lymphoma and leukemia are susceptible to AKI from a variety of causes that can be broadly divided into those directly related to the cancer and those related to therapies utilized in the treatment of the malignancy (Table 1).[28] Many of these etiologies are rare, and the most common causes of AKI are sepsis, nephrotoxicity and radiocontrast exposure, tumor lysis syndrome, and prerenal azotemia.[29,30] A unique etiology of AKI is when leukemic or lymphomatous cell infiltration of the kidney leads to tubular compression and disruption of the renal microcirculation, resulting in falls in glomerular filtration.[31,32] Patients are typically asymptomatic, although flank pain may occasionally occur. Renal imaging with ultrasound or CT is usually diagnostic, with findings of bilaterally enlarged kidneys (Figure 2). Once appropriate chemotherapy is initiated, patients typically show rapid improvement in kidney function.[31]

Clinicians should be aware of the association of leukemia and lymphoma with paraneoplastic glomerular diseases. The most common association is between Hodgkin lymphoma and minimal change disease (MCD), which occurs in 0.4% of cases of Hodgkin lymphoma.[33,34] Other rarer glomerular diseases include monoclonal immunoglobulin deposition disease,[35] amyloidosis,[36] immunotactoid glomerulopathy,[37] and membranous nephropathy.[38] Patients typically present with nephrotic-range proteinuria (> 3 g/d), as well as variable levels of kidney dysfunction. Of note, the diagnosis of the glomerular disease may predate clinical appearance of the malignancy. Typically, treatment of the cancer improves the outcome of the glomerulopathy.[39]

RCC

RCC is a disease of increasing incidence that has the highest mortality rate among genitourinary tract cancers.[40,41] Seventy percent of all RCCs are of the clear cell histologic subtype.[42] Both locally advanced and metastatic disease carry a poor prognosis, as does kidney disease that develops post-nephrectomy.[42] RCCs are more often found incidentally on sensitive abdominal imaging for another disease pro-
The National Cancer Institute notes that > 65,000 new RCCs, predominantly small renal masses, are being diagnosed annually, likely reflective of widespread imaging. This has led to a change in the percentage of early-stage T1 kidney cancers (< 7 cm in size and confined to the kidney), from 43% (2 decades ago) to > 60% more recently.[43] The 5-year survival rate has improved dramatically (> 90% for T1 tumors, and approaching 100% for those < 4 cm).

Surgical treatment of RCC is associated with substantial risk of AKI, with a reported increase in rate from 2% in 1998 to 10.4% in 2010, without an increase in the number of patients requiring dialysis.[44,45] Patients with RCC are more likely to suffer from post-procedure AKI (Figure 2) when underlying pre-nephrectomy chronic kidney disease (CKD) and other comorbidities, such as older age, diabetes mellitus, and hypertension, are present.[43] Preoperative screening of patients at risk for postsurgical AKI includes estimating GFR and measuring albuminuria.[46,47] Nephrotoxin avoidance and maintenance of adequate renal perfusion during surgery reduces the risk of post-nephrectomy AKI.[48] While radical nephrectomy is considered the conventional therapy for large renal masses or nonlocalized tumors, nephron-sparing procedures, including partial nephrectomy, and ablative therapies, are emerging as effective therapies for small tumors.

The majority of data suggest that partial nephrectomy results in comparable oncologic outcomes and overall survival compared with radical nephrectomy.[49] Furthermore, the AKI rate is higher with radical nephrectomy than with partial nephrectomy.[50] Given this risk, partial nephrectomy is recommended whenever technically feasible; in some cases, active surveillance without surgery is recommended for small renal masses, to preserve kidney function.[51] Overall, it appears that partial nephrectomy offers equivalent tumor control with less AKI and should be the preferred modality for stage T1 RCCs. Percutaneous ablative techniques may further lower the incidence of AKI, but more data are needed.

Hematopoietic stem cell transplantation
Hematopoietic stem cell transplantation (HSCT) is an important therapy for cancer patients; however, AKI may develop following the procedure. Radiation injury, conditioning chemotherapy, sinusoidal obstruc-

**Figure 2. CT Scan Demonstrates Massive Renomegaly in a Patient With Lymphoma and Acute Kidney Injury**—Bilateral enlargement of the kidneys is observed in a patient with lymphoma due to infiltration of the renal parenchyma by lymphoma cells.
Acute kidney injury (AKI) in cancer patients is a common complication that can occur with hematopoietic stem cell transplantation (HSCT). AKI can be caused by various factors, including sepsis, sinusoidal obstruction syndrome (SOS), thrombotic microangiopathy (TMA), graft-vs-host disease (GVHD), and nephrotoxic medications. The incidence rates of AKI range from 15% to 73%, depending on the type of transplant and the conditioning regimen used.

TMA that develops with HSCT is often associated with AKI. It is characterized by endothelial swelling and damage with fibrin thrombi within glomerular capillary loops and arterioles. GVHD may promote TMA secondary to direct endothelial cell injury. Treatment options include discontinuing or reducing the dose of calcineurin inhibitors, defibrotide, and therapeutic plasma exchange (TPE).

Acute GVHD that develops during HSCT is an independent risk factor for AKI. AKI occurs with GVHD because of cytokine-mediated kidney inflammation or cyclosporine exposure. Prerenal AKI may also develop from vomiting and diarrhea associated with gastrointestinal involvement by GVHD. Moreover, GVHD promotes cytomegalovirus reactivation, which further contributes to AKI in HSCT recipients. Treatment options include prednisone, antithymocyte globulin, sirolimus, and mycophenolate mofetil.

Anticancer Drug–Induced AKI

Anticancer drug–related nephrotoxicity is a common and notable cause of AKI. Etiologies include primarily acute tubular injury/necrosis (ATI/N), acute interstitial nephritis (AIN), and a variety of glomerular and vascular injuries. AKI can result from treatment with conventional chemotherapy, immunotherapies, or targeted agents. Prevention and treatment strategies include infusions of prostaglandin E, pentoxifylline, and low-dose heparin.

Table 2: Risk Factors for and Causes of Acute Kidney Injury With HSCT

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>(\text{GVHD} = \text{graft-vs-host disease; HSCT = hematopoietic stem cell transplantation; NSAIDs = nonsteroidal anti-inflammatory drugs.})</th>
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<tbody>
<tr>
<td>Nausea/vomiting and diarrhea associated with acute gastrointestinal GVHD</td>
<td></td>
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<tr>
<td>Drug-induced nausea/vomiting</td>
<td></td>
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<tr>
<td>Prerenal/acute tubular injury</td>
<td></td>
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<tr>
<td>Sepsis, sinusoidal obstruction syndrome</td>
<td></td>
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<tr>
<td>Acute GVHD, marrow infusion syndrome</td>
<td></td>
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<tr>
<td>Thrombotic microangiopathy</td>
<td></td>
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<tr>
<td>Acute GVHD, calcineurin inhibitors, total-body irradiation</td>
<td></td>
</tr>
<tr>
<td>Acute tubular injury/crystalline nephropathy</td>
<td></td>
</tr>
<tr>
<td>Amphotericin, vancomycin, aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Polymyxins (colistin), acyclovir, ganciclovir</td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors, NSAIDs, other nephrotoxins</td>
<td></td>
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</tbody>
</table>

Notably, AKI adversely affects survival, with mortality rates approaching 80% in dialysis-requiring individuals. Prevention and treatment strategies include infusions of prostaglandin E, pentoxifylline, and low-dose heparin. Early administration of the antithrombotic defibrotide and a fibrinolytic agent appears to offer some benefit.
timers and plasminogen activator inhibitor, as well as exposure of a denuded endothelial surface to fibrin and platelets, facilitates injury within the renal microvasculature.[65,67-69] Drug discontinuation is standard; plasmapheresis is generally ineffective, while the role of eculizumab is currently unknown.[65,70,71]

ATI/N is the most common pathologic lesion associated with AKI from conventional chemotherapy. The platinums, ifosfamide, pemetrexed, zoledronic acid, and other agents are directly toxic to tubular epithelium. These agents activate intracellular pathways of injury and apoptosis, generate reactive oxygen species, induce oxidative stress, and damage mitochondria.[65,67] The antifolate methotrexate causes AKI via intratubular crystal precipitation, with obstructive and inflammatory interstitial injury. Intravenous fluids and urinary alkalinization are used to prevent and treat AKI, while renal replacement therapy and glucarpidase may be required for severe systemic toxicity.[65,67] A number of chemotherapeutic agents, including ifosfamide, doxorubicin, and carboplatin, have been observed to cause AKI from AIN.[65-67]

**Immunotherapies**

Immunotherapies are an important addition to cancer treatment.[72-74] High-dose interleukin-2 and interferon are older agents that cause AKI.[72,73] High-dose interleukin-2 causes cytokine release with an associated capillary leak syndrome, which results in prerenal azotemia and ATI/N. Drug discontinuation reverses AKI. Interferon toxicity presents clinically with AKI along with high-grade proteinuria from foci cal segmental glomerulosclerosis (FSGS) or MCD.[72] Drug discontinuation (+/− corticosteroids) is fairly effective for MCD, but not for FSGS. The immune checkpoint inhibitors ipilimumab and nivolumab and pembrolizumab enhance tumor killing by preventing dendritic cells and tumor ligands from binding to cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) receptors, respectively. Receptor blockade activates and enhances T-cell killing of tumor cells, which can lead to loss of tolerance to self (and exogenous medications), causing AIN.[69,70] Drug discontinuation and corticosteroids are effective in reversing AKI in this setting.

Chimeric antigen receptor (CAR) T cells are host cells that are harvested and engineered to express receptors that recognize and bind tumor antigens. These T cells directly target and destroy cancer cells but also promote macrophage activation and cytokine release syndrome, which can result in capillary leak and prerenal AKI and ATI/N; AKI due to tumor lysis syndrome may also develop.[74] Prevention and treatment of AKI include chemotherapy and steroids prior to CAR T-cell exposure to reduce the tumor burden. With severe cytokine release syndrome, an interleukin-6 receptor blocker may reduce adverse systemic effects.[74]
Table 3. Anticancer Drug–Induced Acute Kidney Injury (AKI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Kidney Syndrome</th>
<th>Kidney Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum compounds (cisplatin, carboplatin, oxaliplatin)</td>
<td>AKI</td>
<td>Acute tubular injury</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia, NDI, salt wasting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proximal tubulopathy</td>
<td></td>
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<tr>
<td>Ifosfamide</td>
<td>AKI</td>
<td>Acute tubular injury</td>
</tr>
<tr>
<td></td>
<td>NDI, proximal tubulopathy</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>AKI</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Hypertension, hematuria, proteinuria</td>
<td></td>
</tr>
<tr>
<td>Mitomycin-C</td>
<td>AKI</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Hypertension, hematuria, proteinuria</td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>AKI</td>
<td>Acute tubular injury</td>
</tr>
<tr>
<td></td>
<td>NDI, proximal tubulopathy</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>AKI</td>
<td>Acute tubular injury</td>
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<tr>
<td></td>
<td></td>
<td>Crystalline nephropathy</td>
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<tr>
<td><strong>Targeted agents</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anti-VEGF agents (aflibercept, bevacizumab)</td>
<td>AKI</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Hypertension, proteinuria</td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors (axitinib, pazopanib, sorafenib, regorafenib, sunitinib)</td>
<td>AKI</td>
<td>Acute tubulointerstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Hypertension, proteinuria</td>
<td>Acute tubular injury</td>
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<tr>
<td></td>
<td></td>
<td>Focal segmental glomerulosclerosis</td>
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<tr>
<td></td>
<td></td>
<td>Thrombotic microangiopathy</td>
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<tr>
<td>BRAF inhibitors (dabrafenib, vemurafenib)</td>
<td>AKI</td>
<td>Acute tubulointerstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Electrolyte disorders</td>
<td>Acute tubular injury</td>
</tr>
<tr>
<td>ALK inhibitors (crizotinib)</td>
<td>AKI</td>
<td>Acute tubulointerstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Electrolyte disorders</td>
<td>Acute tubular injury</td>
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<tr>
<td></td>
<td>Renal microcysts</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>AKI</td>
<td>Acute tubular injury</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease</td>
<td></td>
</tr>
<tr>
<td><strong>Immunotherapy agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferons (alpha, beta, gamma)</td>
<td>AKI</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>AKI</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Capillary leak syndrome</td>
<td>None</td>
</tr>
<tr>
<td>Chimeric antigen receptor (CAR) T cells</td>
<td>AKI</td>
<td>Capillary leak syndrome with AKI, tumor lysis syndrome</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>Capillary leak syndrome with AKI, tumor lysis syndrome</td>
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<tr>
<td></td>
<td></td>
<td>Capillary leak syndrome with AKI, tumor lysis syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>CTLA-4 inhibitors (ipilimumab)</td>
<td>AKI</td>
<td>Acute tubulointerstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>Lupus-like glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>PD-1 inhibitors (nivolumab, pembrolizumab)</td>
<td>AKI</td>
<td>Acute tubulointerstitial nephritis</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates (pamidronate, zoledronic acid)</td>
<td>AKI</td>
<td>Acute tubular injury</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>AKI</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
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</tr>
</tbody>
</table>

CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; NDI = nephrogenic diabetes insipidus; PD-1 = programmed death 1; VEGF = vascular endothelial growth factor.
Targeted agents
These drugs target specific gene mutations within malignant tissue, thereby inhibiting oncogenic signaling cascades associated with tumor growth and effectively treating cancer. However, these agents are also associated with a number of kidney disorders: AKI, proteinuria, hypertension, and electrolyte disturbances. Antiangiogenesis drugs cause AKI by targeting vascular endothelial growth factor within the renal microvasculature and causing TMA, although AIN and FSGS have also been described.[66] The ALK (anaplastic lymphoma kinase) inhibitor crizotinib causes AKI via acute tubulointerstitial injury, which is partially reversible with drug discontinuation.[68] The BRAF inhibitors vemurafenib and dabrafenib have been noted to cause a dose-related AKI through acute tubulointerstitial injury, although limited histologic data are available. Inhibition of the MAP kinase pathway may underlie this lesion.[75] Treatment hinges on drug discontinuation; AKI reverses in a majority of cases.

Conclusion
In conclusion, AKI is a relatively common complication in patients with cancer. As discussed, a number of malignant diseases, as well as their treatments, can cause kidney damage. Clinicians caring for this patient group should be familiar with these processes.

Financial Disclosure: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

REFERENCES
The Case
A 62-year-old man with American Joint Committee on Cancer (AJCC) 8th Edition clinical stage IIC (cT2aN0M0), Gleason grade group 3 (4 + 3) prostate adenocarcinoma, with a pretreatment prostate-specific antigen (PSA) level of 15.6 ng/mL, elected to proceed with radical prostatectomy as definitive management. The final pathology report showed extracapsular extension (pT3a), negative pelvic lymph nodes (pN0), positive surgical margins (Figures 1 and 2), Gleason grade group 4 (4 + 4), and an undetectable post-prostatectomy PSA level, which was classified as AJCC 8th Edition pathologic stage IIIB. The patient was referred to a radiation oncologist, and the existing randomized data supporting adjuvant radiation therapy were reviewed. Further, GenomeDx’s Decipher test was performed and showed a high-risk score.
Management options, including adjuvant radiation therapy and close observation via serial biochemical testing, were discussed with the patient, who ultimately elected observation. Nine months after prostatectomy, ultrasensitive PSA testing showed a detectable level (0.03 ng/mL). PSA levels 6 weeks and 12 weeks later were 0.07 ng/mL and 0.18 ng/mL, respectively.

What is the most appropriate next step in the management of this patient?

A. Observation until his PSA level is > 0.2 ng/mL, then recommend salvage radiation therapy
B. Recommend salvage radiation therapy now, without androgen deprivation therapy (ADT)
C. Recommend salvage radiation therapy now and consider concurrent ADT
D. Proceed with prostate cancer–specific positron emission tomography (pcPET) imaging, followed by salvage radiation therapy if there is no evidence of metastatic disease

Answer and full discussion appear on page 362.
Correct Answer: C

Discussion
This case highlights several important issues in the management of post-prostatectomy patients with high-risk features. In this discussion, we will review the evidence for initiating adjuvant radiation therapy in patients with extracapsular extension, seminal vesicle invasion, and/or positive surgical margins, and address the controversy regarding early salvage radiation therapy as a substitute for adjuvant radiation therapy. Importantly, the tools available to prostate cancer physicians are increasing rapidly; here, we will review the value of genomic classifiers in adjuvant radiation therapy decision making. Further, we will discuss the role of next-generation prostate cancer-specific imaging in the context of salvage radiation therapy decision making.

Adjuvant vs early salvage radiation therapy
The American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO) guideline statement on adjuvant and salvage radiotherapy after prostatectomy states that patients with adverse pathologic findings, including extracapsular extension, seminal vesicle invasion, and/or positive surgical margins, should be offered adjuvant radiation therapy.[1] These recommendations are based on the results of three randomized studies: Southwest Oncology Group (SWOG) 8794,[2,3] European Organisation for Research and Treatment of Cancer (EORTC) 22911,[4,5] and Arbeitsgemeinschaft Radiologische Onkologie (ARO) 96-02.[6,7] The 10-year follow-up results are available for both the ARO and EORTC studies, each demonstrating an improvement in biochemical progression–free survival, but not overall survival, with adjuvant radiation therapy.[5,6] The 15-year follow-up is available for the SWOG study, which showed that adjuvant radiation therapy reduced metastases and increased survival.[3] Further, these three studies serve as the basis for a Cochrane review published in 2011, which demonstrated an overall survival benefit at 10 years, with a number needed to treat (NNT) of 10.[8]

Despite these data and the AUA/ASTRO guideline statement in favor of adjuvant radiation therapy for high-risk features,[1] fewer than 10% of patients in the United States receive adjuvant radiation therapy in this setting.[9] Concerns about overtreatment and treatment toxicity are likely drivers behind this practice pattern. Relevant to these concerns, it should be mentioned that in the SWOG study (which utilized outdated radiation techniques by today’s standards), global health-related quality of life, while lower in the radiation arm initially, was actually higher than that seen in the observation arm at 5 years.[10]

Another likely contributor to the low rates of adjuvant radiation therapy delivery is the fact that, at present, there are no prospective randomized comparisons of adjuvant vs early salvage radiation therapy, although these studies are well underway (eg, RADICALS, ClinicalTrials.gov identifier: NCT00541047; GETUG-AFU 17, NCT00667069; and RAVES, NCT00860652). Of note, a large multi-institutional propensity score–matched cohort of 1,566 patients demonstrated an improvement in biochemical recurrence, distant metastases, and overall survival in the patients who received adjuvant vs early salvage radiation therapy.[11] Nevertheless, while these prospective randomized studies are very important, and we anxiously await the results, there is emerging evidence that suggests that genomic classifiers may serve as a more personalized tool to select patients for adjuvant radiation therapy:[12,13]

The value of genomic classifiers
Our patient underwent Decipher testing, which contributed to our recommendation for adjuvant radiation therapy (although he ultimately declined). Decipher is a 22-gene expression array that is predictive for the development of metastases after radical prostatectomy.[13] Den et al demonstrated that for patients with high Decipher scores, the 5-year incidence of metastases was significantly lower in the patients who received adjuvant radiation compared with those who received salvage radiation. There was no difference in the incidence of metastases between patients with low Decipher scores who received adjuvant vs salvage radiation.[13]

Dalela et al built on these findings and developed a nomogram incorporating the Decipher score to help tailor recommendations to a patient’s specific risk factors.[12] In their model, risk factors included pT3b/T4 disease, pathologic Gleason score > 8, lymph node invasion, and a high Decipher score. In patients with two or more risk factors, the NNT with adjuvant radiation therapy to prevent one clinical recurrence was 3.1.[12] The use of genomic classifiers, such as Decipher, should be considered to help navigate post-prostatectomy decision making. Based on these data, our patient was very likely to benefit from adjuvant radiation therapy. However, despite this recommendation, he declined adjuvant therapy and is now presenting with a rising PSA level.

Is next-generation imaging at odds with early salvage radiation?
Historically, rates of successful salvage have been disappointing.[14] Contemporary tools such as ultrasensitive PSA testing and next-generation imaging can help further individualize therapy to better select patients likely to benefit from salvage radiation. However, at present, determining how best to use these tools together remains challenging, and one might argue that next-gen-
eration imaging is even in conflict with the goal of early salvage radiation. One reason for the historically low rates of successful salvage is that, in a proportion of patients, a rising PSA level is due to early metastatic disease rather than a prostate bed recurrence.

Conventional prostate cancer imaging techniques (CT and technetium $^{99m}$Tc medronic acid [MDP] bone scan) have a low sensitivity for the detection of lymph node or bone metastases unless PSA levels are very high,[15] and therefore are of little use in ruling out metastatic prostate cancer when the patient has low PSA levels. On the other hand, next-generation imaging, specifically pcPET, can detect prostate cancer recurrences at low PSA levels.[16] Although these technologies are likely to drastically reshape the landscape of prostate cancer management, at present it is unclear how to use these tools in a patient such as the one described here. The current pcPET imaging platforms include C-11/F-18 choline; gallium 68/F-18 prostate-specific membrane antigen (PSMA); and the US Food and Drug Administration–approved Axumin, also known as F-18 anti-1- amino-3-[18F]fluorocyclobutane-1-carboxylic acid (FACBC). A recent comprehensive review of existing studies reported that the sensitivity of PSMA at a PSA level < 1.0 ng/mL, 1.0–2.0 ng/mL, and > 2.0 ng/mL, was 51.5%, 74.0%, and 90.5%, respectively.[16] The sensitivity of the Axumin scan at a PSA level < 1.0 ng/mL, 1.0–2.0 ng/mL, and > 2.0 ng/mL, was 38%, 65%, and 78%, respectively.[16] The sensitivity of the choline scan at a PSA level < 1.0 ng/mL, 1.0–2.0 ng/mL, and > 2.0 ng/mL, was 19.5%, 44.5%, and 76.0%, respectively.[16]

Although the pcPET modalities are significantly more adept at showing prostate cancer recurrences compared with conventional imaging techniques, the optimal PSA range for these modalities is above the PSA range at which salvage radiation therapy should be initiated for the highest likelihood of success. Salvage radiation is most successful in patients with pre-salvage PSA levels < 0.50 ng/mL,[14,17] with data to support that the best outcomes are seen in patients with pre-salvage PSA levels < 0.20 ng/mL.[18] In the updated multi-institutional salvage radiotherapy nomogram from Tendulkar et al, the 5-year rates of freedom from biochemical progression were 71%, 63%, 54%, 43%, and 37%, for patients with pre-salvage PSA levels of 0.01–0.2 ng/mL, 0.21–0.50 ng/mL, 0.51–1.0 ng/mL, 1.01–2.0 ng/mL, and > 2.0 ng/mL, respectively.[18]

Therefore, for a patient such as ours, with risk factors for prostate bed recurrence (ie, positive surgical margins in our patient), who is presenting with a very low (below the sensitivity of pcPET) but detectable and rising PSA, we do suggest proceeding with salvage radiation therapy without first obtaining pcPET. However, for patients with PSA levels that would suggest a reasonable likelihood of detecting recurrence on pcPET, with a pretest sensitivity that appears to rise above 50% with PSA absolute values exceeding 0.5 ng/mL, it would seem appropriate to consider pcPET to evaluate for distant metastatic disease or a gross prostate bed recurrence prior to proceeding with salvage radiation therapy, since these findings might alter management. The impact of

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From the publishers of ONCOLOGY
Postoperative radiation therapy improves oncoplastic outcome in select men undergoing radical prostatectomy with high-risk features for postsurgical recurrence.

Ultra-sensitive prostate-specific antigen (PSA) assays, genomic classifiers, and novel imaging tools may improve risk stratification, enhance patient selection for postoperative therapy, and improve postoperative radiation therapy targeting.

In men with persistent or rising PSA levels following prostatectomy, the addition of androgen deprivation therapy to salvage radiation therapy improves the likelihood of successful salvage and fosters superior cancer-related outcomes compared with radiation therapy alone.

Salvage radiation therapy target volumes, dose, and the benefit of ADT

Again, for our patient, we would recommend proceeding directly to salvage radiation therapy. In our practice, the target volume for salvage radiation therapy includes the prostate and seminal vesicle fossa, which is treated to a dose of 66 Gy with conventional fractionation, using volumetric-modulated arc therapy with daily cone beam CT for image guidance (Figure 3). Importantly, moderately hypofractionated post-prostatectomy radiation is currently being compared with conventionally fractionated post-prostatectomy radiation in NRG Oncology’s NRG-GU003 trial (ClinicalTrials.gov identifier: NCT03274687).

Consideration can be given to electively treating the regional lymph nodes as well, though most of the prospective trials using postoperative radiation therapy have not done so. The role of pelvic lymph node radiation for intact prostate cancer has long been an area of considerable debate. The existing prospective randomized trials fail to provide convincing evidence of a benefit from pelvic lymph node radiation.[19,20] However, both of these studies have been criticized for flaws in their design, and this question is currently being addressed again in Radiation Therapy Oncology Group (RTOG) 0924 (ClinicalTrials.gov identifier: NCT01368588). Meanwhile, there are no prospective randomized trials reporting on pelvic lymph node vs prostate bed-only target volumes in salvage radiation therapy, although this is currently being addressed in RTOG 0534 (ClinicalTrials.gov identifier: NCT00567580).

Importantly, two large multi-institutional prospective randomized controlled trials addressing the role of ADT in salvage radiation have been published in recent years: RTOG 9601 and GETUG-AFU 16.[21,22] Notably, elective nodal irradiation was not allowed in either of these studies, further supporting the omission of elective nodal irradiation in the salvage setting. These studies are the basis for our recommendation to consider ADT with salvage prostate radiation therapy in our patient (Answer C). RTOG 9601 randomized patients after radical prostatectomy with PSA levels 0.2 to 4.0 ng/mL to salvage radiation therapy with 24 months of concurrent and adjuvant bicalutamide or placebo. At 12-year follow-up, improved overall and prostate cancer–specific survival and a reduction in the incidence of metastases were demonstrated in the bicalutamide arm.[21] Similarly, GETUG-AFU 16 randomized patients after radical prostatectomy with PSA levels of 0.2 to 2.0 ng/mL to salvage radiation therapy with or without 6 months of concurrent and adjuvant goserelin acetate, and demonstrated improved freedom from biochemical and clinical progression at 5 years.[22]

In our practice, we use short-term (~6 months) neoadjuvant and concurrent luteinizing hormone-releasing hormone agonist therapy with salvage radiation. Importantly, neither RTOG 9601 nor GETUG-AFU 16 enrolled patients with pre-salvage PSA levels < 0.2 ng/mL.[21,22] Further, post-hoc analysis of RTOG 9601 failed to show a benefit from the addition of ADT for patients with pre-salvage PSA levels < 0.7 ng/mL.[21] However, the benefit from ADT that was observed in GETUG-AFU 16 did persist for patients with pre-salvage PSA levels < 0.5 ng/mL compared with patients with pre-salvage PSA levels > 0.5 ng/mL.[22] Therefore, although we do recommend ADT with salvage radiation for patients with PSA levels < 0.7 ng/mL, our recommendation is not as strong as it is for patients with PSA levels > 0.7 ng/mL, and we will support omission of ADT in these patients if they are opposed to hormone therapy.

Summary

In recent years, the therapeutic and diagnostic tools in prostate cancer, as well as the data available to guide post-prostatectomy decision making and improve salvage radiation therapy outcomes, have evolved substantially. Genomic classifiers can be used to help improve the therapeutic ratio in adjuvant radiation therapy. [12,13] Ultrasensitive PSA testing allows for salvage radiation therapy to be initiated earlier, which, in large multi-institutional datasets, is associated with improved outcomes.[14,17,18] Further, pcPET may be useful in patients with biochemically recurrent or persistent prostate cancer following prostatectomy, although salvage radiation therapy should not be withheld while waiting for PSA levels to reach the range that is appropriate for these imaging modalities. Finally, prospective randomized data support the use of ADT with salvage radiation to further improve outcomes for these patients.

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Harnessing the Immunomodulatory Effects of Radiation Therapy

Allison M. Campbell, MD, PhD1, Roy H. Decker, MD, PhD2,3

ABSTRACT: In this article, we discuss the immunogenicity of radiation-induced cell death and describe the innate immune signaling pathways that precede adaptive antitumoral immunity. The innate and adaptive immune systems work in concert to generate systemic immune responses. In the setting of cancer, DNA damage caused by radiotherapy activates the innate immune system while tumor cell death liberates antigen that serves as a target for adaptive immunity. The immunomodulatory effects of radiation have been investigated in preclinical models; here we summarize the available data, with particular attention to the effects of radiotherapy timing, location, dose, and fractionation strategy on the antitumoral immune response. We synthesize preclinical and clinical information regarding the potential superiority of hypofractionated radiation for induction of proinflammatory responses. Although many questions remain, early successes with combining immunotherapy and radiotherapy merit further inquiry into the dose and fractionation strategies best able to activate and sustain an antitumoral response.

Introduction

Since x-rays were first used to treat cancer in the 1890s,[1] the field of radiation oncology has evolved clinically toward dose and fractionation strategies that maximize tumor control while minimizing side effects. Most of these side effects—inflammation, fibrosis, necrosis—are immunologically mediated. As we have learned more about the way cells die, and the way the immune system preserves self-tolerance to protect us from autoimmunity while fighting foreign pathogens, it has become clear that cell death occurs on a spectrum from immunogenic to tolerogenic. Current clinical dose and fractionation strategies likely lie in the middle of this spectrum because we have empirically selected treatment regimens over decades for the express purpose of killing tumor cells while minimizing attendant inflammation.

Recent successes in combining immunotherapy and radiotherapy have prompted consideration of the role radiation might play in augmenting the antitumoral immune response. Because radiation can kill cells and liberate tumor antigen, it functions as a complete vaccine: both antigen and adjuvant.[2] In the setting of checkpoint inhibition, which removes barriers to activation of the adaptive immune response, all the ingredients of a successful immunologic defense are present: innate immune activation lays the groundwork for a T-cell–mediated systemic defense. In this article, we discuss radiation’s immunomodulatory effects, with particular attention to the impact of dose and fractionation on the antitumoral response.

Radiation-Induced Cell Death: Tolerogenic, Immunogenic, or Both?
The immune system is an antimicrobial arsenal, curated by evolution, and challenged not only with responding effectively to threats from the environment, but also with preserving self-tolerance. It has two arms that work in concert: the innate immune system, which acts quickly to protect the host from imminent danger; and the adaptive immune system, which is capable of “learning” the nature of a threat and mounting a specific defense. Defending the self too robustly can be as deadly to the host as no defense at all. The problem of self/nonself discrimination is central to understanding the immunogenicity of cell death. In normal physiologic conditions, cellular turnover is estimated to be 50 to 70 billion cells per day, with the majority of these cells dying via apoptosis.[3] By necessity, apoptotic cell death is nonimmunogenic or actively tolerogenic, given the daily burden that homeostatic cellular turnover places on clearance mechanisms.[4]

However, there are circumstances in which cell death should elicit an immune response, such as injury to or infection of the host. The most extensively studied forms of proinflammatory cell death are necrosis, necroptosis, pyroptosis, and autophagic cell death.[5-7] While a full description of these processes is beyond the scope of this article, these forms of cellular demise activate the innate immune system, setting the stage for a subsequent adaptive response. How, then, do cells die following irradiation? Mitotic catastrophe and cellular senescence are induced by radiation, but these terms refer to the loss of proliferative capacity, not to the cessation of all cellular processes. True cellular demise involves a loss of morphologic and genomic integrity, followed by a confrontation with the immune system, eliciting a tolerogenic or immunogenic response, depending on the manner of death. Our focus here will be on two mechanisms by which radiation can promote an inflammatory response.
1. AIM2 recognition of DNA damage

In murine models involving exposure to high-dose radiation, innate immune signaling pathways activated by DNA damage have been shown to proceed through cytosolic DNA sensors. AIM2 (absent in melanoma 2) is a cytoplasmic DNA sensor that recognizes double-stranded DNA damaged by radiation. Activation of AIM2 causes assembly of the inflammasome, which results in activation of caspase 1. [8] Activated caspase 1 triggers release of proinflammatory cytokines and promotes the proinflammatory form of cell death known as pyroptosis. [9]

2. cGAS recognition of DNA damage, with activation of STING

Recent work by Vanpouille-Box et al demonstrated the activation of a second innate immune pathway, which depends on the adaptor protein STING (stimulator of interferon genes). [10] They showed that in the presence of a checkpoint inhibitor and a radiotherapy regimen of 8 Gy × 3, the cytosolic DNA sensor cGAS (cyclic GMP-AMP synthase) recognizes damaged DNA and activates STING, which results in the recruitment of dendritic cells, and the priming of antitumoral CD8+ T cells. This dose and regimen reliably results in tumor responses both within and distant from the radiation field, with the latter off-target response termed the abscopal effect (depicted in the Figure). At doses higher than 8 Gy × 3, the DNA exonuclease TREX1 (3’ repair exonuclease 1) is activated, degrades the cytosplasmic DNA, and prevents recruitment of dendritic cells and the subsequent priming of T cells, which eliminates the immunologically mediated response against tumors outside the initial radiation field. [10]

Synergy Between Radiotherapy and Immunotherapy

AAs noted above, the abscopal effect refers to the regression of tumor distant from a treated site. Historically, the physiologic underpinnings of this phenomenon were unknown, but work over the past decade has shown the effect to be immunologically mediated. [11] Particular attention has been paid to abscopal responses documented in case reports, which describe robust off-target effects in patients receiving immune checkpoint inhibitors who also are given radiation. A recent systematic review of case reports of the abscopal effect identified 46 reported cases in the literature. [12] Of particular note is a study in the New England Journal of Medicine by Postow et al, describing a 33-year-old woman with metastatic melanoma. [13] While being treated with ipilimumab, she received palliative radiation to a plural soft-tissue mass, which was treated to 28.5 Gy (9.5 Gy × 3 fractions). When a 1-month follow-up scan showed no evidence of response, she was given another cycle of ipilimumab. The patient’s 4-month follow-up scan showed a dramatic response in the radiated lesion, as well as responses at her other sites of disease: hilar and splenic lesions. Her response correlated with the production of antibodies against the NY-ESO-1 (New York esophageal squamous cell carcinoma–1) melanoma protein and an increase in the number of NY-ESO-1–specific interferon γ-producing CD4+ T cells, indicating that she had mounted an adaptive immune response to tumor antigen.

The most dramatic examples of the abscopal effect have occurred in the presence of immune checkpoint inhibitors, likely because checkpoint inhibition reduces the barrier to creating an engaged and sustained adaptive immune response. The conceptual appeal of synergy between radiation and immunotherapy prompted a secondary analysis of the KEYNOTE-001 trial, which examined disease control in patients who had received radiotherapy prior to receiving pembrolizumab. The original KEYNOTE-001 trial enrolled 98 patients between 2012 and 2014, with the goal of studying pembrolizumab’s safety and efficacy; but 42 of the 98 patients had undergone previous radiotherapy. Median overall survival was 10.7 months in the patients who had received radiation, compared with 5.3 months in patients who were radiation-naïve. [14] The results of this study support the potential for synergy between radiotherapy and immunotherapy. It is also interesting to consider that in the KEYNOTE-001 secondary analysis, patients received radiotherapy before they received pembrolizumab, while in the case report described previously, the patient received radiation after treatment with ipilimumab. Emerging evidence for synergy between radiotherapy and immunotherapy has thus focused attention on how best to combine radiotherapy and immunotherapy.

Maximizing Therapeutic Returns: Questions of Timing, Dose, and Fractionation

Timing

There have been no randomized controlled trials to assess the here have been no randomized controlled trials to assess the comparative effectiveness of administering a checkpoint inhibitor before vs after radiation. Data in the preclinical setting also are lacking. An argument could be made either way. Use of radiotherapy after checkpoint inhibition is intuitively attractive. Under such circumstances, the adaptive immune system is in a state of readiness to respond to antigen liberated by radiation-induced cell death. In a murine model of metastatic breast cancer, administering a checkpoint inhibitor prior to surgical resection of the tumor resulted in significantly longer survival than giving the drug at the time of surgery. [15] Although this study evaluated sequencing with surgery rather than radiation, the findings may translate to radiotherapy, as tumor antigen is potentially liberated in both settings.

Radiotherapy prior to checkpoint inhibition may allow for more effective immunologic priming—meaning that a strong initial immune response is mounted against a broader array of epitopes as more tumor antigen is liberated in the setting of radiation-induced cell death. Those activated antigen-specific T cells would then be amenable to reversal of exhaustion and positioned to mount an effective antitumoral response in the setting of checkpoint inhibition. In the secondary analysis of the KEYNOTE-001 study discussed
Above, a relationship was found between prior radiotherapy and pembrolizumab-induced autoimmune toxicity. This implies that in the setting of radiotherapy, not only is priming against tumor antigen improved, but priming of the antiself response may be enhanced as well.

**Dose and fractionation**

Data in the preclinical setting have been mixed regarding the dose and fractionation strategies that elicit proinflammatory vs anti-inflammatory responses. Multiple in vitro and ex vivo studies of cell lines exposed to varying doses of radiation have shown increased immunologic activation after single doses of 2 to 20 Gy.\[16,17\] Indicators of immune activation have included increased expression of Fas, ICAM-1 (intercellular adhesion molecule 1), and class I major histocompatibility complex. Release of adenosine triphosphate and HMGB1 (high-mobility group B1), markers of proinflammatory cell death, has also been demonstrated.\[18\] An ex vivo model examining the effect of low-dose radiation (0.1 to 0.5 Gy) showed that macrophages behave in an anti-inflammatory manner, exhibiting reduced chemotaxis and decreased cytokine production.\[19\] In the complex context of the tumor microenvironment, however, data collected from cell lines must be interpreted with caution. As a case in point, an in vivo murine model of spontaneous pancreatic islet carcinogenesis was used to study the effect of single doses of radiation of 0.5 to 6 Gy in mice. After 7 days, tumoral T-cell infiltration was assessed and it was found that the lowest radiation dose, 0.5 Gy, resulted in the

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**Figure.** Schematic Representation of Activation of the Innate and Adaptive Immune Systems by Combining Radiation and Checkpoint Inhibition—Radiation causes DNA damage within the tumor, which is detected by the DNA sensor cGAS. That triggers production of type I interferon, which acts on cells of both the innate and adaptive immune system. Cellular debris from radiation-induced cell death is phagocytosed by APCs and presented to T cells. T cells mount an adaptive response to tumor antigen, which can contribute to both local and distant tumor cell killing. Checkpoint inhibition blocks T-cell exhaustion, maintaining the antitumoral response.

Ag = antigen; APC = antigen-presenting cell; cGAS = cyclic GMP-AMP synthase; MHCII = major histocompatibility complex class II; TCR = T-cell receptor.
most infiltrating T cells. This T-cell recruitment required the expression of inducible nitric oxide synthase in tumor-associated macrophages. Tumor burden was reduced and survival increased in mice treated with these low radiation doses.[20,21] The results of this study are at odds with what was seen in the ex vivo model described previously, and the discordance serves as a reminder that immuno-
lógic activation following radiation is dependent on the context in which radiation is given.

Case reports describe the abscopal effect in the settings of both standard fractionation and hypofractionation. In the 46 cases described in the literature between 1969 and 2014, doses ranging from 0.45 Gy to 60.75 Gy were used, with a median total dose of 31 Gy and a median dose per fraction of 3 Gy.[12] Preclinical studies also report systemic antitumoral effects with a variety of dose and fractionation strategies. Camphausen et al demonstrated that mice bearing Lewis lung carcinoma or fibrosarcoma tumors showed impaired growth of distant tumors after irradiation of a single tumor on the leg. Two fractionation strategies were used: 24 Gy in 12 fractions and 50 Gy in 5 fractions. They noted a dose-dependent effect, with the 50-Gy dose demonstrating better distant tumor control.[22] Evidence has accumulated that the etiology of the abscopal effect is immunologic in nature, and this has prompted interest in assessing the combination of immunotherapy and radiotherapy in the preclinical setting.

Murine models have been developed to study the dose and fractionation strategy best able to elicit an abscopal effect in the context of checkpoint inhibition. The strongest effects have been seen with hypofractionated regimens. A study by Dewan et al used mice bearing TSA breast carcinoma tumors on either flank, to interrogate dose hypofractionated regimens. A study by Dewan et al used mice bearing Lewis lung carcinoma or fibrosarcoma tumors showed impaired growth of distant tumors after irradiation of a single tumor on the leg. Two fractionation strategies were used: 24 Gy in 12 fractions and 50 Gy in 5 fractions. They noted a dose-dependent effect, with the 50-Gy dose demonstrating better distant tumor control.[22] Evidence has accumulated that the etiology of the abscopal effect is immunologic in nature, and this has prompted interest in assessing the combination of immunotherapy and radiotherapy in the preclinical setting.

In addition to considerations of dose and fractionation, it is possible that not all target sites are immunologically equal. Most case reports describing abscopal effects have involved visceral organs rather than bone.[30] Immune privilege refers to the phenomenon of certain sites in the body being more tolerant of antigen than others, and thus less apt to facilitate development of an antitumoral response after radiation. A full discussion of this concept is beyond the scope of this article, but bone marrow has been proposed as a site of immune privilege,[31] and it may be that hypofractionated radiation to bone is less likely to be effective at eliciting an abscopal response than radiation to other target sites. Another outstanding question is whether nodal irradiation is beneficial or detrimental to an antitumoral response after radiation. A full discussion of this concept is beyond the scope of this article, but bone marrow has been proposed as a site of immune privilege,[31] and it may be that hypofractionated radiation to bone is less likely to be effective at eliciting an abscopal response than radiation to other target sites. Another outstanding question is whether nodal irradiation is beneficial or detrimental to an antitumoral response after radiation. A full discussion of this concept is beyond the scope of this article, but bone marrow has been proposed as a site of immune privilege,[31] and it may be that hypofractionated radiation to bone is less likely to be effective at eliciting an abscopal response than radiation to other target sites. Another outstanding question is whether nodal irradiation is beneficial or detrimental to an antitumoral response after radiation.
Clinical trials that address dose and timing will answer some of these questions,[30] but the importance of additional basic science research to guide trial design cannot be overemphasized. Further investigation into how the interaction between the tumor micro-environment and the host immune system influences response to different dose and fractionation strategies will form the basis for improving available therapeutic options and increasing the applicability and efficacy of radiation in the clinical setting.

### Table. Selected Preclinical Studies Exploring Dose and Fractionation Strategies In Vivo and In Vitro

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Checkpoint</th>
<th>Dose and Fx</th>
<th>Peak Effect</th>
</tr>
</thead>
</table>
| Vanpouille-Box et al, 2017[10] | In vivo, BALB/c mice            | Anti-CTLA-4      | 8 Gy × 3    | +Abscopal effect  
|                        |                                 |                  |             | Type I IFN genes                                  |
| Prakash et al, 2016[21] | In vivo, RIP1-Tag5 mice          | None             | 2 Gy × 2    | ↑M1 macrophage activation                        |
| Deng et al, 2014[24]    | In vivo, BALB/c and C57BL/6 mice | Anti-PD-L1       | 12 Gy × 1   | ↓Tumor burden  
|                        |                                 |                  |             | ↑T-cell infiltrate in tumor                       
|                        |                                 |                  |             | ↓MDSC in tumor                                    |
| Golden et al, 2014[18] | In vitro, TSA cell line         | None             | 2–20 Gy × 1 | ↑Release of ATP; HMGB1 in a dose-  
|                        |                                 |                  |             | dependent manner  
|                        |                                 |                  |             | ↑Translocation of crafetulin                      |
| Wunderlich et al, 2014[19] | Ex vivo, BALB/c macrophages     | None             | 0.5 Gy × 1  | ↓Macrophage migration  
|                        |                                 |                  |             | ↓IL-1β                                             |
| Klug et al, 2013[20]    | In vivo, RT5 mice               | None             | 0.5 Gy × 1  | ↑M1 macrophage activation  
|                        |                                 |                  |             | ↑CTL infiltration into tumors                     |
| Schaue et al, 2012[25] | In vivo, C57BL/6                | None             | 75 Gy × 2   | ↓Tumor burden  
|                        |                                 |                  |             | ↑T-cell infiltrate in tumor                       |
| Dewan et al, 2009[23]  | In vivo, BALB/c and C57BL/6 mice| Anti-CTLA-4      | 8 Gy × 3    | +Abscopal effect                                  |
| Lee et al, 2009[26]    | In vivo, BALB/c and C57BL/6 mice| None             | 15–25 Gy × 1| ↓Tumor burden  
|                        |                                 |                  |             | ↑T-cell infiltrate in tumor                       |
| Reits et al, 2006[16]  | In vitro, MelJuSo melanoma cell line, M3C8 cell line | None             | 20–25 Gy × 1| ↑MHC I expression in a dose-dependent manner |
| Lugade et al, 2005[27] | In vivo, B16-bearing C57BL/6 mice | None             | 15 Gy × 1   | ↑T-cell infiltrate in tumor  
|                        |                                 |                  |             | ↑IFN-γ production in draining lymph node         |
| Garnett et al, 2004[17]| Ex vivo, 23 human carcinoma cell lines | None             | 10 or 20 Gy × 1| Expression of Fas, ICAM-1, MHC I  
| Camphausen et al, 2003[22] | In vivo, C57BL/6 mice          | None             | 10 Gy × 5 or 2 Gy × 12 | Tumor growth impaired outside field  
|                        |                                 |                  |             | Antitumor effect dependent on p53                |

In several studies, multiple dose and fractionation strategies were tested. For clarity, we only report the dose and fractionation strategy that showed the best effect.

**ATP = adenosine triphosphate; CTL = cytotoxic T lymphocyte; CTLA-4 = CTL-associated antigen 4; fx = fractionation; HMGB1 = high-mobility group box 1; ICAM-1 = intercellular adhesion molecule 1; IFN = interferon; IL = interleukin; MCSC = myeloid-derived suppressor cell; MHC I = major histocompatibility complex type I; PD-L1 = programmed death ligand 1.**

Clinical trials that address dose and timing will answer some of these questions,[30] but the importance of additional basic science research to guide trial design cannot be overemphasized. Further investigation into how the interaction between the tumor micro-environment and the host immune system influences response to different dose and fractionation strategies will form the basis for improving available therapeutic options and increasing the applicability and efficacy of radiation in the clinical setting. ☺

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Peripheral T-Cell Lymphomas: Incorporating New Developments in Diagnostics, Prognostication, and Treatment Into Clinical Practice

PART 1: PTCL-NOS, FTCL, AITL, ALCL

Natalia Pin Chuen Zing, MD, MSc¹, Thais Fischer, MD¹, Jasmine Zain, MD², Massimo Federico, MD³,⁴, Steven T. Rosen, MD²

ABSTRACT: Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of diseases, with low incidence and unique epidemiology and pathobiology; they are usually clinically aggressive, with poor outcomes. There have been significant advances in our understanding of the molecular and signaling alterations seen in these malignancies. These observations have led to novel therapeutic strategies that have had a meaningful impact on outcomes. This two-part series highlights the most important aspects of PTCLs and describes current treatment options and investigatory opportunities. Part 1 will cover PTCL not otherwise specified, follicular T-cell lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic large-cell lymphoma (ALCL), and breast implant–associated ALCL. Part 2 will cover extranodal natural killer/T-cell lymphoma, enteropathy-associated T-cell lymphoma, indolent T-cell lymphoproliferative disorder of the gastrointestinal tract, adult T-cell leukemia/lymphoma, and hepatosplenic T-cell lymphoma.

Introduction
Peripheral T-cell lymphomas (PTCLs) constitute approximately 10% to 20% of non-Hodgkin lymphomas. They are heterogeneous, with more than 20 subtypes, including T-cell and natural killer cell diseases, and most exhibit aggressive behavior and have an unfavorable prognosis.[1-4]

PTCLs have a higher incidence in males, Caucasians, and adults aged 50 to 60 years.[5-9] Over the last decade, there has been an increase in the incidence of PTCLs, which could be partially explained by diagnostic advances and the aging of the population.[10] Several studies have demonstrated the epidemiologic variability found across different geographic populations (Figure 1). The incidence of each subtype is influenced by age, gender, and ethnicity.[3,5,8] Additional risk factors are a family history of hematologic malignancies, immune perturbations (autoimmune etiology or inflammatory response), alcoholism, and smoking.[8,9,11]

Based on clinical presentation, a PTCL may be characterized as one of four subtypes: nodal, extranodal, leukemic, or cutaneous. These subtypes differ in morphology, immunohistochemical phenotype, gene expression profile, and clinical outcome.[4,12] Part of the current World Health Organization (WHO) classification for PTCLs is described in Table 1.[4]

The complexity of the histologic classification and the low incidence explain why diagnosing PTCL is challenging.[3,13] An experienced hematopathologist is essential for an accurate diagnosis and subclassification, as is combining morphologic evaluation with immunohistochemical analysis.[1,5,14-16] Molecular and genetic studies are important tools for distinguishing subtypes.[13]

Once diagnosed, a patient’s risk should be stratified based on clinical, laboratory, and imaging findings.[13] It is crucial to consider the patient’s age, performance status, and comorbidities, because these will have an impact on treatment decisions.

The International Prognostic Index (IPI), specifically devised for assessing the prognosis of aggressive B-cell lymphomas, has also been applied to PTCL and in general correlates with overall survival (OS).[7,17] The Prognostic Index for T-cell lymphoma (PIT), developed by Gallamini et al[18] in 2004, is based on these investigators’ study of Italian patients with PTCL not otherwise specified (PTCL-NOS; Table 2). Although the PIT has already been modified, both these indexes have significant shortcomings. They were developed with small cohorts and before PTCL treatment improved, and they did not differentiate between subgroups.[10,15,18]

In general, patients with PTCL have a poor prognosis. Complete responses are expected in only half of patients, and relapses are common.[9,17] For this reason, autologous stem cell transplant (auto-SCT) is often indicated in first remission.[13]
Other intensive regimens include hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cytarabine and methotrexate) and ACVBP (doxorubicin, cyclophosphamide, vincristine, and prednisone), with the addition of alemtuzumab, denileukin difitox, or bortezomib. [13] AITL is the second most prevalent PTCL. It occurs most often in Europe and North America in persons who are between 60 and 70 years of age. [8] Most patients are symptomatic, with lymphadenopathy, constitutional and associated B symptoms, and often with advanced-stage disease and bone marrow infiltration (more than 70% of cases). [1,2,6,7,18,29,30] AITL has a particular signature,

**Table 1. Peripheral T-Cell Lymphomas (PTCLs) According to the Current World Health Organization Classification**

<table>
<thead>
<tr>
<th>PTCL not otherwise specified</th>
<th>Cytologic and phenotypic heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Three subtypes: overexpression of GATA3, TBX21, and cytotoxic genes</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma (AITL)</td>
<td>Contains atypical B cells, often EBV+, simulates Hodgkin–Reed-Sternberg cells</td>
</tr>
<tr>
<td>Follicular T-cell lymphoma (FTCL)</td>
<td>Contains atypical B cells, often EBV+, simulates Hodgkin–Reed-Sternberg cells</td>
</tr>
<tr>
<td>Nodal peripheral T-cell lymphoma with T follicular helper (TFH) phenotype</td>
<td>An umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype, including AITL, FTCL, and other nodal PTCLs with a TFH phenotype</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma (ALCL), ALK+</td>
<td>Includes cytogenetic subsets that appear to have prognostic implications</td>
</tr>
<tr>
<td></td>
<td>Activation of the JAK/STAT3 pathway</td>
</tr>
<tr>
<td>ALCL ALK−</td>
<td>Activation of the JAK/STAT3 pathway</td>
</tr>
<tr>
<td>Breast implant–associated anaplastic large-cell lymphoma</td>
<td>Noninvasive disease associated with excellent outcome</td>
</tr>
<tr>
<td></td>
<td>In most cases, confined to the seroma</td>
</tr>
</tbody>
</table>

ALK = anaplastic lymphoma kinase; EBV = Epstein-Barr virus.


**PTCL-NOS**

The nodal subtypes of PTCL occur predominantly in patients from Europe and North America, and of these, PTCL-NOS is the most common histology. [8,10] The median age at presentation is approximately 60 years, with a male predominance. Clinically, most patients present with advanced disease. [13]

PTCL-NOS is not a distinct entity. [13] It can be described as an assortment of histologies with cytologic and phenotypic heterogeneity that cannot be subclassified as other PTCLs. [4,8]

Gene expression profiling has identified three subtypes of PTCL-NOS: TBX21-overexpressing, GATA3-overexpressing (associated with the worst prognosis), and PTCLs expressing other cytotoxic genes (Table 3). [3,4,19]

Conventional cytogenetic tests suggest limited recurrent karyotype abnormalities, which in most cases lack disease specificity. [6] MicroRNA profiling is being explored as another alternative for characterization and as an aid in improving our understanding of tumor biology. [16,20]

The treatment regimens developed for PTCL were derived from those designed for B-cell lymphomas. [21-24] In particular, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), with or without consolidation radiotherapy, is the regimen most often employed. The addition of etoposide to CHOP (CHOEP or dose-adjusted EPOCH) potentially benefits a subset of younger patients. Although adding etoposide to CHOP does not affect OS, it is associated with improved treatment-free intervals. [22-24]

Other CHOP-based combinations for first-line therapy feature the addition of alemtuzumab, denileukin difitox, or bortezomib. Other intensive regimens include hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate and cytarabine) and ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), but to date, none of these regimens has been shown to be superior to the others. [13]

Due to the heterogeneity of PTCL-NOS and its poor outcomes, there is no standard of care for treatment. [13,25-27] However, most centers will consider consolidation with high-dose chemotherapy and autoSCT. [24]

In cases of relapsed/refractory disease, there are several options for second-line therapy (Table 4). [24] It is important to note that not all are approved by the US Food and Drug Administration for use in PTCL-NOS, and even fewer have been approved for this indication by the European Medicines Agency.

Patients with PTCL-NOS have a poor prognosis, with a 5-year OS rate of approximately 30%. [8] Those with a higher IPI score usually have an even worse OS. [13]

**Follicular T-Cell Lymphoma**

Initially classified as a PTCL-NOS variant, although with some clinical and morphologic features similar to those of angioimmunoblastic T-cell lymphoma (AITL), PTCL characterized by expression of follicular helper T cells has been included in the latest WHO classification as a new entity called follicular T-cell lymphoma (FTCL). [4,28] Although the majority of patients present with advanced disease, a subset has localized disease and mild symptoms. [4]

FTCL typically contains an infiltrate of monotonous lymphoid cells with round nuclei and pale cytoplasm. The lymphoma expresses pan T-cell markers with a CD4+ T helper cell phenotype (eg, PD1 [programmed death 1], CXCL13 [C-X-C motif ligand 13], BCL6 [B-cell lymphoma 6], CD10, and ICOS [inducible T-cell costimulatory]). Similar to AITL, interfollicular CD20+ B immunoblasts with Epstein-Barr virus (EBV) reactivity are present in half of cases. About 20% of cases carry a t(5;9)(q33;q22) translocation, leading to an ITK-SYK fusion that appears specific for this entity. The rarity of FTCL makes prognostication difficult, although current data suggest that 50% of patients die within 2 years. [4,28]

**AITL**

AITL is the second most prevalent PTCL. It occurs most often in Europe and North America in persons who are between 60 and 70 years of age. [8] Most patients are symptomatic, with lymphadenopathy, constitutional and associated B symptoms, and often with advanced-stage disease and bone marrow infiltration (more than 70% of cases). [1,2,6,7,18,29,30] AITL has a particular signature,
which is associated with hepatosplenomegaly, dysgammaglobulinemia, immune compromise, and cutaneous manifestations (eg, rash).[31,32] The diagnosis often follows an immune event, such as exposure to a medication, an infection, or an allergic reaction.[33] The autoimmune phenomena typical of AITL are likely related to the similarity between neoplastic and follicular helper T cells.[34]

Pathologic diagnosis is often difficult due to the presence of atypical B cells that are often EBV-positive and simulate Reed-Sternberg cells.[34] As in Hodgkin lymphoma, neoplastic cells are in the minority and the microenvironment of AITL is composed of an infiltration of reactive small lymphocytes, eosinophils, plasma cells, epithelioid cells, immunoblasts, histiocytes, and follicular dendritic cells.[34,35] The hyperplasia of follicular dendritic cells and the high concentration of endothelial venules are also typical histologic changes of AITL; patients with PTCL usually do not have these characteristics, helping us to differentiate between the two groups.[4,8,28] However, the immunohistochemical and genetic abnormalities are similar in both, demonstrating a concordant cellular origin.[28,34] RHOA, TET2, and DNMT3A mutations are seen in the majority of patients.[36]

First-line therapy for patients with AITL remains an anthracycline-based regimen, similar to the regimen used for the majority of patients with T-cell lymphomas.[23,24] Complete responses are expected in only half of patients, and relapses are common.[9,17] For this reason, and similar to PTCL-NOS and anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphoma (ALCL), high-dose chemotherapy followed by autoSCT has been utilized to consolidate treatment in chemo-sensitive patients. Those who achieve a complete response have better outcomes. Timing of high-dose chemotherapy and autoSCT remains controversial.[7,12,21,22,30,37,38]

Older or unfit patients should not receive intensive treatment. Although cyclosporine with or without prednisone has provided some short-term benefit, results are not optimal.[13]

Patients with chemotherapy-refractory AITL, similar to those with refractory PTCL-NOS, may respond to a variety of new drugs, available as mono- or combination therapy (Table 4).[25,29,37,39]

**ALCL**

ALCL, in particular the ALK-positive subtype, affects a younger population (median age, 35 years).[5,8] Clinically, ALCL can be...
Nodal entities

PTCL-NOS
AITL
ALCL ALK−
ALCL ALK+

Chemosensitive (PR, CR) and transplant eligible

AutoSCT

Extranodal entities

ALCL ALK+
ALCL ALK−
DUSP22+

Stage I/II
Surgery

Stage III/IV
Surgery
Chemo + RT

BIA ALCL

Figure 2. Treatment Algorithm for Initial Presentation of PTCL.

ALCL ALK + patients with a high-risk profile (eg, IPI > 2) should be considered for autologous stem cell transplant; autologous stem cell transplant is not recommended for low-risk patients or DUSP22+ ALK− patients.

Capsulectomy.

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large-cell lymphoma; ALK = anaplastic lymphoma kinase; autoSCT = autologous stem cell transplant; BIA = breast implant–associated; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CHOP + IVE = CHOP + ifosfamide, epirubicin, and etoposide; CR = complete response; DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; HyperCVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone—alternating with methotrexate and cytarabine; IPI = International Prognostic Index; PTCLNOS = peripheral T-cell lymphoma not otherwise specified; PR = partial response; RT = radiation therapy.

Data from: National Comprehensive Cancer Network Guidelines.[24]
divided into three subtypes: cutaneous, systemic, and breast implant–associated (BIA).[4,8] Patients with systemic disease usually have generalized lymphadenopathy, characteristic of stage IV disease, and extranodal involvement. Bone marrow, bone, and lung are the sites most often affected.[13] Although ALCL has variable morphologic features, the presence of large, highly irregular cells with wreath-like or horseshoe-shaped nuclei is a hallmark.[40] CD30 and ALK protein expression are the signature markers of this distinctive entity; these give ALCL unique clinical features and a distinctive prognosis. The rearrangement of the ALK gene is a classic biomarker, present in > 50% of ALCLs and with prognostic significance. The most common rearrangement—t(2;5)(p23;q35)—creates a fusion gene composed of nucleophosmin and ALK.[13] Patients with ALK-positive ALCL have a higher OS rate than ALK-negative patients (OS at 5 years: 70% vs 49%).[8,20,41] However, this survival difference is not seen in patients younger than 40 years.[13]

Other prognostic markers, seen in ALK-negative ALCL, are rearrangements of DUSP22 and T63; these are associated with a better and worse prognosis, respectively.[20] The CHOP-like regimens are also used for ALCL, as first-line treatment in both ALK-positive and ALK-negative patients.[23,37] Patients with ALK-positive ALCL typically have a good outcome.[23,24] For this reason, autoSCT is only indicated for relapse.[37,42] AutoSCT can be considered in ALK-negative patients without rearrangement of DUSP22 (Table 2). To achieve more consistent and durable responses in the first line, studies have explored combining new drugs, such as brentuximab vedotin (an anti-CD30 immunonconjugate) and crizotinib (oral ALK inhibitor), with CHOP Targeted agents are also used for salvage treatment.[12,29,30,39]

### BIA-ALCL

The correlation between breast implants and ALCL has recently been recognized, and BIA-ALCL has been incorporated into the WHO classification as a new provisional entity (Table 1).[4] Different from primary breast lymphoma, BIA-ALCL does not compromise the parenchyma; it presents clinically as a localized seroma involving the implant and is associated with pain and swelling.[4,11] A minority of patients may present with a mass, and in these cases the disease is much more aggressive.[40,43] Irrespective of presentation, systemic symptoms are rare.[44]

There are several theories regarding the etiology and pathogenesis of this rare entity. An inadequate response of the immune system to the implant could explain the lymphomatous proliferation.[43] Implants with a more textured surface are more susceptible to bacterial proliferation, which activates lymphocytes and causes a chronic inflammatory process secondary to a bacterial biofilm infection around the implant. Currently, this is the most compelling theory that has been put forth to explain the development of BIA-ALCL.[43,44] *Ralstonia* species, gram-negative bacilli found in soil and water, have been associated with nosocomial infections, especially implant-related infection.[11,43]

Similar to ALK-negative ALCL, BIA-ALCL has an anaplastic morphology, with an immunophenotype that includes expression of CD30, CD4, CD43, CD45, and CD2, and the absence of ALK.[11,44] The expression of SOCS3 (suppressor of cytokine signaling 3) is also identified in BIA-ALCL cases, as in systemic ALCL.[44]

Most often, complete surgical excision, including removal of the implant and capsulectomy, results in an excellent outcome.[40] In contrast, when the lymphoma invades the capsule or is systemic, primary treatment should be complemented with chemotherapy. In these cases, relapse is not uncommon and the prognosis is worse.[11]

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### Table 2. The Prognostic Index for Peripheral T-Cell Lymphomas: Factors Associated With Worse Overall Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>OS at 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 y</td>
<td>70</td>
</tr>
<tr>
<td>ECOG PS ≥ 2</td>
<td>59</td>
</tr>
<tr>
<td>LDH elevated</td>
<td>70</td>
</tr>
<tr>
<td>BM involvement</td>
<td>49</td>
</tr>
</tbody>
</table>

**Key:** BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase.

*Data from: Gallamini et al. Blood. 2004.[18]*

---

### Table 3. Peripheral T-Cell Lymphomas (PTCLs) and Genetic Alterations

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Immunophenotype</th>
<th>Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>AITL NOS</td>
<td>Heterogeneous</td>
<td><strong>TBX21, GATA3, and cytotoxic genes</strong></td>
</tr>
<tr>
<td>AITL</td>
<td>CD10, BCL6, PD1, CXCL13, EBV</td>
<td><strong>TET2, DNMT3A, RHOA, IDH2, CD28</strong></td>
</tr>
<tr>
<td>FTCL</td>
<td>CD10, BCL6, PD1, CXCL13, ICOS, SAP, CCR5, EBV</td>
<td><strong>TET2, DNMT3A, RHOA, IDH2, CD28</strong></td>
</tr>
<tr>
<td>AITL ALK+</td>
<td>CD30, ALK</td>
<td><strong>ALK, SOCS3</strong></td>
</tr>
<tr>
<td>AITL ALK−</td>
<td>CD30</td>
<td><strong>STAT3, TET2, DNMT3A, TP63, DUSP22, IRF4, SOCS3</strong></td>
</tr>
<tr>
<td>BIA-ALCL</td>
<td>CD30, CD4, CD43, CD45, CD2</td>
<td><strong>STAT3, SOCS3, DNMT3A, TP53</strong></td>
</tr>
</tbody>
</table>

**Key:** AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large-cell lymphoma; ALK = anaplastic lymphoma kinase; BCL6 = B-cell lymphoma 6; BIA = breast implant–associated; CXCL13 = C-X-C motif ligand 13; EBV = Epstein-Barr virus; FTCL = follicular T-cell lymphoma; ICOS = inducible T-cell costimulatory; PD1 = programmed death 1; PTCLNOS = peripheral T-cell lymphomas, not otherwise specified.


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**Table 4. New Drugs for Peripheral T-Cell Lymphomas**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>FDA Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histone deacetylase inhibitors</td>
<td>Romidepsin</td>
<td>Affects cellular function: causes apoptosis, differentiation; inhibits angiogenesis</td>
<td>GI symptoms</td>
<td>PTCL 2nd line</td>
</tr>
<tr>
<td></td>
<td>Vorinostat</td>
<td>Asthenia</td>
<td></td>
<td>CTCL</td>
</tr>
<tr>
<td></td>
<td>Panobinostat</td>
<td>Prolonged QTc</td>
<td></td>
<td>MM</td>
</tr>
<tr>
<td></td>
<td>Belinostat</td>
<td></td>
<td></td>
<td>PTCL 2nd line</td>
</tr>
<tr>
<td>Folate analog</td>
<td>Pralatrexate</td>
<td>Dihydrofolate reductase inhibits uninterrupted DNA synthesis; 5x more powerful than MTX</td>
<td>Hematologic toxicity, mucositis</td>
<td>PTCL 2nd line</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>Bendamustine</td>
<td>Prevents cell replication</td>
<td>Cytopenias</td>
<td>CLL, indolent B-cell NHL</td>
</tr>
<tr>
<td>Aurora A kinase inhibitor</td>
<td>Alisertib</td>
<td>Regulates the mitotic process</td>
<td>Cytopenias, fatigue</td>
<td>Not approved</td>
</tr>
<tr>
<td>ALK and ROS1 inhibitor</td>
<td>Crizotinib</td>
<td></td>
<td>GI symptoms, visual events</td>
<td>ALK+ disease</td>
</tr>
<tr>
<td>Multikinase inhibitor</td>
<td>Sorafenib</td>
<td>Affects cell cycle and differentiation; promotes cell death</td>
<td>GI symptoms, fatigue, skin reaction</td>
<td>Hepatocellular carcinoma, renal cell carcinoma, thyroid carcinoma</td>
</tr>
<tr>
<td>PI3K inhibitor</td>
<td>Duvelisib</td>
<td>Affects cell survival, proliferation, and differentiation</td>
<td>Autoimmune toxicity</td>
<td>Not approved</td>
</tr>
<tr>
<td>Fusion proteins</td>
<td>Denileukin diftitox</td>
<td>Inhibits protein synthesis</td>
<td>Hypoalbuminemia, transaminase elevation</td>
<td>CTCL CD25+</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Mogamulizumab</td>
<td>Targets CCR4; inhibits T-cell proliferation &amp; migration, and angiogenesis</td>
<td>Lymphopenia</td>
<td>Not approved</td>
</tr>
<tr>
<td></td>
<td>Brentuximab vedotin</td>
<td>Targets CD30; potent antimicrotubule agent conjugated to antibody delivered to tumor cells</td>
<td>Neuropathy</td>
<td>ALCL 2nd line</td>
</tr>
<tr>
<td></td>
<td>Alemtuzumab</td>
<td>Targets CD52</td>
<td>Immunosuppression, CMV reactivation</td>
<td>Multiple sclerosis, CLL</td>
</tr>
<tr>
<td></td>
<td>Zanolimunab</td>
<td>Targets CD4</td>
<td></td>
<td>Not approved</td>
</tr>
<tr>
<td></td>
<td>Forodesine</td>
<td>Apoptosis, inhibition of proliferation of lymphocytes</td>
<td>Infection, fatigue, peripheral edema</td>
<td>Not approved</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Activation of NK/T cells, modulation of tumor microenvironment, inhibition of angiogenesis</td>
<td>Myelosuppression, fatigue, pruritus, rash</td>
<td>MM, MDS</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib</td>
<td>Affects cell cycle regulation, promotes cell death</td>
<td>Neuropathy</td>
<td>MM, mantle cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib</td>
<td></td>
<td>Neutropenia</td>
<td>MM</td>
</tr>
<tr>
<td>Nucleoside analogs</td>
<td>Pentostatin</td>
<td>Cytotoxic; antineoplastic activity</td>
<td>Immunosuppression</td>
<td>CLL</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td></td>
<td>Immunosuppression</td>
<td>CLL</td>
</tr>
<tr>
<td>Cyclic depsipeptide</td>
<td>Plitidepsin</td>
<td>Oxidative stress leading to apoptosis</td>
<td>Nausea and fatigue</td>
<td>ALL</td>
</tr>
</tbody>
</table>

<sup>a</sup>Second-generation.

ALCL = anaplastic large-cell lymphoma; ALK = anaplastic lymphoma kinase; ALL = acute lymphocytic leukemia; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CTCL = cutaneous T-cell lymphoma; GI = gastrointestinal; MDS = myelodysplastic syndromes; MM = multiple myeloma; MTX = methotrexate; NHL = non-Hodgkin lymphoma; NK = natural killer; PI3K = phosphoinositide 3-kinase; PNP = purine nucleoside phosphorylase; PTCL = peripheral T-cell lymphoma.

Figure 3. Treatment Algorithm for Relapsed/Refractory PTCL.

aBelinostat, pralatrexate, or romidepsin.

bIndicated only for patients with intention to proceed to transplant ≥ DHAP; ESHAP; GDP; GemOx, and ICE.

cActivity has been demonstrated in small clinical trials.

AITL = angioimmunoblastic T-cell lymphoma; ALCCL = anaplastic large-cell lymphoma; AlloSCT = autologous stem cell transplant; autoSCT = autologous stem cell transplant; BV = brentuximab vedotin; CR = complete response; DHAP = dexamethasone, high-dose cytarabine, and cisplatin; ESHAP = etoposide, methyl-prednisolone, high-dose cytarabine, and cisplatin; GDP = gemcitabine, dexamethasone, and cisplatin; GemOx = gemcitabine and oxaliplatin; GVD = gemcitabine, vinorelbine, and liposomal doxorubicin; HDACI = histone deacetylase inhibitors; ICE = ifosfamide, carboplatin, and etoposide; PR = partial response; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified.
How to Make a Treatment Decision

To help in therapeutic decision making, there are algorithms based on diagnosis, molecular characterization, and prognosis that provide treatment options for newly diagnosed and relapsed/refractory patients. As mentioned, autoSCT is very important in treatment of PTCL; therefore, the distinction between patients who are “fit/eligible” and those who are “unfit/inelegible” for autoSCT is fundamental when deciding on the best therapeutic approach.[38]

In very unfit or frail patients, delivery of optimal therapy may be impossible; thus, alternative palliative treatments must be considered.[29,38]

Allogeneic Stem Cell Transplantation

Despite the availability of several new drugs, salvage therapy remains a challenge. So far, with the vast majority of new compounds (with the exception of brentuximab vedotin), only short-lasting remissions have been achieved in ALCCL. In contrast, allogeneic stem cell transplantation (alloSCT) seems to be associated with promising outcomes (the 5-year freedom from relapse and OS rates are about 50%). AlloSCT should be considered mainly in younger patients with a human leukocyte antigen–matched sibling donor.[13,45] In this context, these new drugs may assume the role of a bridge to transplantation.[45]

However, there are challenges related to alloSCT, including patient eligibility, donor availability, and treatment-related toxicity and mortality; these affect about 40% of cases.[45-47] Advances in alloSCT include an extension of the donor pool—utilizing matched unrelated donors, umbilical stem cell transplants, and haploidentical transplants—to ensure sources for more patients. Reduced-intensity conditioning nonmyeloablative transplants have extended the age and comorbidities of patients who may be considered as candidates for treatment. Improvements in the management of graft vs host disease and the infusion of donor lymphocytes at the time of residual disease and/or relapse have also had a profound effect.[25]

Currently, alloSCT has to be considered for patients with bone marrow involvement, those in partial remission, and those with relapsed/refractory disease. Advances in clinical care, eg, reduced-intensity conditioning and management of graft-vs-host disease, have been associated with a lower mortality rate, making alloSCT a more realistic approach for PTCL patients.[25]

It is important to emphasize that patients with active disease at transplant have worse outcomes, impacting OS.[25] Before advocating transplantation, one must take into account a patient’s performance status and comorbidities.[29,38]

Conclusions

The low incidence and heterogeneity of PTCLs pose a significant challenge in developing effective therapies. Fortunately, advances in our understanding of the critical pathways, the cellular targets, and the role of the microenvironment in these diseases have led to the emergence of both small-molecule agents and biologic approaches that may have a profound impact on their prognosis. In addition, important strides in immunotherapy, including chimeric antigen receptor T-cell therapy and checkpoint inhibitors, potentially in conjunction with stem cell transplantation, hold great promise. PTCLs lend themselves to the application of precision medicine and may serve as a paradigm for future investigators. ☀

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