Managing Cancer Pain in the Opioid Epidemic

Judith A. Paice

POINT/COUNTERPOINT

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Introduction
Cancer patients commonly suffer from pain that is difficult to manage. Compounding this challenge are two public health crises: widespread chronic pain in the general population and the current opioid misuse epidemic.[1-4] Oncology professionals are seeing more patients with cancer and concomitant chronic pain that has often been inadequately managed or managed with high doses of opioids. Additionally, the number of people with a current or past substance use disorder (SUD) who also require cancer treatment is increasing.[5] Furthermore, cancer therapies can lead to pain conditions that seriously compromise quality of life.[6] Oncologists, oncology nurses, and others in this field are at the nexus of these converging challenges and often report little preparation for the safe and effective care of these patients with complex needs. Heightening the complexity of caring for those with cancer and pain is the challenge in navigating access to all pain treatments, particularly to opioid therapy.[7,8]

Prevalence of Cancer Pain
More than half of people with cancer report experiencing pain in the previous week, with 44% describing moderate to severe pain.[9] For those receiving curative-intent therapy, the prevalence of moderate to severe pain ranged from 43% to 57% and up to 75% in those with advanced disease.[9] A systematic review of the cancer pain literature revealed pain prevalence rates of 39% after curative treatment, 55% during treatment, and 66% in those with metastatic disease.[9,10] As advances in diagnosis and treatment expand, so too are survival rates. Estimates suggest that there are now 14 million cancer survivors in the United States, and therefore, the number of people with cancer living with pain is believed to be increasing.[11] Many of these persistent pain states are complications of cancer therapies (Table 1).[6,12,13] The consequences of unrelieved cancer pain include difficulties with daily activities, emotional distress, and impaired quality of life.[14-17] Oncology professionals realize the urgency in comprehensively treating cancer pain, yet face numerous regulatory, financial, institutional, and legal obstacles.[18]

Prevalence of Chronic Pain
Approximately 100 million American adults experience chronic pain.[1] In “Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,” the Institute of Medicine outlines the public health burden of chronic pain along with strategies for improvement.[1] The National Pain Strategy provides a framework for comprehensive management of chronic pain.[19] Unfortunately, chronic pain remains poorly managed, in part due to limited access to multidisciplinary treatment that is not limited to pharmacologic management, but also includes physical, psychological, interventional, stimulatory, and integrative therapies (Table 2).[20] Reimbursement, inadequate numbers of specialists, and lack of awareness remain serious obstacles to the use of these treatments.

Prevalence of Substance Use Disorder
Another serious public health concern is the rising prevalence of misuse of opioids and resultant opioid-related deaths. According to the 2015 National Survey on Drug Use and Health, 91.8 million (37.8%) adults in the United States used prescription opioids, 11.5 million (4.7%) misused these drugs, and 1.9 million (0.8%) had an SUD.[3] Most respondents stated that their primary motivation for misuse was to relieve physical pain (63.4%). Those at greatest risk for misuse were individuals who were socioeconomically disadvantaged (eg, uninsured, unemployed, low income) or had behavioral health issues. Risk factors for SUDs are listed in Table 3.

ABSTRACT: Cancer pain remains prevalent throughout the course of the disease, and it can be challenging to manage adequately. The challenge is compounded by the current opioid misuse epidemic. Substance use disorders (SUDs), including opioid use disorder, are common in the general population and may be seen with greater frequency in oncology settings. Risk factors contributing to the development of cancer, such as smoking or excessive drinking of alcohol, may place some patients at increased risk for SUDs. Additionally, cancer patients have a higher rate of psychological distress than the general population; psychological distress is an important risk factor for SUDs. Careful assessment of pain, function, and risk factors for SUDs, along with physical examination and review of imaging findings, are strategies to define the etiology of pain and guide development of a treatment plan. Multimodal pain therapies are warranted to reduce reliance solely on opioids, and universal precautions are essential to mitigate risk of misuse. Complex care is required for those with comorbid chronic noncancer pain or with past or current SUDs.
Daily reports in the media highlight the fallout of this rise in substance misuse. Drug overdoses accounted for 52,404 deaths in the US in 2015, and 33,091 (63%) of these involved an opioid.[21] Other psychoactive substances, including benzodiazepines, are often implicated in fatal overdoses, yet coprescribing of opioids and benzodiazepines has increased significantly in the last few years.[2,22,23] Zolpidem and eszopiclone, which are frequently prescribed for cancer patients for pain, anxiety, antiemesis, and sleep, are also associated with increased risk of death when used with other sedating drugs.[23]

Prevalence of SUDs in Oncology

The prevalence of SUDs in cancer is unknown. Approximately 9% of Americans meet the diagnostic criteria for SUDs, so oncology practices likely provide care for more than a few of these individuals. In fact, cancer may place some patients at higher risk for SUDs than the general population because of their higher rate of psychological distress, which is an important risk factor for SUDs.[24] In a study of cancer patients screened to assess for risk of SUDs, 29% were found to be at high risk. Younger individuals and those with high levels of anxiety/depression were at greatest risk.[25] Advanced cancer patients who were current or former smokers had a higher risk of illicit drug use.[26] Using the CAGE questionnaire (Cut down, Annoyed, Guilty, and Eye opener), a prospective study of advanced cancer patients found that approximately 18% met criteria for chemical coping. Chemical coping places the patient at risk for using an opioid in a nonprescribed manner to cope with stressors.[5] Therefore, it is probable that people with cancer may have similar or even higher risk of SUDs than the general population.

Strategies for Oncology

Oncology professionals are faced with an extraordinary dilemma. How do we safely and effectively manage pain to allow full function and improved quality of life in our patients while reducing the potential for unsafe use of opioids? Opioids are essential pain management agents, yet there are risks inherent in their use. Core approaches include careful assessment of pain, medication use, function, and risk of SUD. When developing a treatment plan, reliance on multimodal pain therapy is crucial, rather than use of opioids alone. Universal precautions are essential measures to guide prescribing of agents with abuse potential to mitigate the risk of addiction and misuse.

Assessment

A comprehensive assessment should be conducted to discern the organic etiology of the pain. Review medical records and imaging results and conduct a full examination — all components of excellent oncology care. Function is a vital component of this assessment and will guide the goal of pain interventions. It may be helpful to ask, “If we can do a better job with pain control, what will you be able to do that you cannot do now?” This helps focus the patient and provider on the expected outcome of improved function, which can be used as a measure of efficacy for treatment strategies. Function will of course vary, depending on prognosis and disease burden. Some patients may aim to return to work, while others will hope to be able to hold a grandchild or sit with their loved ones and enjoy a meal.

A comprehensive review of pain medications, current and past, should note any adverse effects, challenges with obtaining medications, and reasons for discontinuing. An important measure of opioid use is actual intake versus prescribed dose. Many patients may have an immediate-release opioid ordered every 3 hours as needed, yet take only 1 dose per 24 hours, even in the face of ongoing pain. Is the patient limiting intake due to fears of addiction, cost concerns, or family reluctance, or are there other barriers that may be leading to underdosing?[27] The prescription drug mon-
Monitoring program (PDMP) is extremely helpful in evaluating dispensing information. Currently, 49 states have PDMPs, and many allow access to information from other states. Use of these programs has been shown to reduce nonmedical use of opioids.[3,28-30]

Assessing risk factors for SUDs is part of comprehensive pain assessment (Table 3). Some advocate for the use of screening questionnaires to evaluate risk of SUDs, while others incorporate these questions into the interview. Urine toxicology can determine intake of substances that have not been prescribed, or conversely, the absence of positive results when an opioid has been prescribed. Careful interpretation of the results is warranted, as there are many false-positives and false-negatives.[31,32] Although some professionals view aberrant results as a reason to “fire” a patient from their practice, unexpected findings should initiate a thoughtful conversation between prescriber and patient. This may be motivating for the patient who is already concerned about his or her behavior and willing to take action towards sobriety.

### Management

Universal precautions, a term initially used in infection control, describe techniques to be applied to all patients when opioids are considered as part of the treatment plan. This stepwise approach (Table 4) should be incorporated into the care of all patients who will receive an opioid, not just those perceived to be at risk for misuse. Because of implicit bias, people who are socioeconomically disadvantaged may not be fully believed when reporting pain and often receive less than adequate pain control.[33,34] In a study of people being treated for cancer pain, minority patients were twice as likely to be undertreated when compared with non-Hispanic whites.[35]

### Complex Care

Pain management has become more difficult in the oncology setting as a result of these convergent public health problems. Table 5 lists some strategies for reducing the complexity by streamlining safe opioid prescribing in a busy oncology practice. Additional complexities persist and new challenges develop regularly. Unintended consequences of efforts to mitigate the opioid abuse epidemic are leading to shortages of opioids in both inpatient and outpatient settings and delays in access as a result of reimbursement obstacles in the form of prior authorizations. Reduced production quotas set by the Drug Enforcement Administration,[36] along with other factors, have led to shortages of parenteral fentanyl, hydromorphone, and morphine. Hospitals are limiting their use to avoid running out, and are encouraging use of oral opioid and nonopioid agents.[37] Third-party payers often require prior authorizations, which can delay access to medication, and in some cases abstinence syndrome may result.[7] Many of these plans are setting limits on medications, dosing formulations, and numbers of tablets/patches to be dispensed, even for those with cancer or other life-limiting diagnoses.

### Patients With Chronic Noncancer Pain

Another consequence of the current environment is that many medical professionals and practices no longer prescribe opioids. [38] As a result, patients with chronic noncancer pain who are also in cancer treatment may ask their oncologist to prescribe these medications. Table 6 provides suggestions for managing chronic pain in oncology practices that want to offer compassionate care for patients who are abandoned by other providers. As each setting is unique, these recommendations may not be feasible for all practices.

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**Table 2. Multimodal Pain Therapies**

<table>
<thead>
<tr>
<th>Physical</th>
<th>Psychological</th>
<th>Interventional</th>
<th>Stimulatory</th>
<th>Integrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Acceptance-based therapy</td>
<td>Epidural steroid injections</td>
<td>Peripheral nerve stimulation</td>
<td>Acupuncture/acupressure</td>
</tr>
<tr>
<td>Heat/cold</td>
<td>Active coping</td>
<td>Kyphoplasty, vertebroplasty</td>
<td>Spinal cord stimulation</td>
<td>Aromatherapy</td>
</tr>
<tr>
<td>Lymphedema management</td>
<td>Biofeedback</td>
<td>Nerve blocks</td>
<td>Transcranial stimulation</td>
<td>Massage</td>
</tr>
<tr>
<td>Orthotics</td>
<td>Cognitive behavioral therapy</td>
<td>Neuraxial infusion</td>
<td>Radiofrequency ablation</td>
<td>Meditation</td>
</tr>
<tr>
<td>Physical/occupational/recreation therapy</td>
<td>Distraction</td>
<td>Epidural steroid injections</td>
<td>Art therapy</td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Guided imagery</td>
<td>Hypnosis, Mindfulness</td>
<td>Music therapy, Tai chi, Yoga</td>
<td></td>
</tr>
</tbody>
</table>

TENS = transcutaneous electrical nerve stimulation.

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**Table 3. Risk Factors for Substance Use Disorders**

<table>
<thead>
<tr>
<th>Smoking history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past or current alcohol use disorder; risky alcohol intake (eg, binge drinking)</td>
</tr>
<tr>
<td>Past or current use of recreational substances</td>
</tr>
<tr>
<td>First use of substances at an early age (eg, 15 years of age or younger)</td>
</tr>
<tr>
<td>Family history of alcohol abuse or substance use disorder</td>
</tr>
<tr>
<td>Trauma (eg, sexual abuse, posttraumatic stress disorder)</td>
</tr>
<tr>
<td>Legal problems, history of incarceration, other issues</td>
</tr>
</tbody>
</table>
Patients With Previous or Current SUD

The person with SUD may have difficulty adhering to the cancer treatment plan, in part due to limited coping strategies.[39] Thus, attention to measures that enhance recovery from an SUD may also improve cancer outcomes. The person with a history of alcohol or drug use who is scheduled to undergo potentially painful cancer treatments should be encouraged to initiate, resume, or continue contact with the supports that have fostered their sobriety, such as 12-step programs and regular meetings with sponsors. Exercise, sleep hygiene, and healthy eating should also be encouraged. Unfortunately, aggressive cancer treatments can interfere with many of these activities and additional support may be warranted. Availability of additional support will depend on the resources of practices and communities, which may be limited.

For the person who is in medication-assisted therapy (MAT), contact the treatment clinics to alert them regarding the planned oncology treatment. In my experience, some programs will increase supportive measures knowing that the patient will be under additional stress. If opioids and/or benzodiazepines are part of the cancer treatment plan, discuss with program staff the need for these medications to ensure that patients are not discharged when their urine drug screens are positive. Additionally, if patients are on methadone or buprenorphine for MAT, use an alternate opioid for pain control.[39]

Some patients develop tolerance to the analgesic effect of opioids, usually necessitating a higher dose when prescribing for pain. On a regular basis, monitor for potential drug–drug interactions and also for possible QTc prolongation by obtaining electrocardiograms.[40,41] Negotiate with MAT treatment clinics, particularly those administering methadone, to allow less frequent visits (eg, weekly, rather than daily) if the patient’s physical functioning declines because of cancer or its treatment.

In my experience, many patients in prolonged and successful recovery deeply value their sobriety and are hesitant to use opioids unless absolutely necessary. For patients with less prolonged recovery, constant reassessment of pain, medication use, and evidence of

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**Table 4. Universal Precautions for Opioid Use in Chronic Cancer Pain Management**

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
</table>
| 1. | Assess pain and risk of opioid misuse.  
- Assess pain and risk for substance use disorder.  
- Conduct examination and review medical record.  
- Review prescription drug monitoring program.  
- Conduct urine drug screening. |
| 2. | Decide whether or not to prescribe.  
- Stratify risk of diversion and abuse. |
- Optimize adjuvant analgesics.  
- Use multimodal pain therapy.  
- Obtain treatment for psychiatric illness, including anxiety, depression, and sleep disorders. |
- Evaluate effectiveness (decreased intensity and improved function).  
- Review and treat adverse effects.  
- Monitor adherence. |
| 5. | Respond to aberrant behaviors.  
- Assess for behaviors that may indicate uncontrolled pain, compulsive use, use to treat other conditions (anxiety, depression, sleep), or diversion.  
- Intervene by prescribing small amounts at shorter intervals, using pill counts, and using drug screening more frequently.  
- Consult psychiatric and/or addiction specialists. |


**Table 5. Strategies for Streamlining Opioid Prescribing in Oncology Practices**

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Employ a simple screening tool (eg, CAGE [Cut down, Annoyed, Guilty, and Eye-opener] or others) on first encounter; this can be distributed by support staff.</td>
</tr>
</tbody>
</table>
| 2. | Assign a designee to access the prescription drug monitoring program (PDMP) for each encounter for every patient receiving controlled substances.  
- Print out and bring into exam/consultation room.  
- Use to assist in determining correct agent, previous dose, number of doses dispensed, next time insurance will reimburse, multiple prescribers.  
- Many states require documentation that PDMP has been reviewed (although most exempt cancer patients). |
| 3. | Order urine drug screens as part of all new patient encounters and annually for long-term patients; these can be in place as part of standing orders for new patients. |
| 4. | Develop smart phrases (also called dot phrases or shortcuts) regarding opioid education, safe opioid use, storage and disposal, expectations regarding refills, and other instructions to facilitate documentation (eg, “informed patient to store opioids in locked box or cabinet”; “informed patient that it is not safe to use opioids to treat anxiety or depression”). |
| 5. | Compile documents to distribute to patients to facilitate cancer pain and opioid education. Examples:  
| 6. | Consider having an advanced practice provider (if available in practice) follow pain and symptom management in concert with oncologist’s cancer care. |
should also consider the danger of benzodiazepines and other
medications, or admission to a facility (eg, nursing home) where
amounts of drug at a time, engaging family members to dispense
the patient with advanced disease and a significant disease bur-
den, mitigation strategies may include prescription of very small
amounts of drug at a time, engaging family members to dispense
medications, or admission to a facility (eg, nursing home) where
professionals administer opioid therapies. Currently, there are no
guidelines for pain management in people with cancer and a co-
morbid SUD.

Conclusion
Two public health crises, the epidemics of chronic pain and of
opioid misuse, are creating challenges for cancer pain manage-
ment. Assessment of pain, function, and risk for SUD, along with
the implementation of universal precautions, provide a founda-
tion for safe and effective care. Strategies for safe opioid use
should also consider the danger of benzodiazepines and other
aberrant behavior is warranted. Addiction is a relapsing and remit-
ting disease. Clear, nonjudgmental communication and education
are essential. For patients who continue to use illicit substances,
referral to psychiatry and/or addiction specialists is essential. For
the patient with advanced disease and a significant disease bur-
den, mitigation strategies may include prescription of very small


dating agents. Education about safe storage and disposal should
be offered to patients and families. Evidence-based guidelines
are needed to guide practice.

Financial Disclosure: The author has no significant financial inter-
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REFERENCES
1. Relieving pain in America: a blueprint for transforming prevention, care, education, and
4. Paice JA. Cancer pain management and the opioid crisis in America: how to preserve hard-
5. Kwon JH, Tanco K, Park JC, et al. Frequency, predictors, and medical record documentation of
45.
7. Paice JA. Under pressure: the tension between access and abuse of opioids in cancer pain
8. Tanco K, Bruera SE, Bruera E. Insurance company denial of payment and enforced changes in
the type and dose of opioid analgesics for patients with cancer pain. Palliat Support Care. 2014;
9. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. High prevalence of pain in
10. van den Beuken-van Everdingen MH, Hoxtenen LM, Joosten EA, et al. Update on preva-
ience of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom
in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical
breast cancer survivors: prevalence, predictors, and effects on quality of life. Breast Cancer
19. Department of Health and Human Services. National pain strategy: a comprehensive popula-
20. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescrip-
65:1445-52.
21. Bachhuber MA, Hennessey S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescrip-
8.
compared with spouses and healthy controls: a systematic review and meta-analysis. Lancet
of prescription drugs, and heroin use: evidence from the National Survey of Drug Use and Health.
Addict Behav. 2017;89:95-77.
28. Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid
29. Centers for Medicare and Medicaid Services. Best practices for addressing prescription opioid

Table 6. Managing Chronic Noncancer Pain in the Oncology Setting

1. Partner with the referring primary care physician (PCP); agree to continue to fill prescriptions for opioids used for chronic noncancer pain for the duration of cancer treatment but have PCP resume care once active treatment is completed. For patients with cancer who have completed treatment and are on stable doses, refer to the PCP for ongoing pain care.
2. Safe pain care requires regularly conducted monitoring (eg, every 3 months, as this is the usual duration that prescriptions are valid – 90 days from date of writing).
3. Does the practice have the necessary processes in place to manage the patient’s pain? For example, is the electronic medical record linked to the prescription drug monitoring program (PDMP)? Is urine toxicity screening available either in house or through an outside vendor? If not, these processes should be put in place and used for all patients receiving opioids (eg, universal precautions).
4. Are there pain treatment programs that might partner with the practice and provide care for these patients?
5. If the oncologist determines that he/she will provide this pain care, expectations regarding timing of visits, provision of prescriptions during face-to-face encounters only, and use of urine drug screens need to be discussed (consider developing a smart phrase for the electronic medical record). Most states allow multiple prescriptions to be written with the notation “can be filled on or after February 1st” and “can be filled on or after March 1st” so that prescriptions for multiple months can be provided.
6. If a patient known to the oncologist presents in distress because his or her PCP has decided to no longer prescribe, and the patient is out of medication, the prescriber should evaluate the PDMP for accuracy and may agree to provide a 1-to-2-week supply of medication. This will allow time to verify the information, discuss the situation with the PCP, and schedule an additional encounter to more fully conduct a pain and substance use disorder assessment.
7. Partner with addiction professionals for referral when patients demonstrate aberrant behavior surrounding opioids or other controlled substances.
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Multidisciplinary Approaches to Chest Wall Recurrences of Breast Cancer

Cletus Arciero, MD, FACS1, Peter Thompson, MD2, Jane Lowe Meisel, MD3, Caitlin E. Taylor, MD4, Mylin A. Torres, MD1, William C. Wood, MD1

ABSTRACT: The management of postmastectomy chest wall recurrences of breast cancer has long challenged clinicians. A tissue diagnosis combined with proper imaging and staging of patients to ensure the disease is localized are the first steps in management. Multimodal therapy offers patients the best chances of cure. In properly selected patients, complete surgical resection to negative margins, including full-thickness chest wall resection when required, followed by reconstruction that is well planned, can provide local control with very low surgical mortality and acceptable morbidity. Radiation therapy provides additional local control, while systemic therapy is an adjunct that prolongs survival in many cases. Multidisciplinary care combined with careful patient selection are the keys to successful chest wall resection for locally recurrent breast cancer after mastectomy.

Introduction
Chest wall recurrences of breast cancer not only cause distress to the patient, but also present a challenge to the clinician. These recurrences are often linked to a short disease-free interval combined with high-risk features of the original breast cancer: high nuclear grade, basal phenotype, and advanced stage at presentation. Once considered just a harbinger of distant disease and eventual death from breast cancer, local recurrence of breast cancer after mastectomy is now understood to be treatable, even in cases in which a full-thickness chest wall resection is required. A multidisciplinary approach to these patients, including surgical resection with reconstruction, systemic therapy, and radiation therapy, can often lead to long-term survival.

Initial Workup and Patient Selection
Postmastectomy chest wall recurrences most often manifest as palpable skin-flap masses (96%), either subcutaneous or dermal. [1] The spectrum of clinical severity of locoregional recurrence of breast cancer can extend from a small nodular recurrence along the surgical scar to complete involvement of the chest wall, including the bony thoracic cage, overlying muscles, and soft tissue, and even regional great vessels or nerves. Imaging of the mass with ultrasound and/or MRI helps to define the local extent of the disease process. These imaging studies help in preoperative evaluations and help to identify patients whose disease is unresectable. Following imaging, tissue sampling is paramount to confirm the suspected diagnosis. It is also crucial to ensure proper analysis of the sampled tissue, whether obtained via core biopsy or excisional biopsy. Assessing the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of a recurrent tumor guides further therapy. In a recent meta-analysis, 20% of ER, 33% of PR, and 8% of HER2 status tumors were discordant with the original tumor.[2] Alterations in the biologic activity of a recurrent breast cancer can markedly change the therapeutic approach to the patient. Careful imaging and definitive tissue diagnosis provide the information required to achieve local control of a recurrent breast cancer.

Prior to initiating therapy, it is important to determine the extent of disease. Buchanan et al, examining their institutional experiences, noted that although the locoregional recurrence after mastectomy was only 8.8%, 36% presented with synchronous metastasis, while an additional 33% would go on to develop distant metastasis.[3] In a recent examination of the National Cancer Database, Neuman et al noted that locoregional recurrence is less common in the era of modern oncologic care, but that its association with distant disease is apparent.[4] Specifically, in patients with a postmastectomy chest wall recurrence, 30% presented with synchronous metastatic disease. In keeping with established guidelines (National Comprehensive Cancer Network [NCCN]), systemic staging is required prior to the consideration of any local therapy. This staging can be in the form of positron emission tomography/computed tomography (PET-CT) or CT chest/abdomen/pelvis combined with a bone scan to exclude metastatic disease. In the absence of systemic disease, the multidisciplinary team can approach the patient with curative intent.

It cannot be emphasized enough that patient selection is the most important factor in determining the utility of full-thickness chest wall resection in the management of a local recurrence of breast cancer (Figure). Patients with surgically resectable disease and no evidence of metastasis can be considered for aggressive local control. Further selection is based on favorable tumor and patient characteristics. Hormone receptor–positive tumors have notably better outcomes following chest wall resection than triple-negative tumors.
The stage of the original disease can indicate long-term outcomes, with locoregional recurrence of node-negative cancers leading to longer OS.[6] In contrast, patients with tumors that display a more aggressive phenotype through a shortened disease-free interval may not gain a benefit from surgical resection.[6] Patients with poor prognostic indicators—including triple-negative or HER2-positive disease, advanced disease at original diagnosis, and short disease-free intervals—should be approached with caution, because the potential benefit of a full-thickness chest wall resection may be limited (Figure).

**Surgical Resection**

As noted in the NCCN guidelines, surgical resection is recommended in cases of local recurrence, if possible.[7] Once considered heroic or radical, the full-thickness resection of the chest wall for complete extirpation of a breast cancer recurrence has been notably successful in extending survival in well-selected patients. Several recent single-institution reviews noted complete surgical resection with low mortality, acceptable morbidity, and relatively good quality-of-life outcomes.[8-10] A more recent meta-analysis examined 48 studies, combining morbidity, mortality, survival, and quality-of-life data. The examination of 1,305 patients revealed 30-day morbidity was 20.2% (95% CI, 15.3–26.3) and mortality was less than 1%.[6] Although quality of life was noted to be excellent in 8 studies, the evaluation methods were not standardized. In patients undergoing surgical resection with curative intent, 5-year survival was 41.3% (95% CI, 35.3–47.3). Patients with longer disease-free intervals, hormone receptor–positive tumors, and a lower overall burden of disease had improved survival. Thus, resection of full-thickness chest wall recurrences of breast cancer can clearly provide a survival benefit with acceptable morbidity and mortality.

It has been questioned whether surgery is better than treating the patient with systemic therapy alone. Most studies have pointed to good local control with chest wall resection. There has been little research, however, comparing survival between surgical and nonsurgical groups. In a study comparing 44 patients receiving chest wall resection and 32 treated nonsurgically, survival was statistical equivalent.[5] The patients undergoing surgical resection were admitted well selected, with 95% receiving neoadjuvant therapy either having responsive disease or at least stable disease. The researchers suggest that treating patients with systemic therapy upfront, followed by chest wall resection, may lead to better outcomes.

The strict tenet of surgical resection of isolated chest wall recurrences is negative margins. This is a relatively simple task when the recurrent disease only involves soft tissue (skin, muscle), but it is a more complex task when achieving negative margins requires full-thickness chest wall resection.

Axillary management should be considered largely on a patient-by-patient basis, and the extent to which the axilla is interrogated is determined by clinical history (extent of previous nodal sampling), physical exam, and imaging. Management of the axillary nodes is an extension of local control in this patient population and should be treated as such.

Regardless of the timing of surgery, it is clear that in well-selected patients, surgical resection of their local recurrence can be beneficial. Successful resection of the cancer, however, is only one part of the treatment algorithm. Reconstruction of the resultant defect is often the more complex surgical problem.

**Reconstructive Surgery**

Planning the reconstruction requires close communication between the oncologic and plastic surgery teams. Preoperative planning involves a discussion of the extent of resection, which can be guided by a review of cross-sectional imaging. Prior radiation treatment can decrease compliance of the chest wall and limit the availability and viability of local tissues and muscles for reconstruction. Previous surgical procedures for locally advanced breast cancer, such as axillary dissection or sternal resection, may damage the vascular pedicle of commonly used muscle flaps, such as the latissimus dorsi or the rectus muscle. To a certain extent, medical comorbidities and overall health will determine the fitness of a patient to undergo longer forms of reconstruction with inherently increased morbidity.

Radical resection of chest wall recurrence may result in a large, full-thickness defect inclusive of soft tissues and underlying skeletal support structures. One of the main concerns in reconstruction of a full-thickness chest wall defect is maintenance of chest wall stability to avoid paradoxical wall motion and disruption of respiratory mechanics. Restoring continuity of the thoracic cage is also important to protect the underlying viscera, such as the heart, lungs, and great vessels. Restoration of soft-tissue coverage of the bony chest is crucial to prevent infection and promote wound healing. The ideal soft-tissue coverage should be compliant, robustly vascularized, and durable. Importantly, the patient should be able to withstand radiation treatment, since many patients with locoregional recurrence will require adjuvant radiotherapy. Finally, the ideal soft-tissue coverage should minimize donor-site morbidity, given that significant complications or problems in wound healing may create an unacceptable delay in the patient’s progression to adjuvant therapy.

Intraoperative evaluation of the chest wall defect will determine the final plan for reconstruction. Size of the defect, location on the chest wall, and extent of resection should all be carefully determined. Resection of local chest wall recurrences can involve resection of skin, pectoralis muscle, intercostal muscle, ribs, and sternum. The first important decision is whether restoration of rigid skeletal stability is necessary. In general, the larger the bony defect, the more likely thoracic cage reconstruction will be necessary. Wound diameter greater than 5 cm and resection of more than two ribs are generally considered indications for skeletal fixation. Previous radiation therapy may decrease the risk of paradoxical wall motion due to fibrosis of underlying viscera. Lateral chest wall wounds are more likely to

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ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS

Suspected local recurrence following mastectomy

Assessment of extent of disease

1. Physical exam
2. Local and distant disease imaging
3. Tissue sampling and receptor status

Resectable disease?

Consider neoadjuvant chemotherapy

Yes

Resectable disease?

Factors favoring surgery:
1. Hormone receptor positive
2. Long disease-free interval
3. Node-negative initial disease

Consider surgical resection

Yes

Surgical resection and reconstruction

No

Nonsurgical management of disease

Adjuvant therapies

Endocrine therapy (ER+ and/or PR+ disease)

Chemotherapy (ER−, PR−, HER2− disease)

Radiation therapy

Figure. Algorithm for the Management of Locally Recurrent Breast Cancer Following Mastectomy.
ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.
develop instability, since this location lacks support provided by the sternum anteriorly and the spine/scapula posteriorly.[11] Choice of soft-tissue coverage depends on patient factors, defect size, and location, as well as availability of local and regional tissue. Various algorithms can assist in guiding flap choice.[12,13]

Restoration of skeletal stability can be accomplished with placement of mesh or more-rigid constructs. Commonly used materials include synthetic and biologic meshes such as polypropylene, polytetrafluoroethylene, and acellular dermal matrix. When more-rigid fixation is necessary, a common technique involves creation of a methylmethacrylate sandwich between a synthetic mesh bilayer.[14]

Local options for coverage of the chest wall include thoracoepigastric and thoracoabdominal rotation flaps. These fasciocutaneous flaps are based on intercostal or superior epigastric artery perforators and can cover large defects of the chest wall. Local tissues may be damaged and not usable in the setting of previous radiation, and they can create a substantial scar burden on the anterior trunk.[15] Regional options include muscle flaps such as the latissimus dorsi and rectus muscles. Both of these options provide robust, reliable coverage and may be designed as a myocutaneous flap, providing both bulk to fill dead space and replacement for skin. The latissimus flap is based on the thoracodorsal artery pedicle, has a wide arc of rotation, and can be used to resurface the entire ipsilateral chest as well as midline sternal defects. Considered the workhorse of chest wall reconstruction, the latissimus is a versatile option with an acceptably low complication profile.[16] The omentum may even be harvested as a flap based on the gastroepiploic arcade for use in coverage of chest wall defects. Because of the need for intra-abdominal dissection and harvest, omental flaps are usually reserved as a salvage option when regional muscle flaps have failed or are unavailable.

Finally, free tissue transfer can be used in appropriately selected patients. Latissimus muscle, deep inferior epigastric perforator, and anterolateral thigh are potential sources for free tissue transfer. The large number of local and regional options in chest wall coverage, however, means that free tissue transfer is rarely indicated.

**Radiation Therapy**

Among radiation-naïve breast cancer patients who develop a chest wall recurrence, up to 75% will experience this recurrence locally following excision alone, even with widely negative margins.[17-19] Local failure rates can be reduced to approximately 23% to 28% by the addition of adjuvant radiation.[18-20] Radiation also significantly improves distant metastasis–free survival and OS in patients treated for chest wall recurrences.[18,21-23] Complete excision of the recurrence with negative margins coupled with radiation to the entire ipsilateral chest wall and regional lymph nodes is associated with the highest rates of disease-free survival (DFS).[18,22,24,25] Local regional control rates in these patients are not improved by radiation doses higher than 50 Gy, with a 10-Gy boost given in standard fraction.[20,24] For patients with inoperable disease, however, at least 60 Gy is recommended for lesions less than 3.0 cm, and up to 70 Gy is recommended for larger tumors. The addition of concurrent chemotherapy for these patients may or may not improve local control depending on the study, agent used, and tumor subtype. In one study, patients with non–triple-negative tumors had the most benefit from concurrent capecitabine.[22,24,26,27]

Re-irradiation of the chest wall for the treatment of tumor recurrences or new primary tumors has traditionally been avoided for perceived lack of efficacy and fear of toxicity. Several studies have indicated that re-irradiation is not only safe but also may lead to local control rates as high as 60% to 100%, with more favorable outcomes in patients who do not have gross disease at the time of radiation (ie, patients who have had previous surgical treatment with negative margins).[28-30] In these studies, doses between 40 and 60 Gy in standard fractions were administered during the second course of radiation, with the median cumulative radiation dose for both courses being 106 Gy in a multi-institutional study (range, 74.4–137.5 Gy).[28-30] Less than 5% of patients developed grade 3 or 4 acute toxicities, namely moist desquamation, and no patients developed a grade 3 or 4 long-term toxicity.[28-30]

Hyperthermia is a potent radiosensitizer that has been used in combination with radiation for the treatment of chest wall recurrences, including in patients who have been previously irradiated.[31] The most recent studies of hyperthermia have primarily focused on patients with inoperable chest wall disease.[31-36] Among these studies, hyperthermia in combination with radiation improved complete response rates over radiation alone but did not have a significant impact on OS.[27,31-35] This research has been limited by small patient numbers, but a meta-analysis confirmed the complete response rate benefit of hyperthermia, even in patients who have been previously irradiated, with low rates of acute and late grade 3 and 4 toxicities (~14% and ~5%, respectively).[31] Hyperthermia is more effective in tumors that are 5 cm or less in size and when the medial thermal equivalent doses of 42.5°C or 43°C are administered for at least 200 or 100 minutes, respectively.[37,38]

Radiation therapy is an important part of multidisciplinary treatment for operable and inoperable chest wall recurrences of breast cancer and appears to benefit even patients who have been previously irradiated, without significant toxicity.

**Systemic Therapy**

Considerable debate exists regarding optimal systemic treatment for isolated local or regional recurrence of breast cancer. Although adjuvant and endocrine therapies are well studied regarding their application to primary breast cancers, evidence for these therapies in the setting of disease recurrence is limited. The phase III CALOR (Chemotherapy as Adjuvant for LOcally Recurrent breast cancer) trial, the final analysis of which was recently reported, is perhaps the most well-known trial in this space.[39,40] The trial randomized patients with isolated locoregional recurrence of breast cancer to receive chemotherapy or no chemotherapy, with surgery mandatory and radiation given to those with microscopically involved margins. It demonstrated that adjuvant chemotherapy is beneficial for patients with isolated locoregional recurrence (ILRR) following complete resection among patients with ER-negative malignancy. Five-year DFS in patients who received chemotherapy was greater than that in the nonchemotherapy group (70% vs 34%; hazard ratio [HR], 0.29), when compared with DFS in the ER-positive patients (62% vs 58%; HR, 0.94). A greater trend also was observed toward...
improved OS with chemotherapy in patients with ER-negative ILRR (73% vs 53% at 10 years) than with chemotherapy in patients with ER-positive ILRR (76% vs 66%). This trial supports the recommendation for adjuvant chemotherapy in patients with ER-negative locoregional recurrences, with much less support for its use in ER-positive patients. The exact chemotherapy regimen is determined by a patient’s treatment history, other medical history, and a discussion of risks vs benefits of treatments along with their common side effects and dosing regimens.

Although data are limited, endocrine therapy has improved post-recurrence DFS in patients with ER-positive breast cancer. The SAKK 23/82 (Swiss Group for Clinical Cancer Research) study, a long-term analysis of tamoxifen vs observation for patients with ILRR after excision and radiation therapy, demonstrated an increased DFS in the tamoxifen group (61% vs 40%). This increase was most notable in postmenopausal patients (61% vs 33%; P = .006); however, there was no statistically significant improvement in OS. Five-year DFS in premenopausal women was the same in both the tamoxifen and observation groups (60%).[41] Prior analysis of this population (pre- and postmenopausal ER-positive patients) at 6.3 years’ median follow-up demonstrated improved DFS in 5-year DFS from 36% to 59%, which persisted in this long-term study (mean follow-up, 11.6 years) pointing toward overall benefit in regard to DFS.[41,42]

Few trials have evaluated neoadjuvant therapy for ILRR; however, it is often used to improve surgical outcomes by decreasing tumor burden and concomitantly increasing chances of complete resection. Given the association of ILRR both as a marker of metastatic disease and a potential source of new metastases, complete resection is important for optimal and potentially curative treatment.[43,44] Neoadjuvant therapy has the additional advantage of helping to facilitate recognition of early disseminated disease in order to avoid patients having to undergo local treatment unnecessarily.

Systemic therapy, therefore, is part of the standard of care for many patients with local recurrences. Some of these patients will be long-term survivors, but others will develop unresectable metastatic disease despite our best efforts. Regardless, these patients are at higher risk for unwanted side effects from treatment, as well as depression and anxiety related to fear of recurrence. Outcomes for patients with metastatic disease have been shown to improve with early integration of palliative care along with active treatment.[45] We would recommend offering palliative services and psychiatric support to patients with locoregional recurrence, as well as in other situations where these services seem applicable.

Conclusion

A chest wall recurrence of breast cancer following mastectomy is a complex clinical problem that can push centers to the limits of their resources. A comprehensive workup including detailed imaging, staging, and recharacterization of the tumor prepares the patient for possible resection. A complete resection of the recurrence followed by reconstruction of the ensuing defect requires oncolgic and plastic surgeons to work together. Adjuvant radiation aids in the control of local recurrence. Systemic therapy also decreases local recurrences and helps to improve OS in these patients. A well-coordinated multidisciplinary approach in well-selected patients with an isolated chest wall recurrence of breast cancer is not only feasible but also desirable for long-term local control and improved survival.

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

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Eileen Parkes on why cancer researchers are excited about STING agonists

STING agonists are a relatively new class of cancer drugs. STING stands for “stimulator of interferon genes.” STING is a protein that is part of a signaling pathway that results in upregulation of molecules that are part of the innate immune response. ONCOLOGY recently interviewed Dr. Eileen Parkes of Queen’s University in Belfast, whose laboratory studies the STING pathway, to find out why researchers are excited about targeting this pathway as a potential cancer therapy.

1 First, can you tell us what is known about the STING pathway and its role in innate immunity?

DR. PARKES: The STING pathway is such an interesting pathway. This pathway is key to our response to infection. You can think of it as being like the emergency services. So, when our bodies are hit with an infection, it’s the STING pathway that is the emergency first responder. The DNA from an attacking virus or bacteria ends up in the cytoplasm of the cell that is invaded. But DNA doesn’t belong in the cytoplasm, so it is detected as foreign by a protein called cGAS [cyclic GMP-AMP synthase], which activates the STING pathway. This leads to interferon production, which is really the alarm call of the cell. The STING pathway turns on the interferon response, then it attracts the first immune cells—natural killer cells—to infected cells, and then it calls in the expert cells—the acquired immune system cells—to let the rest of the immune system know there is a problem.

Interestingly, sometimes the STING pathway also drives a subgroup of autoimmune diseases—such as lupus, for example—by inappropriately recognizing a body’s own DNA as foreign. This STING response is also seen in some cancers, where inability to repair DNA results in abnormal DNA in the cytoplasm that is picked up by cGAS, activating STING, which in turn activates the interferon response.

2 What is the evidence that modulating this STING pathway might be a good approach for an anticancer therapy?

DR. PARKES: It’s always interesting to see what pathways the cancer itself hijacks, and STING is one of those pathways. We know that cancers are dedicated to their own survival and will use any means possible to bypass the immune system, which, in an ideal world, should destroy all cancerous cells. One of the ways the cancer hides itself is by shutting down the immune response. Given STING’s key role in turning on the immune response, being that first responder and turning on interferon, researchers hypothesized that turning on the STING pathway would result in immune activation, stimulating the immune cells to attack the cancer. And this is what has been shown in preclinical models. So, STING agonists have been developed that are injected directly into the cancer, activating the immune cells and the local environment, and hopefully resulting in tumor shrinkage.

3 Are there currently any cancer clinical trials that are testing STING agonists that you could highlight?

DR. PARKES: There are a couple of very interesting trials using STING agonists in combination with immune checkpoint–targeted treatment. Both in the United Kingdom and the United States, there are ongoing or proposed studies of STING agonists alone, as well as of STING agonists in combination with anti-PD-1 [anti–programmed death 1] im-

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mune checkpoint treatments. We and others had previously shown that you need STING to upregulate expression of PD-L1, the ligand for PD-1. And cancers with high PD-L1 expression, we already knew, are those that are most likely to respond to immune checkpoint blockade. Moreover, given STING’s role in turning on the immune system, it’s a very neat way of making a cold tumor hot—and that is what an immune response is all about, turning these cold tumor microenvironments with few immune cells into hot microenvironments with many infiltrating immune cells, which then could be “turned up” further using immunotherapies.

Certainly mouse studies of STING agonists alone showed that you got a response not just in the injected tumor site, but also in other tumor sites. Additionally, that response was even better in those preclinical studies with the addition of an immune checkpoint blockade antibody. So, our hope is that giving that spark, a STING agonist, to ignite the immune system, along with immune checkpoint blockade, will improve responses to immune checkpoint agents not just in the injected tumor but in the patient’s other tumors as well.

4 Are you and other clinicians thinking about approaches to personalizing STING agonist therapy?

DR. PARKES: Yes, definitely. I think understanding the STING pathway really helps us understand how the cancer behaves in relation to the immune system. Some cancers will hijack the pathway, and keep it on, which not only results in inflammatory tumors with lots of growth factors for the cancer, but also turns on immune checkpoints, meaning that those immune cells can’t attack the cancer. So these cancers might be the ones that do well with immune checkpoint–targeted therapy alone. Other cancers will shut down STING completely, and there’s been some great work recently showing that cGAS and STING are often methylated, often shut down in cancers. So giving a STING agonist to patients with these cancers may help overcome that immune block, and result in a response to just a STING agonist or a STING agonist along with immune checkpoint–targeted treatment. A limitation of the current STING agonists is the need to deliver them by direct injection into the tumor. But many companies are working on overcoming this by developing STING agonists that can be given intravenously or even orally. There’s also some evidence that other systemic agents, such as DNA-damaging treatments, can act as STING agonists too.

In terms of personalized STING treatments, we know already that there is no one-size-fits-all anticancer treatment. Our understanding of the role of the immune system has made a massive difference in our ability to treat cancer successfully. So, improving our understanding and using new drugs like STING agonists will continue to result in improvement—but to provide truly personalized medicine, we need to understand which patients need a single-agent approach and which need a combination, and which patients may not benefit from either. But we haven’t yet developed or validated the biomarkers to tell us these things. That’s an important goal for the future.

Financial Disclosure: The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
Can Chemotherapy Be Eliminated in the Treatment of Follicular Lymphoma?

Yes—Chemotherapy Need Not Be Routinely Used

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Follicular lymphoma is a common non-Hodgkin lymphoma subtype characterized by an indolent clinical course and heterogeneous clinical outcomes. Most patients present with advanced-stage disease and will experience high initial response rates and favorable remissions, coupled with recurrent relapse.[1] Given the heterogeneity and chronicity of follicular lymphoma, many patients can anticipate a normal life expectancy despite the relapsing nature of this disease.[2] Therefore, clinicians are tasked with balancing the efficacy of a treatment option with its impact on quality of life and potentially life-threatening toxicities. The goal of therapy, despite these challenges and the rapidly evolving treatment landscape, is to achieve a durable, quality remission for all patients.

The typical clinical course of follicular lymphoma has improved significantly over the past several decades.[3,4] Improvement in survival was not achieved with the evolution or intensification of chemotherapy regimens, but largely through the incorporation of monoclonal antibodies such as rituximab and novel targeted agents. Despite marked improvements in overall survival (OS) for the majority of patients, outcomes remain poor for approximately 20% of patients, who experience early relapse within 24 months of frontline chemoimmunotherapy.[2,5] Median survival for this poor-risk group is approximately 5 years, far short of the nearly 20-year projections of others.[2,4] Early relapse is a robust predictor of survival in follicular lymphoma and identifies a high-risk subset of patients in need of novel (non-chemotherapy) approaches.

Risk Stratification

The available clinical prognostic models, such as the Follicular Lymphoma International Prognostic Index

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No—Chemotherapy Remains an Essential Part of Therapy for Follicular Lymphoma

Paul M. Barr, MD

For asymptomatic patients with follicular lymphoma, observation remains the standard of care.[1] Similarly, single-agent rituximab is reasonable for patients with low-burden symptomatic disease.[2] However, given that most patients have advanced-stage disease at diagnosis and will progress over time, the majority of follicular lymphoma patients ultimately require chemotherapy. Of the 2,728 follicular lymphoma patients enrolled in the National LymphoCare Study, two-thirds had advanced-stage disease and two-thirds had intermediate- or high-risk disease as defined by the Follicular Lymphoma International Prognostic Index.[3] Most were treated with initial systemic combination chemotherapy, while observation and single-agent rituximab were felt to be appropriate for 18% and 14% of patients, respectively.

The reasoning behind these therapeutic choices is straightforward. The course of follicular lymphoma has improved over time, in large part due to treating physicians’ ability to administer combination chemotherapy plus immunotherapy. Specifically, the median overall survival (OS) of patients treated at Stanford University was estimated to be 11 years between 1960–1986 and increased to > 19 years between 1987–2003.[4] While the introduction of anti-CD20 therapy has also clearly contributed to the improved outcomes, these survival gains largely preceded routine use of rituximab. The patients diagnosed between 1987 and 1996 achieved a median OS of 18.6 years, with only 27% of patients receiving rituximab at any point. This time period primarily corresponds with the development of combination chemotherapy and advances in supportive care, such as growth factor use, enabling more effective treatment of advanced-stage, high-risk patients, as well as those developing grade 3 or transformed disease. While these data are derived

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Among high-tumor-burden patients, improvement in survival was only achieved with the addition of rituximab to chemotherapy, and not via the evolution of chemotherapy regimens.
point of significant improvement in PFS and complete response rates at 30 months, the findings suggest that R\textsuperscript{+} may be a reasonable option for patients who are not appropriate candidates for chemotherapy. Since the first remission is still anticipated to be the longest, achieving this with a safe, non–chemotherapy-based approach, if possible, is preferred.

**Relapsed/Refractory Disease**

The relapsed setting poses more challenges for clinicians, given the greater heterogeneity in presentations and outcomes. The preferred approach for high-risk patients is unknown, including whether intensification of chemotherapy (ie, myeloablative therapy) or a targeted approach should be pursued. Several phase II studies in the pre-rituximab era suggested that high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) is associated with longer remission duration than can be expected with conventional therapy; however, the best results were achieved when the treatment was administered earlier in the course of the disease and in the setting of remission.[21-24] Concerns regarding mortality from secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) curbed initial enthusiasm for this approach. A retrospective analysis attempted to address the utility of HDT/ASCT in the modern era and reported similar findings: nearly half of patients achieved meaningful remissions when treated early in the course of the disease.[25] The rates of secondary MDS/AML were not insignificant (12.4%). If the risk is high, but the reward is a prolonged second remission, then this approach should be restricted to the highest-risk patients—those who experience early relapse following frontline chemoimmunotherapy.

A separate retrospective analysis examined the outcomes among patients with early treatment failure (lymphoma progression within 24 months of frontline therapy) who underwent HDT/ASCT.[26] There was no difference in 5-year OS between the non-HDT/ASCT and the HDT/ASCT group. However, in a planned subgroup analysis, patients who received HDT/ASCT soon after treatment failure (≤ 1 year) had higher 5-year OS rates than those who did not undergo HDT/ASCT (73% vs 60%; \( P = .05 \)). If HDT/ASCT is only worthwhile in the highest-risk patients if performed soon after treatment failure, intensive chemotherapy is not a viable option for the vast majority of patients.

Radioimmunotherapy—a radiation-emitting radionuclide combined with an antibody targeting CD20—is an effective therapy in follicular lymphoma as consolidation following frontline chemotherapy or in the relapsed setting.[27,28] Myelosuppression is the primary toxicity, and secondary MDS and AML rates appear similar to those observed with chemotherapy. The most favorable outcomes are observed in patients with low-bulk disease, fewer prior therapies, and retained rituximab sensitivity. With one-dose administration, this may be an attractive approach for a select group of patients.

Targeting the B-cell receptor (BCR) signaling pathway has been an attractive approach for refractory follicular lymphoma. There are currently two phosphatidylinositol 3-kinase (PI3K) inhibitors approved by the US Food and Drug Administration for the treatment of relapsed/refractory follicular lymphoma patients in whom two prior lines of therapy have failed—idelalisib (PI3K\( \delta \) inhibitor) and copanlisib (pan-PI3K inhibitor). Idelalisib was associated with an overall response rate of 57% in relapsed/refractory indolent non-Hodgkin lymphoma, with a median PFS of 11 months.[29] The most common grade 3 or higher adverse events were neutropenia (27%), transaminitis (13%), diarrhea (13%), and pneumonia (7%).

A post hoc analysis of this study revealed similar outcomes among high-risk follicular lymphoma patients (early relapse), suggesting that targeted therapy may overcome chemotherapy resistance.[30] Similarly, copanlisib was associated with a favorable efficacy profile in relapsed/refractory follicular lymphoma, with a different safety profile: less gastrointestinal toxicity, and higher rates of hyperglycemia and hypertension. The toxicity profile associated with PI3K inhibitors may have curbed enthusiasm for these agents; however, recognition and early intervention may be the key to avoiding significant morbidity. In contrast, ibrutinib, a proximal BCR signaling pathway inhibitor with a predictable safety profile, has only modest activity in follicular lymphoma (overall response rate, 20.9%; median PFS, 4.6 months).[31]

Tazemetostat, an EZH2 inhibitor, has been associated with promising results in early-phase studies,[32] with high response rates particularly in those with the EZH2 mutation, and a favorable toxicity profile, and may provide another non-chemotherapy option targeting one of the most common mutations in follicular lymphoma. The existence of effective targeted options for chemo-refractory disease highlights the progress made with rational biologic targeting in relapsed follicular lymphoma.

**Conclusion**

A personalized approach to follicular lymphoma is warranted to minimize acute and late toxicity associated with chemotherapy. Improved risk stratification
and predictive biomarkers are needed. Until these become reality, balancing the goal of obtaining a durable remission and that of avoiding a negative impact on quality of life argues against the routine use of chemotherapy in follicular lymphoma.

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

REFERENCES


> Counterpoint. BARR CONTINUED FROM PAGE 404 from a cohort of relatively young patients, these observations are similar to analyses of follicular lymphoma outcomes based on the National Cancer Institute’s Survival, Epidemiology, and End Results Program database.[5]

Prospective clinical trials further support these observational studies. However, chemotherapy together with anti-CD20 antibodies has become the foundation of clinical trials, given the survival benefit achieved with the combination.[6,7] Improved progression-free survival (PFS) rates have been steadily
Table. Long-Term Efficacy of First-Line Chemoimmunotherapy for Advanced-Stage Follicular Lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Event-Free/Progression-Free Survival</th>
<th>Overall Survival</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHVP + I</td>
<td>44% (8-yr)</td>
<td>79% (8-yr)</td>
<td>FL2000[21]</td>
</tr>
<tr>
<td>R-FND + I</td>
<td>51% (10-yr)</td>
<td>73% (10-yr)</td>
<td>MD Anderson[22]</td>
</tr>
<tr>
<td>R-FM</td>
<td>52% (8-yr)</td>
<td>79% (8-yr)</td>
<td>FOLL05[11]</td>
</tr>
<tr>
<td>R-CVP</td>
<td>42% (8-yr)</td>
<td>85% (8-yr)</td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td>49% (8-yr)</td>
<td>83% (8-yr)</td>
<td></td>
</tr>
<tr>
<td>Chl/CVP/CHOP/Flu-RIT</td>
<td>41% (8-yr)</td>
<td>84% (8-yr)</td>
<td>Fit[23]</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>42% (10-yr)</td>
<td>81% (10-yr)</td>
<td>SWOG S0016[24]</td>
</tr>
<tr>
<td>CHOP-RIT</td>
<td>56% (10-yr)</td>
<td>75% (10-yr)</td>
<td></td>
</tr>
<tr>
<td>R-CHOP/CVP/FCM</td>
<td>35% (10-yr)</td>
<td>80% (10-yr)</td>
<td>PRIMA[14]</td>
</tr>
<tr>
<td>R-CHOP/CVP/FCM + MR</td>
<td>51% (10-yr)</td>
<td>80% (10-yr)</td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td>38% (10-yr TTNT)</td>
<td>66% (10-yr)</td>
<td>StiL NHL1[12]</td>
</tr>
<tr>
<td>BR</td>
<td>57% (10-yr TTNT)</td>
<td>71% (10-yr)</td>
<td></td>
</tr>
</tbody>
</table>

BR = bendamustine and rituximab; Chl = chlorambucil; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHVP + I = cyclophosphamide, doxorubicin, etoposide, and prednisolone, plus interferon alfa-2a; CVP = cyclophosphamide, vincristine, and prednisone; FCM = fludarabine, cyclophosphamide, and mitoxantrone; FIT = First-line Indolent Trial; Flu = fludarabine; FM = fludarabine and mitoxantrone; FND + I = fludarabine, mitoxantrone, and dexamethasone, plus interferon; MR = maintenance rituximab; NHL = non-Hodgkin lymphoma; R = rituximab; RIT = radioimmunotherapy; StiL = Study Group Indolent Lymphomas; SWOG = Southwest Oncology Group; TTNT = time to next treatment.

achieved in randomized studies with the use of chemotherapy plus rituximab in the first-line setting. [8-10] Early results from this era showed follicular lymphoma patients to be achieving response rates of > 90%, median PFS durations of 6 to 7 years, and 5-year OS rates approaching 90%. With long-term follow-up, roughly one-third to one-half of patients are alive and without lymphoma progression at 10 years (Table). Additionally, OS rates in the 70% to 80% range demonstrate the tolerability of contemporary chemoimmunotherapy, with the ability to re-treat patients later if necessary.

Several lessons have been learned from these studies, allowing physicians to administer treatment regimens that provide disease control while minimizing toxicity. While more immunosuppressive therapies provide excellent disease control, late adverse effects may reduce survival rates over the long term. In the FOLL05 study, higher rates of secondary malignancies were noted following anthracycline- or fludarabine-based therapy, as compared with R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone).[11] Fewer long-term data are available for bendamustine plus rituximab, but OS appears similar, with better tolerability compared with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).[12] Though designed to prolong remissions, consolidative and maintenance strategies have raised somewhat similar concerns. The 10-year follow-up of the Southwest Oncology Group S0016 trial showed that R-CHOP plus radioimmunotherapy provided a higher PFS rate of 56% compared with 42% for R-CHOP alone. However, this translated into a numerically lower OS rate of 75% compared with 81% with R-CHOP alone, due in part to the higher incidence of death related to myelodysplastic syndrome or acute myeloid leukemia in the radioimmunotherapy arm.[13]

Maintenance anti-CD20 therapy can clearly improve PFS rates but may have varying effects following different induction regimens. The PRIMA study demonstrated an improved PFS rate with 2 years of maintenance rituximab, predominantly following R-CHOP.[14] While a similar benefit has yet to be demonstrated following bendamustine plus rituximab, retrospective analyses suggest some degree of improved disease control. However, a higher rate of fatal events, primarily during maintenance administration, was noted following bendamustine in the GALLIUM study.[15] The lack of a clear OS benefit and toxicity concerns in some settings have therefore limited widespread adoption of maintenance therapy.
Multiple clinical investigators are focused on developing less toxic combinations using agents with novel targets. However, severe side effects have been observed with several “chemo-free” regimens.[16–18] While few have demonstrated adequate risk/benefit ratios to warrant upfront testing, lenalidomide plus rituximab has demonstrated promise. Phase II study results in previously untreated patients yielded 5-year PFS and OS rates of 70% and 100%, respectively.[19] Given these outcomes, the phase III RELEVANCE trial was conducted to compare lenalidomide plus rituximab vs chemoimmunotherapy, with more than 70% of patients receiving R-CHOP induction in the chemoimmunotherapy arm. No difference in overall response rate, complete remission rate, or PFS was observed. Despite differences in the toxicity profiles, roughly 30% of patients in each arm discontinued therapy early.[20]

Based on these data, chemotherapy remains standard of care in the treatment of follicular lymphoma. Long-term reports have led some to speculate that a proportion of patients are cured with chemoimmunotherapy. Given the indolent natural history of follicular lymphoma and the continued downward slope of the survival curves, it is premature to draw this conclusion. Nonetheless, it is clear that chemoimmunotherapy has redefined the history of the disease, producing survival rates measured in decades.

...it is clear that chemoimmunotherapy has redefined the history of the disease, producing survival rates measured in decades

Financial Disclosure: Dr. Barr has been a consultant for Celgene and Genentech.

REFERENCES
Obese Breast Cancer Patients and Survivors: Management Considerations

Jennifer Y. Sheng, MD1, Dipali Sharma, MS, PhD2, Gerald Jerome, PhD3, Cesar Augusto Santa-Maria, MD4

ABSTRACT: Excess body weight is a significant risk factor for many cancers, especially breast cancer. Patients with breast cancer or those with a history of the disease who are overweight or obese have an increased risk of therapy-related morbidity, recurrence, and breast cancer–related mortality. Obesity may also affect quality-of-life factors for survivors, including sexual dysfunction, neuropathy, cardiotoxicity, chronic fatigue, and lymphedema. Most cancer guidelines recommend that breast cancer survivors who are overweight or obese lose weight and that those with a normal body mass index (BMI) maintain a stable body weight. The cornerstone of interventions to treat or prevent obesity is lifestyle modification with diet and exercise; however, integrating these things into clinical practice is challenging. This article will present feasible weight loss interventions, and will discuss practical implications of ongoing chemotherapy and endocrine therapy with regard to weight gain, and the impact of obesity on therapy-related conditions during breast cancer survivorship.

Introduction
Many epidemiologic studies have consistently demonstrated that excess body weight is a major risk factor for breast cancer.[1] With 268,670 new breast cancer cases and 41,400 breast cancer deaths projected in 2018 in the United States, breast cancer and obesity are both significant public health issues.[2] Obese patients with breast cancer have an increased relative risk of recurrence of 40% to 50% and a relative risk of breast cancer–related mortality of 53% to 60%.[3,4] Obese women with hormone receptor–positive operable breast cancer have inferior outcomes in terms of disease-free survival (DFS; hazard ratio [HR], 1.24; 95% CI, 1.06–1.46; \( P = .0008 \)) and overall survival (OS; HR, 1.37; 95% CI, 1.13–1.67; \( P = .002 \)), compared with non-obese women.[5] Overall, approximately 15% of breast cancer cases in postmenopausal women may be attributable to weight gain.[6] In premenopausal women, short-term weight gain may increase breast cancer risk, although data are mixed.[7]

Obesity Increases Inflammation, Cytokines, and Endogenous Hormones
The biological relationship between obesity and breast oncogenesis is likely mediated by several pathways. Obesity has been associated with increased levels of inflammatory cytokines, including interleukin-1(β), interleukin-6, tumor necrosis factor α, and monocyte chemoattractant protein 1. Altered levels of these cytokines drive pro-proliferative pathways, such as angiogenesis, influx of macrophages, and antiapoptotic pathways.[8] Another untoward effect of obesity is increased synthesis of estrogens from androgens via augmented aromatization of androstenedione in peripheral adipose tissue in postmenopausal women. Breast carcinogenesis has also been associated with increased serum leptin levels and low adiponectin levels. Leptin is an adipocytokine synthesized by adipocytes; it acts as a satiety hormone at the hypothalamus level to reduce appetite and is paradoxically elevated in obese individuals.[9] High levels of leptin lead to concomitant activation of various oncogenic pathways, resulting in increased tumor growth, angiogenesis, and acquisition of a migratory and invasive mesenchymal phenotype.[10] Adiponectin counters obesity by modulating glucose metabolism, increasing fatty acid oxidation and insulin sensitivity, and decreasing production of inflammatory cytokines. Increased adiposity also increases circulating levels of

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insulin and insulin-like growth factor 1, which may also promote cell proliferation. Favorable changes in estrogens, sex hormone binding globulin, insulin, and leptin are observed to be associated with weight loss of at least 5%.[11]

Furthermore, weight loss of at least 10% has been associated with modulation of serum and tissue biomarkers, such as Ki-67, adiponectin, adiponectin-to-leptin ratio, sex hormone binding globulin, estradiol, testosterone, and insulin.[12] These biological data not only provide insight into how obesity can increase the risk of breast cancer, but suggest that weight loss may reverse some of these deleterious biological changes associated with obesity.

**Concerns About Breast Cancer Therapy and Obesity**

**Chemotherapy can lead to weight gain**

Chemotherapy-associated weight gain is experienced by most patients during the first year after diagnosis.[13] The Women’s Healthy Eating and Living (WHEL) study found that women treated with chemotherapy were 65% more likely to gain weight compared with those not receiving chemotherapy. [1] Studies have shown that women have decreased levels of physical activity after the diagnosis of breast cancer, which may contribute to weight gain. Moreover, adjuvant chemotherapy may also decrease resting rates of metabolism.[14] Additionally, the hormonal changes of menopause can affect metabolism and lead to weight gain.[2,3]

**Endocrine therapy does not significantly affect weight and is effective in obese patients**

A common question asked in clinical practice is whether endocrine therapy causes weight gain. In the International Breast Cancer Intervention Study (IBIS-I), which investigated tamoxifen vs placebo, the mean weight gain was 0.1 kg (standard deviation [SD], 0.1) vs 0.3 kg (SD, 0.1), respectively ($P = .3$). In the IBIS-II study, which compared anastrozole vs placebo, the median weight gain was 0.8 kg (SD, 5.3) vs 0.5 kg (SD, 7.4), respectively ($P = .5$). In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which compared anastrozole vs tamoxifen, there was no significant difference between the two therapies (median weight gain, 1.4 kg [SD, 3.9] vs 1.5 kg [SD, 4.0], respectively; $P = .4$). [15] Recent data from the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial, however, suggest that patients receiving an aromatase inhibitor (AI) may be less likely to gain weight than those receiving a selective estrogen receptor modulator (odds ratio [OR], 0.54; 95% CI, 0.31–0.93).[16] While these data may be conflicting, and there are numerous other variables such as chemotherapy and menopausal status that can affect weight gain, there is insufficient evidence to suggest that, in general, endocrine agents cause a significant amount of weight gain. Efforts at weight management should be directed at lifestyle changes rather than therapy discontinuation.

An additional question that often comes up is whether AIs are as effective in obese patients. In obese patients, the total level of body aromatase is elevated, and studies suggest that circulating estradiol may not be fully suppressed by AIs; however, this has never been definitively linked to inferior outcomes.[17] One study found that obese women who received anastrozole had plasma drug concentration levels that exceeded those of women with normal body weight by 25%, as well as lower mean follicle-stimulating hormone levels, indicating higher estradiol activity.[18]

In the Anastrozole vs Letrozole: Investigation into Quality of Life and Tolerability (ALIQUOT) study, baseline estrogen levels were significantly correlated with body mass index (BMI) and three times higher in obese patients compared with patients of normal weight. Estrogen levels in patients receiving treatment with both anastrozole and letrozole were greater at higher BMI levels, but this was significant only for letrozole ($P = .013$ for estradiol and $P = .035$ for estrone sulfate). Suppression of both estrogen types was greater with letrozole across the full range of BMI.[19] Other studies, however, have shown that changes in estrone and estradiol levels were not associated with BMI.[20] While data on the pharmacodynamic effects of obesity on AI-induced estrogen reduction may be variable, there are no conclusive data that suggest that AIs are clinically inferior to other endocrine regimens, and these still remain the therapy of choice for postmenopausal women, irrespective of BMI.

In the Breast International Group (BIG) 1-98 study, increased mortality risk among obese women was similar regardless of the type of endocrine therapy administered (tamoxifen: HR, 1.18; 95% CI, 0.91–1.52 and letrozole: HR, 1.22; 95% CI, 0.93–1.60).[21] Thus, in patients with an indication for an AI, we do not recommend routinely changing endocrine therapy on the basis of BMI, or recommend one AI over another.

**Effects of Obesity on Quality of Life in Survivors**

Obesity at and following breast cancer diagnosis is significantly associated with poor health-related...
KEY POINTS

- Women with early-stage breast cancer who are overweight or obese at diagnosis and/or gain weight after diagnosis may have a higher risk of recurrence compared with women of normal weight.

- Obesity may increase the risk of treatment-related toxicities, such as sexual dysfunction, neuropathy, chronic fatigue, cardiotoxicity, and lymphedema.

- A standard-of-care approach and specific guidelines to manage weight loss and to improve physical activity levels among patients with a history of early-stage breast cancer are needed.

Quality of life and functional health, and may increase the risk of adverse treatment effects.

Obesity can affect body image, sexual function, and genitourinary function in breast cancer survivors

Evaluation and treatment of female sexual dysfunctions is often under-addressed in breast cancer survivors, in spite of the availability of safe and effective treatments.[22] While early menopause induced by chemotherapy and hormonal alterations associated with AIs can contribute to altered sexual function, surgery and radiation for breast cancer may also alter sexuality by changing body contour and sensation, decreasing arousal or lubrication, and reducing nipple sensation after nipple-sparing mastectomy.[23] A cross-sectional survey of 255 patients who were at least 1 year from surgery showed that obese and overweight women reported more appearance dissatisfaction (18.1% and 13.0%) compared with normal-weight women (4.1%; P = .02). A greater proportion of overweight women (94.7%) reported that their chest played an important role in intimacy before and after surgery, as compared with normal-weight women (80.6%), but a postoperative decline in the importance of this role was observed in all groups (overweight, P = .01; normal weight, P < .001).[24]

Furthermore, being overweight or obese at baseline was associated with more problems with urinary incontinence and tendency to nap, and with poorer physical functioning and more bodily pain (vs BMI < 25 kg/m²).[25]

Neuropathy is more common in obese patients

Chemotherapy-induced peripheral neuropathy (CIPN) has been reported in up to 44% of patients receiving chemotherapy, particularly taxanes.[26] Higher BMI is associated with a higher incidence of neuropathy, with studies demonstrating a prevalence of 48.4% in participants with normal weight, 60.2% in overweight participants, and 66.7% in obese participants. Compared with women of normal weight, being obese was associated with an increased risk of CIPN (adjusted OR, 1.94; 95% CI, 1.03–3.65).[27] Neuropathy was significantly more likely to occur in overweight patients compared with normal-weight patients receiving taxane treatment at 24 months, and less likely to occur in patients with high moderate-to-vigorous physical activity levels compared with those with lower activity levels at 24 months.[28]

While studies have not shown that weight loss can reverse neuropathy, these data suggest that physical activity may help decrease neuropathy. Furthermore, primary prevention with baseline normal weight may also be important.

Obesity is a risk factor for cardiotoxicity

Because obesity is already a strong risk factor for cardiovascular disease, cancer treatment in obese patients can further increase overall risk for adverse cardiac effects.[29] A recent meta-analysis suggests that being overweight or obese may be a risk factor for cardiotoxicity from anthracyclines, especially when these are administered in sequence with trastuzumab.[30]

Other studies have found obesity to be associated with an increased risk of cardiac dysfunction in women using trastuzumab.[31] Additionally, in elderly patients (over 65 years of age), obesity is an independent risk factor for trastuzumab-related cardiac toxicity.[32]

Obesity can lead to chronic fatigue

About one-third of breast cancer survivors have chronic fatigue and about one-fourth will have persistent fatigue after 2 years.[33] Although the development of fatigue in breast cancer patients seems largely due to cancer therapy, the long-term persistence of fatigue is related to preexisting medical conditions and lifestyle factors. Higher BMI at baseline is significantly associated with increased physical fatigue during and after cancer treatment.[34] The Mammary Carcinoma Risk Factor Investigation (MARIE) study demonstrated that both a physically inactive lifestyle and obesity were associated with persistent physical fatigue, independent of chemotherapy and radiation therapy.[35] In a study of patients who were overweight or obese, fatigue after chemotherapy was lower in an exercise group than in a non-exercise group.[36] Higher BMI, associated with a greater tendency to catastrophize about fatigue and amplify physical symptoms, was predictive of fatigue beyond 9 months.[37] These studies demonstrate the importance of an ideal body weight, since chronic fatigue is associated with emotional distress and limits function and willingness to exercise.

Lymphedema is more common in obese patients

Cancer treatments such as lymph node dissection and radiation therapy can damage lymphatic drainage routes, leading to fluid build-up, discomfort, and reduced mobility and function. Excess adiposity may increase risk of lymphedema via increased inflammation, added stress on the lymphatic system, or slower healing times after surgery.[38] Data suggest that obesity increases the risk of lymphede-
ma after treatment for breast cancer. Prospective studies have reported statistically significantly higher lymphedema risk for obese compared with normal-weight women (OR, 2.48; 95% CI, 1.05–5.84). Breast cancer survivors who were obese at the time of treatment were approximately 3.6 times more likely to develop lymphedema at 6 months after diagnosis than those who were not obese.[40] In a pilot study among overweight breast cancer survivors, a 12-week diet intervention resulted in a significant reduction in BMI and swollen arm volume (reduced from 24% to 15%; P = .02).[41]

Weight Loss in Breast Cancer Survivors Is Feasible

Studies have demonstrated that modest weight loss is possible and improves survival outcomes in women with early-stage breast cancer.[42,43] Dietary guidelines suggest that patients with a history of early-stage breast cancer should receive a nutritional assessment immediately after diagnosis, since diet quality is an important component of maintaining a healthy body weight.[44]

Data from the Women’s Health Initiative found that an intervention group that received teaching by dietitians 4 times a year (≥ 5 fruit and vegetable servings, ≥ 6 whole grain servings, and < 20% fat in their diet recommended) had a 26% decrease in risk of death by any cause and a 42% decrease in risk of death related to breast cancer compared with a control group.[45] In the Women’s Intervention Nutrition Study (WINS), women participating in conventional treatment for early-stage breast cancer (N = 2,437) were randomly assigned either to a group that also received a dietary intervention (to reduce the percentage of calories from fat to 15%) or to a control group. Those in the dietary intervention group who experienced weight loss had a 24% lower risk of relapse at 5-year follow-up compared with those not receiving the dietary intervention. Of note, body weight was not an intervention target, and there was only a difference of 2.7 kg between groups through 5 years of observation (P = .005).[46]

However, the WHEL study randomized women with early-stage breast cancer to a dietary intervention (a telephone counseling program as well as cooking classes and newsletters that promoted 5 vegetable servings, 3 fruit servings, and 15% to 20% of energy intake from fat) or to printed “5-A-Day” diet guidelines. The dietary intervention arm did not achieve significant weight loss and did not demonstrate a reduction in breast cancer, compared with the arm with printed materials.[47] These studies suggest that alteration in diet alone may be insufficient, and that weight loss is required to achieve improvements in breast cancer-related outcomes.[48]

In-person programs, which help with behavioral modification in the areas of diet and exercise, have been successful in achieving weight loss. A systematic review of overweight and obese patients in a primary-care setting shows that intensive, face-to-face behavioral counseling for at least 3 months, with at least 6 months’ follow-up, can induce clinically meaningful weight loss.[49] The mean 6-month weight changes from baseline in the intervention groups ranged from a loss of 0.3 kg to 6.6 kg. In the control groups, the mean change ranged from a gain of 0.9 kg to a loss of 2.0 kg.[49]

Since limitations on in-person weight loss interventions include time and cost constraints, remote interventions with similar efficacy may be more amenable to real-world integration. The Practice-Based Opportunities for Weight Reduction (POWER) trial demonstrated equivalent weight loss outcomes between in-person coaching and a remotely supported weight loss intervention (telephone calls by a health coach, accelerometers to assess physical activity, self-directed dietary and activity monitoring, and web-based learning modules).[50,51] This intervention has been adapted for patients with stage 0 to III breast cancer who have completed all local therapy and chemotherapy, and was found to have promising results in a randomized study.[51] Other studies have also suggested that remotely supported weight loss programs can produce results similar to those of in-person programs (Table 1). Some evidence supports the effectiveness of mobile technology interventions that incorporate self-monitoring, feedback on performance, and networks of social support, although success has been variable.[52] These experiences demonstrate that not only are weight loss interventions feasible, but that remotely supported approaches may be adaptable and ultimately integrated into clinical practice.

While definitive data are pending, initial data suggest that weight management for improved cancer-related outcomes is an important aspect of survivorship care. To confirm the positive impact of weight loss on survival outcomes (such as DFS), a large randomized study has been designed and is actively accruing.[53] The Alliance Breast Cancer Weight Loss trial (BWEL) is testing the 10-year impact of a telephone weight loss program on invasive disease–free survival in 3,136 women with a BMI ≥ 27 kg/m² with a recent diagnosis of stage II to III estrogen receptor–positive or triple-negative breast cancer.[54] Patients will be randomized to a 2-year weight loss intervention consisting of a health education program that includes standardized mailings and twice-yearly conferences or to a program that...
also includes telephone calls from a trained coach.

While the aforementioned studies involved patients who had completed chemotherapy, remote lifestyle interventions at the time of diagnosis or early on during adjuvant treatment may provide an opportunity to prevent treatment-associated weight gain. Data suggest that healthy lifestyle programs can be integrated during chemotherapy for many patients; however, these programs may need to be adjusted for those patients who are less likely to participate. Patient participation is variable across different studies and can range from 11% to 65%.[55,56] In one study, patients who did not wish to exercise were less likely to be employed and had a lower level of education, more fatigue and lower quality of life, more negative attitudes about exercise, and less social support compared with participants who exercised.[57] Regardless of patients’ inclination to participate in healthy lifestyle programs, given the possible benefits, we recommend that patients stay active during administration of chemotherapy for early-stage breast cancer, and that they discuss any limitations on types of physical exercise and activity levels with their healthcare providers.

### Guidelines and Recommendations

Cancer organizations and foundations recommend a healthy diet, adequate exercise, and a healthy body weight for all breast cancer survivors (Table 2). While cancer survivors often seek ways to minimize the risk of recurrence and death from breast cancer, many struggle with achieving sustainable weight loss.[58] An analysis of adherence to World Cancer Research Fund/American Institute for Cancer Research recommendations for breast cancer patients demonstrated that complying with five recommendations (being physically active as part of everyday life, limiting consumption of energy-dense food and avoiding sugary drinks, eating mostly foods of plant origin, limiting intake of red meat and avoiding processed meat, and limiting alcohol) vs complying with none or only one was associated with a 57% lower prevalence of metabolic syndrome.[59]
morbidity, and numerous quality-of-life factors. Recognition of the importance of weight management and implementation of feasible weight loss interventions are urgently needed. Furthermore, additional data are needed to define strategies that are effective, standardized, and scalable to real-world settings. As part of survivorship care, oncologists should recommend that all breast cancer survivors maintain an ideal body weight with healthy diet and regular exercise.

Financial Disclosure: Dr. Jerome, as a member of the Johns Hopkins faculty, receives a portion of the fees paid to Johns Hopkins for its faculty’s monitoring of the Innergy weight-loss program. Dr. Santa-Maria receives research funding from MedImmune and Pfizer and is on the advisory board for Polyphor. The other 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.

Acknowledgment: We would like to thank Janelle Wilder Coughlin, PhD (Associate Professor, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine), for offering her expertise in developing this manuscript.

REFERENCES


31. Santa-Maria C, Coughlin J, Blackford A, POWER-remote: a randomized controlled trial evaluating the effect of a remote-based weight loss program in women with early stage breast cancer. Presented at the 2016 San Antonio Breast Cancer Symposium; December 6-10, 2016; San Antonio, Texas. Abstract P4-14-01.

Carboplatin/Paclitaxel Induction in Ovarian Cancer: The Finer Points

Leslie R. Boyd, MD1, Franco M. Muggia, MD2

ABSTRACT: The carboplatin/paclitaxel doublet remains the chemotherapy backbone for the initial treatment of ovarian cancer. This two-drug regimen, with carboplatin dosed using the Calvert formula, yielded convincing noninferior outcomes when compared with the prior, more toxic, regimen of cisplatin/paclitaxel. Carboplatin’s dose-limiting toxicity is thrombocytopenia; however, when this drug is properly dosed and combined with paclitaxel, the doublet’s cycle 1 dose in chemotherapy-naive women is generally safe. Carboplatin (unlike cisplatin) contributes minimally to the cumulative sensory neuropathy of paclitaxel, thus ensuring noticeable reversibility of neuropathy symptoms following completion of 6 cycles and only occasionally requiring cessation or substitution of the taxane. Paclitaxel is responsible for the hair loss associated with the carboplatin/paclitaxel doublet; preventive measures must be considered for patients who would otherwise refuse treatment. Several first-line phase III trials, as well as ongoing trials for which only preliminary results have been published, have fueled debates on the optimal dose and schedule; these have focused not only on weekly vs q3-weeks paclitaxel, but also on other modifications and the advisability of adding bevacizumab. Our view is that results of this doublet in the first-line treatment of ovarian cancer are driven primarily by carboplatin, given that ovarian cancer is a platinum-sensitive disease. Consequently, the roles of the accompanying paclitaxel dose and schedule and the addition of bevacizumab are currently unsettled, and questions regarding these issues should be decided based on patient tolerance and comorbidities until additional data are available.

Introduction

The regimen consisting of carboplatin and paclitaxel represents the backbone of ovarian cancer treatment: 95% of women diagnosed with ovarian cancer will receive this regimen. It has been 15 years since the publication of the results of Gynecologic Oncology Group (GOG) 158, an 840-patient noninferiority trial led by Robert Ozols that established carboplatin as a suitable replacement for cisplatin in the initial treatment of advanced ovarian cancer following primary debulking surgery.[1] Clinicians who treat gynecologic malignancies can recite chapter and verse about what is involved in administering the carboplatin/paclitaxel regimen and anticipating its toxicities. Despite our years of experience, including worldwide trials that use the original carboplatin/paclitaxel regimen as a control while exploring additions and dose/schedule modifications, we should not be lulled into believing that the majority of patients will sail through this therapy. Here, we reflect on our experience administering the carboplatin/paclitaxel regimen to scores of ovarian cancer patients over the past decade and a half. While some of these reflections represent our personal views, we hope what we have to say will help readers become more familiar with the key issues.

The successful combination of carboplatin and paclitaxel was the result of initial research efforts focused on the pharmacology of carboplatin and its clinical development that took place at the Royal Marsden Hospital/Institute of Cancer Research. These studies were led by Hilary Calvert, a disciple of Eve Wiltshaw, who had established cisplatin's unprecedented activity in ovarian cancer.[2,3] The Calvert formula for dosing carboplatin, reinforced by the initial pharmacodynamic observations of Merrill Egorin and colleagues that focused on the drug's dose-limiting toxicity of lowering platelet counts, became widely adopted as a reliable way of determining the maximum initial carboplatin dose that could be safely administered to chemotherapy-naive patients.[4,5]
Carboplatin’s usual doublet partner, paclitaxel, a water-insoluble compound first isolated from bark of the Pacific yew tree by the US Department of Agriculture for the National Cancer Institute, was introduced in the 1980s for clinical study in a formulation based on cremophor solubilization. Significant problems were encountered during laborious phase I trials: not only did paclitaxel require special tubing for its administration, but treatment also led to sudden deaths from anaphylaxis, resulting in cessation of its development. Development was not resumed until a combination of measures such as glucocorticoid premedication (given orally, starting the evening and morning before the first administration of paclitaxel), and lengthening of its administration yielded reproducible safety. Most importantly, these measures were coupled with outstanding nursing practices, such as observing patients carefully, especially during the first minutes of administration of the drug and periodically thereafter. Paclitaxel’s activity in ovarian cancer, initially demonstrated by William McGuire and colleagues, led to phase III trials that resulted in its displacing cyclophosphamide and other drugs in first-line combination regimens used in ovarian cancer treatment.[6,7]

The current treatment paradigm for patients with ovarian cancer continues to rely on a platinum-taxane doublet: the carboplatin/paclitaxel q21-days backbone used in GOG 158 has been the comparator arm for several trials attempting to improve on the original high response rates and more favorable progression-free and overall survival outcomes seen in the trial.[8] Even larger trials than GOG 158 tested mostly paclitaxel dose/schedule modifications or the addition of targeted drugs in attempts to improve on those original results. Leaving aside the controversy around intraperitoneal (IP) therapy for patients who have undergone successful cytoreduction to less than 1 cm of residual disease (recently discussed for ONCOLOGY by Keiichi Fujiwara and Robert Ozols[9]), we would like to comment on the paclitaxel dose/schedule alterations.

The Japanese Gynecologic Oncology Group (JGOG) studied weekly dosing of paclitaxel—a schedule that was optimal compared with the q3-weeks schedule in breast cancer for single-agent paclitaxel—and combined this with q21-days carboplatin. A striking survival advantage was observed, as well as impressive long-term results.[10,11] In a more recent GOG trial, the benefit of this weekly schedule was only observed in the minority of patients who did not receive bevacizumab in a q21-days schedule.[12] Other groups have reported on additional comparative trials; their results have added to the uncertainty surrounding paclitaxel dose/schedule alterations as a determinant of outcome in ovarian cancer. Tolerance is another aspect of such schedule changes that is important to consider; this will be the focus of the next several sections.

**Hematologic Toxicity**

Thrombocytopenia is the dose-limiting toxicity of carboplatin, and this was a principal consideration when Egorin and colleagues developed the initial pharmacodynamic dosing in a study that included patients with abnormal renal function.[13] Paclitaxel lessens the impact of carboplatin on platelet counts and actually speeds up recovery from platinum-induced marrow suppression—an effect that is particularly obvious when platinum/paclitaxel doublets are compared with other platinum doublets[6] or are used in previously treated patients.[14] It is unlikely that an area under the curve (AUC)-based first dose of carboplatin in a chemotherapy-naïve patient will result in dose-limiting hematologic toxicity: platelet counts that drop below 50,000/μL and require platelet transfusions for bleeding in previously untreated patients are extremely uncommon events, particularly when carboplatin is administered in combination with paclitaxel. Because this carboplatin toxicity usually begins to appear after day 14 and is predictably cumulative, one should use the nadir platelet count of the preceding cycle and baseline upon recovery as signals to consider a carboplatin dose reduction. For example, if platelet counts are over 200,000/μL at the beginning of cycles 1 and 2, but are barely over 100,000/μL at the beginning of cycle 3, a pre-emptive dose adjustment that lowers the AUC by 20% is appropriate (even though this would not be called for by protocol adjustments that rely on drops below the normal range for platelet counts). Marrow tolerance in the preceding cycle (as determined by platelet nadir and recovery) is the best guide to dosing in the subsequent cycle; in fact, the absence of any effect on the platelet count is a signal that carboplatin may have been under-dosed. Moreover, if the platelet count does not fall to dose-limiting levels, it is unlikely that the patient will develop clinically significant neutropenia. A related corollary: granulocyte colony-stimulating factor administration is seldom, if ever, necessary in patients who are naïve to chemotherapy.

Of course, paclitaxel is expected to add some myelosuppression of its own—and it does, particularly when given weekly. This and other practical aspects are reasons why the senior author has for years preferred a “divided-dose” regimen on days 1 and 11 of...
The senior author has for years preferred a ‘divided-dose’ regimen [for paclitaxel] on days 1 and 11 of the cycle: if dosed at no higher than 100 mg/m², paclitaxel’s effects on peripheral blood count nadirs (which usually occur on day 11±1) are transient, and perhaps lessen carboplatin-induced thrombocytopenia. As noted previously, paclitaxel accelerates bone marrow recovery, decreases platelet toxicity, and promotes the ability to give the next doublet cycle on time—likely enhancing the safety of this suggested “divided-dose” schedule.[15]

Neuropathy
Except in the case of weekly regimens, adjustments to the dose of paclitaxel are primarily made because of peripheral neuropathy. There are no clinically applicable quantifiable measures of sensory neuropathy, but analyses of randomized studies reinforce the relationship of neurotoxicity to taxane dose and schedule. [16] Encyclopedic listings of toxicities should not distract the clinician from the importance of personally monitoring sensory neuropathy—since this is the dose-limiting toxicity most commonly encountered in attempts to complete 6 cycles of treatment. Assessment of cycle-to-cycle patient-reported paresthesias is the most reliable way of detecting this problem early. Even though symptoms are not easily quantified, patients will often accurately describe their onset, location, and duration. Therefore, it cannot be sufficiently emphasized that caregivers must directly and routinely inquire about the extent and pattern of paresthesias. Continuous paresthesias during the entire interval between cycles should prompt implementation of dose reductions, and if the paresthesias reach a continuous level of grade 2, paclitaxel should be stopped. In the JGOG trial, weekly paclitaxel was associated with greater neuropathy than q3-weeks administration. It is notable that this remains the only first-line trial in which taxane dosing was a determinant of ovari-an cancer survival. If it weren’t for this benefit, there would be little justification for continuing a neurotoxic drug when medication is required to ameliorate its symptoms (ie, ongoing grade 2 or higher neuropathy).

In fact, neuropathy will invariably worsen for 2 to 3 weeks after paclitaxel is administered; it can eventually lead to impairment in activities of daily living that may be irreversible. Severe neuropathy after only 1 or 2 cycles is rare, but if this does occur, it may justify substituting docetaxel for paclitaxel. Beyond the early cycles, one may question whether the risk/benefit tradeoff associated with additional taxane dosing warrants continuation of the drug—especially considering that in first-line trials, platinums appeared to be the key determinant of outcome.[17,18] Therefore, stopping paclitaxel should be considered when there is persistent grade 2 neuropathy; clinical trial results reflect these sorts of protocol-driven dose adjustments and wide variations in taxane administration. In general, gabapentin should not be routinely used to suppress neuropathy symptoms, but this can be considered if symptoms interfere with sleep or daily activities. Also consider that pain resulting from growth factor support may be a confounder. Physicians need to allay patients’ fears about adjustments to the paclitaxel dose and reassure them that these are part of good clinical practice and unlikely to compromise survival.

The foregoing remarks about paclitaxel-associated sensory neuropathy were even more pertinent during the cisplatin era, because of the much greater neurologic damage resulting from cisplatin as opposed to carboplatin. Staggered doses of paclitaxel and cisplatin, with cisplatin given on the day following paclitaxel administration, would be expected to diminish the accelerated risk of sensory neuropathy by minimizing the pharmacologic interactions that would compound neuropathy risk. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel), which lacks paclitaxel’s cremophor effect, offers yet another way of minimizing pharmacologic interactions of two drugs that may result in accelerating cumulative sensory neuropathy.[16,19]

Other Toxicities
Paclitaxel causes hair loss: this effect becomes manifest 3 weeks after administration of the drug and generally persists throughout treatment, with hair regrowth noted within 3 to 6 months of cessation of paclitaxel. Although it is almost always reversible, hair loss is one of the main reasons given for reduced quality of life by women treated with the carboplatin/paclitaxel regimen.[20] The late Syd Salmon introduced cold caps in the 1970s when doxorubicin was incorporated into the breast cancer armamentarium. Cold caps work by decreasing the temperature at the scalp; the resulting vasoconstriction and reduction in hair follicle metabolism reduce the effects of paclitaxel on the hair follicles. Although results vary, a large national registry in the Netherlands showed that up to 50% of scalp-cooled patients did not wear a head cover during their last taxane chemotherapy session.[21]

Carboplatin was developed in the early 1980s to overcome some of the serious toxicities of cisplatin. It markedly lowered the potential for nephrotoxicity, ototoxicity, and hyperemesis seen with cisplatin. [22] When tested by Bristol-Myers Squibb, carboplatin was the only platinum among a dozen non-nephrotoxic analogs that did not induce vomiting
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From the publishers of ONCOLOGY
### How an Expert Approaches It

The Oncology Journal, August 2018

#### Table. Selected Phase III Studies of Adjuvant Therapy for Advanced Ovarian Cancer After Initial Surgery

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Regimens *</th>
<th>No. of Patients</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 158[1]</td>
<td>Paclitaxel (135 mg/m², 24 h) + cisplatin (75 mg/m²)</td>
<td>425</td>
<td>14.5 mo</td>
<td>48 mo</td>
<td>Demonstrated noninferiority of carboplatin</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC6)</td>
<td>415</td>
<td>15.5 mo</td>
<td>52 mo</td>
<td></td>
</tr>
<tr>
<td>JGOG 3016[11]</td>
<td>Paclitaxel (180 mg/m²) and carboplatin (AUC6)</td>
<td>319</td>
<td>17.5 mo</td>
<td>62.2 mo</td>
<td>Showed superiority of weekly paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (80 mg/m²) weekly + carboplatin (AUC6)</td>
<td>312</td>
<td>28.5 mo</td>
<td>100.5 mo</td>
<td></td>
</tr>
<tr>
<td>MITO-7[24]</td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC6)</td>
<td>404</td>
<td>17.3 mo</td>
<td>NR</td>
<td>Paclitaxel at a lower dose intensity was not superior</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (60 mg/m²) weekly + carboplatin (AUC6)</td>
<td>406</td>
<td>18.3 mo</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>GOG 262[12]</td>
<td>Paclitaxel (80 mg/m²) weekly + carboplatin (AUC6) plus optional bevacizumab in cycles 2–6 and q3 wk until progression</td>
<td>346</td>
<td>14.7 mo</td>
<td>42 mo (est)</td>
<td>Addition of bevacizumab blunted advantage of weekly paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC6) (× 6 cycles) plus optional bevacizumab in cycles 2–6 and q3 wk until progression</td>
<td>346</td>
<td>14.0 mo</td>
<td>42 mo (est)</td>
<td></td>
</tr>
<tr>
<td>GOG 218[25]</td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC6) (× 6 cycles) plus placebo in cycles 2–22</td>
<td>625</td>
<td>10.3 mo</td>
<td>39.3 mo</td>
<td>Bevacizumab had an effect on PFS</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC6) (× 6 cycles) plus bevacizumab in cycles 2–6 → placebo in cycles 7–22</td>
<td>625</td>
<td>11.2 mo</td>
<td>38.7 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC6) (× 6 cycles) plus bevacizumab in cycles 2–22</td>
<td>623</td>
<td>14.1 mo</td>
<td>29.7 mo</td>
<td></td>
</tr>
<tr>
<td>ICON7[26]</td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC5 or AUC6) plus bevacizumab (75 mg/kg) (× 6 cycles) → bevacizumab in cycles 7–18</td>
<td>764</td>
<td>19.0 mo</td>
<td>45.5 mo</td>
<td>Results similar to those of GOG 218, but bevacizumab had effect on OS in poor-risk subset</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC5 or AUC6) (× 6 cycles)</td>
<td>764</td>
<td>17.3 mo</td>
<td>44.6 mo</td>
<td></td>
</tr>
<tr>
<td>GOG 252[27]</td>
<td>IP cisplatin + IV/IP paclitaxel plus bevacizumab</td>
<td>520f</td>
<td>27.8 mo</td>
<td>NR</td>
<td>Carboplatin arms, either IV or IP, with weekly paclitaxel were noninferior</td>
</tr>
<tr>
<td></td>
<td>IP carboplatin (AUC6) + IV paclitaxel (80 mg/m²) weekly</td>
<td>520f</td>
<td>28.7 mo</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IP carboplatin (AUC6) + IV paclitaxel (80 mg/m²) weekly IV carboplatin (AUC6) + IV paclitaxel (80 mg/m²) weekly</td>
<td>520f</td>
<td>26.8 mo</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>ICON8[28]</td>
<td>Paclitaxel (175 mg/m²) + carboplatin (AUC5 or AUC6) (× 6 cycles)</td>
<td>530f</td>
<td>17.9 mo</td>
<td>46.5 mo</td>
<td>Preliminary results: no clear superiority of weekly dosing</td>
</tr>
<tr>
<td></td>
<td>IV carboplatin (AUC6) + IV paclitaxel (80 mg/m²) weekly</td>
<td>533f</td>
<td>20.6 mo</td>
<td>48.1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin (AUC2) + paclitaxel (80 mg/m²), both given weekly (× 6 cycles)</td>
<td>534f</td>
<td>21.1 mo</td>
<td>54 mo</td>
<td></td>
</tr>
</tbody>
</table>

*aControl arms are bolded.

*bq3 wk unless specified.

*cOptimally debulked patients only.

*d1–3 hr unless stated.

*eIncluded some stage IC/II patients.

*fNumber of patients in each arm from meeting presentations (2016 Annual Meeting of the Society of Gynecologic Oncology, European Society for Medical Oncology 2017 Congress).

AUC = area under the curve; est = estimated; GOG = Gynecologic Oncology Group; ICON = International Collaboration on Ovarian Neoplasms; JGOG = Japanese Gynecologic Oncology Group; MITO = Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies; NR = not reported.

when administered to ferrets. Subsequent preclinical studies (in rats) of platinums and their interaction with membrane organic cation transporter 2 (OCT2) demonstrated clearly that carboplatin—unlike cisplatin—interacts only minimally with OCT2 present in renal tubules and the cochlea.[23] One may generally reassure patients about the low risk of nephrotoxicity, ototoxicity, and hyperemesis with carboplatin, while on the other hand stressing its hematologic toxicities. However, one should underscore (as noted previously) that thrombocytopenia is the best indicator of carboplatin’s effects; this has been demonstrated not only by clinical trials, but also by Bristol-Myers Squibb databases.[5] Another major advantage of carboplatin over cisplatin, other than the favorable nonmalignant organ toxicity spectrum, is the much greater predictability of the former’s pharmacodynamic effects.

It is critical to spend time with the patient, personally reviewing the expected side effects of treatment. Printed information, while potentially useful as a resource, if not directly discussed at the outset, may promote unnecessary fears and may not adequately emphasize what to expect.

Other Recommended Practices When Treating With Carboplatin/Paclitaxel

While carboplatin/paclitaxel is a fairly easy doublet to administer, one should not underestimate the possibility of issues arising because of comorbidities and advanced cancer presentations. It is important to pay attention to the details of a patient’s history to help get through the requisite number of cycles.

Before initiating treatment, one should ascertain whether corticosteroids are contraindicated (eg, as they are in patients with active hepatitis, uncontrolled diabetes, or psychoses). Substitution of nab-paclitaxel for paclitaxel should be considered (but is dependent on access to this drug formulation). Use of nab-paclitaxel also overcomes difficulties with venous access and often makes it unnecessary to use central venous lines to deliver 6 cycles of carboplatin/paclitaxel.

Going over a patient’s list of medications with an eye to stopping or replacing any that may potentially cause problems can be helpful. Possible problem medications include aspirin and diuretics. Aspirin may unnecessarily raise the risk of gastritis and bleeding, and may trigger unnecessary workup and, in the setting of a lower hemoglobin level, undue concerns about abdominal pain complicated by treatment-related anemia. When possible, substitute other classes of antihypertensives for diuretics, or consider intermittent use of loop diuretics. It is also wise to advise patients to reduce the number of pills they take, since any tablet or capsule intake may induce vomiting. Some of these practices are carryovers from cisplatin days, when electrolyte imbalances were common, but they do apply to a certain extent to carboplatin.

Specific Comments on the Ongoing Carboplatin and Paclitaxel Scheduling Debates

1. Do not focus on the white blood cell count and the absolute neutrophil count (ANC) except when a patient is febrile or pancytopenic (including a low platelet count); remember that the platelet count is the major indicator of carboplatin toxicity. One can redose the doublet when the ANC is below 1,000 cells/μL as long as the platelet count has shown brisk recovery and the absolute monocyte count plus the ANC total 1,000/μL (monocytes are a sign of rebounding marrow, and so is the increase in platelets that occurs as the number of white cells dips). In fact, the divided-dose regimen[15] documents such patterns better by dosing at the paclitaxel ANC nadir; this regimen may also allow better titration of drug doses.

2. Weekly carboplatin, validated as noninferior to q3-weeks carboplatin in the recent ICON8 trial, requires further discussion upon publication of the trial’s full results. The senior author has seen instances where physicians were confused about continued dosing: they were uncertain which agent was contributing to observed hematologic changes, or which agent was the culprit when a rash raised concerns of hypersensitivity. In addition, the required weekly antiemetics may wreak havoc with a patient’s bowels, as well as causing other problems. (Note: paclitaxel as a single agent only requires small doses of dexamethasone to protect against its mild associated nausea—if any.)

3. Weekly paclitaxel regimens need to undergo frequent modifications in dose or require the addition of growth factor support. We recently published data on patient tolerance of a divided-dose paclitaxel schedule that we were using prior to publication of the JGOG studies on weekly paclitaxel; under certain circumstances there were concerns of intolerance of the higher paclitaxel doses, such as in frail patients with advanced presentations requiring neoadjuvant chemotherapy.[15]

4. The Table summarizes median progression-free survival and overall survival data from worldwide phase III trials, starting with the GOG 158 noninferiority trial that resulted in carboplatin displacing cisplatin in the upfront platinum doublet. The outstanding results of JGOG 3016 made the weekly paclitaxel regimen the front-runner, but these results were not replicated by MITO-7 (perhaps because of the lower

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**KEY POINTS**

- Carboplatin is the key drug of the carboplatin/paclitaxel doublet, and is most accurately dosed using the Calvert formula.
- Adjusting the dose of carboplatin requires that the clinician be mindful of baseline and nadir platelet counts; neutropenia has few consequences unless preceded by severe thrombocytopenia.
- Questions regarding the optimal dose and schedule for paclitaxel are part of an ongoing debate, with recent trials addressing these issues.
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1. REFERENCES

m to benefit and minimize the risk of cytopenias and hair loss, as well as knowledgeable about strategies for adjusting carboplatin dosing so as to maximize benefit and minimize the risk of cytopenias and the need for growth factors.

Conclusion
Since the publication of GOG 158, the IV carboplatin/paclitaxel doublet × 6 cycles has become the standard chemotherapy backbone for ovarian cancer patients after primary surgical debulking. Phase III trials in which bevacizumab has been added to both IP and IV standard regimens have raised doubts about the advantages of the IP route for optimally cytoreduced patients, and about the weekly paclitaxel schedule for all others. Full publication of these well-conducted trials is awaited before guidelines are adopted for isoelectric point 

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


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

PART 2: ENKTL, EATL, Indolent T-Cell LDP of the GI Tract, ATLL, and Hepatosplenic T-Cell Lymphoma

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

ABSTRACT: The World Health Organization classification for peripheral T-cell lymphomas (PTCLs) continues to evolve based on genetic and clinical distinctions of each entity. In Part 1, an overview was provided of PTCL not otherwise specified, follicular T-cell lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma (ALCL), and breast implant–associated ALCL. In Part 2, this review is extended to extranodal natural killer (NK)/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. Each NK/T-cell malignancy has its own signature, requiring knowledge of the appropriate diagnostic, prognostic, and therapeutic considerations when caring for afflicted individuals. Future directions will depend on discoveries that further our understanding of each disease and clinical trials that test the latest treatment options.

Introduction
Peripheral T-cell lymphomas (PTCLs) include a spectrum of mature T-cell and natural killer (NK)-cell neoplasms. PTCLs differ from one another in clinical presentation, pathobiology, prognosis, and therapeutic strategies.[1,2] Their heterogeneity, the challenge of diagnosis, and new knowledge from molecular studies have led to a recent revision of the World Health Organization (WHO) classification for PTCLs.[3]

As described in Part 1, the incidence of PTCLs shows epidemiologic variability worldwide, influenced by factors such as ethnicity, diseases affecting immunity, and virus epidemiology (Figure 1).[4-9]

The current WHO classification for PTCLs includes new subtypes, but due to their low incidence, detailed knowledge of each entity continues to evolve.[3] These subtypes, which will be highlighted in this article, are described in Table 1.[3]

Extranodal NK/T-Cell Lymphoma
NK/T-cell lymphoma is a rare and aggressive disease with a high rate of relapse and poor prognosis.[10] Extranodal NK/T-cell lymphoma (ENKTL) has a male predominance, with a median age at diagnosis of approximately 65 years.[5,9,11] Asia, Central America, and South America demonstrate a higher incidence of NK/T-cell lymphoma.[12] The geographic distribution may in part be explained by the prevalence of Epstein-Barr virus (EBV) and the associated aberrant expression of its receptor, CD21.[8] EBV likely plays a role in the pathogenesis of this cancer, affecting cellular proliferation and the microenvironment, including the expression of programmed death ligand 1 on the malignant cells.[13]

ENKTL has two subtypes. The most common is the nasal type, but extranasal presentations are seen, with different clinical manifestations.[11] The majority of patients with nasal-type ENKTL present with early-stage disease involving the nasal region and the upper aerodigestive tract.[11,14] Symptoms associated with this presentation typically include nasal obstruction, swelling, and bleeding (epistaxis).[11]

Pathologic findings include angiodestruction, necrosis, and ulcers, with the malignant cells embedded in an inflammatory microenvironment. The NK cells express CD2, CD5, cytoplasmic CD3ε, and CD56. These cells are commonly CD8-negative. CD30 is not usually expressed.[11] A spectrum of cytogenetic alterations has
been noted without a signature chromosomal translocation. The most common abnormalities are del(6)(q21q25) and i(6)(p10), although it is not clear if these represent primary or progression-associated events.

Clinical staging should include a detailed ear, nose, and throat examination, positron emission tomography–CT imaging, and, in select instances, bone marrow biopsies.[11]

Prognostication using the International Prognostic Index (IPI) is problematic because IPI scores do not correlate with survival. In fact, more than 80% of patients are in the IPI low-risk group, but many still have unfavorable outcomes.[15] The Korean Prognostic Index appears to be a meaningful advance, in particular for patients with nasal presentations.[15] Guidelines from the National Comprehensive Cancer Network recommend the use of the prognostic index of natural killer cell lymphoma (PINK) or PINK-E (incorporating EBV status; Tables 2 and 3).[16-18] Additional prognostic factors include fasting blood glucose level, total protein, and CD30 expression.[15,19]

The treatment for lymphomas originating from NK cells differs from that for other PTCLs, with distinct approaches depending on location (nasal or extranasal) and extent of disease.[20] For the nasal type, radiotherapy is a key component of treatment with curative intent.

In cases of regional disease, an intensive combined-modality approach of sequential or concomitant chemotherapy and radiotherapy is most effective.[10,12,20,21] Chemotherapy alone has been associated with worse outcomes and lower overall survival (OS) when compared with radiotherapy and combined-modality treatment,[12] Regimens containing anthracyclines are not recommended because of inferior outcomes and overexpression of the P-glycoprotein efflux membrane transporter. Regimens containing L-asparaginase or pegylated asparaginase have proved the most successful for patients
**Figure 2. Treatment Algorithm for NK/T-Cell Lymphoma.**

*AutoSCT should be considered for patients with stage I/II disease, but it is not absolutely needed.
AlloSCT = allogeneic stem cell transplantation; AspaMetDex = pegylated asparaginase, methotrexate, and dexamethasone; autoSCT = autologous stem cell transplantation; NK = natural killer; P-GEMOX = pegylated asparaginase, gemcitabine, and oxaliplatin; RT = radiotherapy; SMILE = dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide.

Data from: NCCN guidelines 2017.[23]

**Table 1. Peripheral T-Cell Lymphoma (PTCL): Current World Health Organization Classification**

<table>
<thead>
<tr>
<th>Entity or Subtype</th>
<th>Distinctive or Particular Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extranaodal NK/T-cell lymphoma (ENKTL), nasal type</td>
<td>EBV+</td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma (EATL)</td>
<td>Closely linked to celiac disease/polymorphic cellular composition/most cases, αβ</td>
</tr>
<tr>
<td>Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)</td>
<td>Formerly type II EATL, segregated from type I, and given a new name due to nature and lack of association with celiac disease/monomorphic cellular composition; usually CD8+, CD56+, and MATK+</td>
</tr>
<tr>
<td>Indolent T-cell lymphoproliferative disorder of the GI tract</td>
<td>New indolent provisional entity with superficial monoclonal intestinal T cells, in some cases showing transformation</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma (ATLL)</td>
<td>HTLV-1–infected and CCR4+</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Mutation of STAT5B and less often STAT3</td>
</tr>
</tbody>
</table>

EBV = Epstein-Barr virus; GI = gastrointestinal; HTLV-1 = human T-cell leukemia virus type 1; NK = natural killer.

Data from: Swerdlow et al. Blood. 2016.[3]
presenting with advanced-stage NK-cell lymphoma, especially for those with extranasal disease.[10,12,20,21] For patients with early-stage disease (stages I and II) or for those too frail to tolerate chemotherapy, another option is radiotherapy alone. [12,14]

Patients with advanced-stage NK/T-cell lymphoma—either nasal-type or extranasal disease—should be treated with one of the chemotherapy regimens discussed previously. Those who achieve complete response are also candidates for consolidation with autologous stem cell transplantation (autoSCT).[20] For patients with chemotherapy-refractory NK/T-cell lymphoma, autoSCT does not have a clear benefit, and allogeneic SCT (alloSCT) may be a more appropriate therapeutic intervention.[18,22,23]

Pembrolizumab, an anti–programmed death 1 checkpoint inhibitor, has recently been shown to be highly effective for relapsed/refractory cases and has been used after alloSCT with good outcomes (Figure 2).[13,18]

**Enteropathy-Associated T-Cell Lymphoma**

The involvement of the gastrointestinal (GI) tract is more commonly observed in B-cell non-Hodgkin lymphoma.[24] Enteropathy-associated T-cell lymphomas (EATLs) are rare, typically involve the small intestine, and are divided into two distinct entities in the WHO classification, based on morphology, immunophenotype, and molecular features.[3,6,24] Type I is the most prevalent (~80% to 90% of cases) and has a high prevalence in northern Europe. Type II is now formally designated as monoclonal

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**Table 2. Risk Factors Included in the Different Prognostic Indices for NK/T-Cell Lymphoma**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>KPI</th>
<th>PINK</th>
<th>PINK-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>B symptoms present</td>
<td>Age &gt; 60 yr</td>
<td>Age &gt; 60 yr</td>
<td></td>
</tr>
<tr>
<td>Stage III or IV disease</td>
<td>Stage III or IV disease</td>
<td>Stage III or IV disease</td>
<td></td>
</tr>
<tr>
<td>LDH level &gt; 1× upper limit of normal</td>
<td>Distant lymph node involvement</td>
<td>Distant lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>Regional lymph node involvement</td>
<td>Non-nasal-type disease</td>
<td>Non-nasal-type disease</td>
<td></td>
</tr>
<tr>
<td>EBV (DNA) present</td>
<td>EBV (DNA) present</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EBV = Epstein-Barr virus; ENKTL = extranodal NK/T-cell lymphoma; KPI = Korean Prognostic Index; LDL = lactate dehydrogenase; NK = natural killer; NKCL = natural killer cell lymphoma; PINK = prognostic index of natural killer cell lymphoma; PINK-E = prognostic index of natural killer cell lymphoma with EBV.


**Table 3. Overall Survival by PINK and PINK-E Risk Group**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>PINK</th>
<th>PINK-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>95%; 3-yr</td>
<td>95%; 3-yr</td>
</tr>
<tr>
<td>Intermediate</td>
<td>62%; 3-yr</td>
<td>55%; 3-yr</td>
</tr>
<tr>
<td>Stage III or IV disease</td>
<td>25%; 3-yr</td>
<td>28%; 3-yr</td>
</tr>
</tbody>
</table>

Low: 0 risk factors; Intermediate: 1 risk factor; High: > 2 risk factors.

PINK = prognostic index of natural killer cell lymphoma; PINK-E = prognostic index of natural killer cell lymphoma with Epstein-Barr virus.


**Table 4. PTCL and Genetic Alterations**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Immunophenotype</th>
<th>Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENKTL</td>
<td>CD2+, CD56+, CD3+, CD5+</td>
<td>TP53, JAK3, DOX3X, STAT3, STAT5B</td>
</tr>
<tr>
<td>ATLL</td>
<td>CD2+, CD3+, CD4+, CD56+, CD25+</td>
<td>CCR4, FoxP3</td>
</tr>
<tr>
<td>EATL type I</td>
<td>CD3+, C7+, CD103+</td>
<td>NOTCH1, ABL1, VAV2</td>
</tr>
<tr>
<td>MEITL</td>
<td>CD3+, CD8+, CD56+, CD103+</td>
<td>MATK, STAT5B, SETD2, MYC</td>
</tr>
<tr>
<td>ITCLD GIT</td>
<td>CD3+, CD8+, CD5+</td>
<td>STAT3</td>
</tr>
<tr>
<td>HSTCL</td>
<td>CD3+, CD56+, CD8+</td>
<td>STAT5B, STAT3</td>
</tr>
</tbody>
</table>


epitheliotropic intestinal T-cell lymphoma (MEITL) and is more common in individuals of Asian and Hispanic descent.\[3,10,25\] The majority of patients are diagnosed in their 6th decade.\[10,25\]

Celiac sprue and the human leukocyte antigen–DQ2/DQ8 phenotype is associated with type I EATL.\[6,10,24\] Independent of subtype, the malignancy tends to be aggressive.\[6\] Clinical presentation is characterized by abdominal pain, change in bowel habits, and anorexia.\[10\] B symptoms are not commonly noted.\[26\]

EATL type I is typically polymorphic, while MEITL has a monomorphic cellular composition. The characteristic immunophenotype is different for the two subgroups. Most cases of EATL express CD30 and have an α/β T-cell receptor expression, while CD30 expression is uncommon in MEITL cases, which also tend to be more frequently γ/δ-expressing.\[3,26\] Genetic alterations, including a 9q34 region gain or a 16q21.1 deletion, are frequently detected in EATL patients with celiac disease. Patients without celiac disease frequently have a chromosome 8q gain.\[10\] Abnormal nuclear p53 protein expression is noted in 75% of cases. Mutations of STAT5B and SETD2 are observed in cases of MEITL of γ/δ origin. Abnormalities aff ecting MYC signaling are also common in MEITL (Table 4).\[3,25\]

EATL has a poor prognosis, with a median OS of less than 1 year.\[26,27\] No standard treatment exists for these patients. Historically, the combination of surgery and anthracycline-based combination chemotherapy, with or without radiotherapy, was employed.\[26\] Another option for first-line therapy is IVE/MTX (ifosfamide, etoposide, epirubicin/methotrexate), developed by the Scotland and Newcastle Lymphoma Group, which showed an improvement in outcomes when compared with traditional regimens.\[25,28\] For patients who achieve a complete response, autoSCT is a consideration.\[18,25,27\]

Indolent T-Cell Lymphoproliferative Disorder of the GI Tract

Indolent T-cell lymphoproliferative disorder (LPD) of the GI tract is an entity recently incorporated into the WHO classification of lymphoid neoplasms.\[3\] This lymphoma has a male predominance, with a median age at diagnosis of 45 years.\[24,27\] There is no association with celiac disease, but some patients have a history of Crohn disease.

Presentation with diarrhea is common. At times, there is also abdominal discomfort.\[24,29\] Fever, weight loss, and night sweats are relatively rare.\[24\]

The disease usually has an indolent course, without lymphadenopathy or organomegaly. Involvement of the small bowel is most common, although any GI site can be involved and often there are multiple locations.\[3\] Endoscopic findings are extremely varied and include nodules, ulcers, diverticula, and erosions.\[24\]

Classically, indolent T-cell LPD of the GI tract is characterized by an infiltration of small, monotonous, and mature lymphocytes involving the lamina propria, with focal infiltration of the muscularis mucosae and submucosa. The mitotic index (or Ki-67 expression) is usually low (eg, Ki-67 expression less than 5%), and EBV is not expressed. CD30+ cells are rare.\[24,29\]

A limited number of cases have been reported in the literature. Recently published research has demonstrated that progression and transformation are rare.\[24,27\] Aggressive chemotherapy is of minimal value, and watchful waiting is usually the most appropriate approach.\[24,27\]

Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is linked to infection with the retrovirus human T-cell leukemia virus type 1 (HTLV-1).\[23,30-32\] The transmission of HTLV-1 predominantly occurs vertically through exposure to breast milk or blood.\[31\] The malignant cells show monoclonal integration of the virus.

The epidemiology of the disease reflects the prevalence of HTLV-1 in endemic regions in southwestern Japan, Central America, South America, the Caribbean basin, and western Africa. The incidence is 2.5% among HTLV-1 carriers and is slightly more pronounced among males in their 6th decade, suggesting that infection alone is not sufficient for the development of this malignancy.\[32\]

Four classic clinical presentations of ATLL have been described: acute, lymphomatous, chronic, and smoldering.\[33\] The acute presentation is most common and is characterized by lymphocytosis, lymphadenopathy, hepatosplenomegaly, constitutional symptoms,
lytic bone lesions, skin rash, and involvement of other organs. Hypercalcemia and elevated lactic dehydrogenase (LDH) levels are frequent laboratory findings. This subtype carries the worst prognosis.[31-33]

The lymphomatous variant is characterized by lymphadenopathy without lymphocytosis. Skin involvement is common and can manifest as an erythematous rash, papules, or nodules.[33]

Patients with the chronic form typically present with skin manifestations, without significant lymphocytosis or lymphadenopathy. Patients with the smoldering subtype have normal peripheral blood counts with skin and/or lung lesions. Enhanced susceptibility to opportunistic infections has been observed in all subtypes and is potentially exacerbated by treatment.[30,33,34]

Generally, ATLL is considered an aggressive disease composed of a pleomorphic lymphoid infiltrate.[31] The "fl ower cell" or "clover leaf" is the name given to malignant cells with convoluted nuclei that express CD2, CD3, CD4, CD5, and CD25. Associated large transformed cells may be CD30+.[30,31]

The T-cell receptor genes are clonally rearranged. There is no signature cytogenetic abnormality, although generalized genomic mutations (ie, PLCG1, PRKCB, VAV1, IRF4, FYN, CARD11, CCR4, CCR7, and STAT3) and prominent CpG island DNA hypermethylation are noted. The tax gene, a nonstructural gene on the HTLV-1 genome, appears to play a critical role in leukemogenesis, but it is not critical to sustain tumor cell growth. HBZ is one of the few genes consistently overexpressed in most ATLL cases.[30,31] Mutations or deletions involving p53 are also seen and are more common with disease progression.[30]

Watchful waiting is recommended for patients who are asymptomatic.[32] Antiretroviral treatment, combining zidovudine (AZT)
and interferon alfa (INF-α), appears to be an option for first-line therapy, in particular for the acute subtype of ATLL. A meta-analysis by Bazarbachi et al evaluated the use of AZT/IFN-α for each subtype of ATLL and its effect on OS (Figure 3).[34] Polychemotherapy containing anthracyclines has historically been used as first-line therapy for patients with the lymphomatous subtype who require treatment, although response rates are low, with frequent relapses and short survival (median, 13 months).[30] Mogamulizumab (anti-CCR4 monoclonal antibody) is approved in Japan for the treatment of relapsed/refractory cases.[31] Alemtuzumab (anti-CD52 monoclonal antibody) also has activity but is associated with severe immunosuppression.[30] AlloSCT should be considered in patients with the acute form who achieve remission, but it is associated with significant morbidity and high relapse rates (Figure 4).[18,30,32]

**Hepatosplenic T-Cell Lymphoma**

This rare lymphoproliferative disorder, which represents less than 1% of non-Hodgkin lymphomas, predominantly affects young men with a median age of approximately 35 years.[9,18,35] An association with chronic immunosuppression is seen in as many as 20% of individuals.[10,34]

The clinical presentation suggests a very aggressive disease and includes systemic symptoms, hepatosplenomegaly, and pancytopenia.[10] A proliferation of cytotoxic (TIA1+ and granzyme M+) medium-sized T cells is seen infiltrating the sinusoids of the liver, spleen, and bone marrow.[3,35]

There are two types of hepatosplenic T-cell lymphoma. The most common type is derived from γ/δ T cells (expressing the Vδ1 chain), and a small percentage derive from α/β T cells.[3,35]

Due to the aggressive nature of the disease, combination chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] or hyper-CVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate and cytarabine]) followed by stem cell transplantation is usually recommended.[35] AlloSCT is the preferred front-line consolidation in cases of γ/δ hepatosplenic lymphoma. AutoSCT is reserved for elderly patients or those with significant comorbidities.[36] Unfortunately, most patients do not achieve a complete response with induction chemotherapy, compromising the stem cell transplantation results.[35]

**Conclusion**

PTCLs represent a heterogeneous spectrum of malignancies. The low overall incidence of each entity has historically presented a challenge to advancing our knowledge about each disease. It is recommended that the diagnosis be reviewed by an experienced pathologist, in part because a more comprehensive understanding of the molecular, cellular, and phenotypic characterization of the different subtypes has emerged. In most instances, prognosis remains poor, underscoring the importance of having patients participate in clinical trials. In addition, there has been recognition of indolent subtypes that should be observed without immediate intervention. Fortunately, encouraging therapeutic approaches are on the horizon that should have a profound impact on our ability to treat these unique non-Hodgkin lymphomas.

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**Financial Disclosure:** Dr. Zain serves as a consultant for Spectrum Pharmaceuticals, and serves as a consultant and on the speakers bureau for Seattle Genetics. The other 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.

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**REFERENCES**