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Insights From an Oncology Pharmacist
BTK Inhibitors & Atrial Fibrillation
Kelly Valla

Review Article
Role of TMZ in CNS Cancers
Karisa C. Schreck, Stuart A. Grossman
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541 ONCOLOGY Contributors Take the Stage

To honor our board members and authors, we rounded up a list of their presentations at the American Society of Hematology meeting this December in San Diego.

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Considerations in the Care of Non–Small-Cell Lung Cancer: The Value Imperative

Ronan Kelly, MD, MBA, and Stefanie Houseknecht, PharmD, BCOP

ABSTRACT: Cancer costs in the United States continue to escalate at an alarming and unsustainable rate. These costs are not driven exclusively by a higher demand for services or by an aging population; rather, a number of systemic failures, highlighted by the Institute of Medicine (IOM), continue to plague our cancer care delivery systems and need to be rectified. Drug costs, plus expensive diagnostic tests, hospital admissions/readmissions, and unreasonable end-of-life care, combine to inflate the total cost of care. Cancer, particularly lung cancer, is one of the most expensive diseases in the United States. While individual oncologists are unlikely to influence costs in the short term, they can become more proficient at evaluating the value derived from new treatment options and maximizing the clinical benefit for their patients. Discussions of cost and patient values need not hinder patient-physician relationships, and, in fact, can strengthen them. This article discusses ways in which the oncologist can incorporate value into the management of patients with lung cancer and comply with the underlying principles of the Choose Wisely Campaign, as well as recent American Society of Clinical Oncology and European Society for Medical Oncology initiatives, to bend the cost curve downwards while maintaining efficacy.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States, with an estimated 234,030 new cases and 154,050 deaths anticipated in 2018.[1] It is also a high-cost disease state throughout the continuum of care. In 2017, the total cost of care associated with lung cancer in the United States was estimated at $13.9 billion, with approximately 43% ($6 billion) of costs occurring during initial care and 41% ($5.8 billion) occurring within the last year of life.[2] These numbers are expected to increase as cancer drug costs rise and utilization of treatment increases, especially in the last year of life.[3] Recent data have demonstrated that the mean total and net monthly costs of medical care are consistently higher for lung cancer compared with breast cancer, prostate cancer, and colorectal cancer, regardless of the patient’s stage of disease or age.[3]

The management of non–small-cell lung cancer (NSCLC) has changed dramatically over the last decade: personalized, biomarker-driven therapeutics and immunotherapy—most notably, checkpoint inhibitors—have helped improve patient survival, safety, and quality of life. Table 1 lists all therapies indicated for the treatment of lung cancer that have been approved by the US Food and Drug Administration over the past 5 years.[4] While nearly every therapy listed in Table 1 demonstrated an improvement in progression-free survival (PFS) when compared with the existing standard, a substantial increase in costs also occurred. This trend is not sustainable, and many countries outside of the United States have not approved expensive medicines based on cost-efficacy analyses, with each jurisdiction determining the acceptable threshold for reimbursement. The management of lung cancer continues to be challenging for healthcare providers and patients alike. However, through collaboration and education, the oncologist can play a significant role in improving the value derived from therapeutic interventions for patients with lung cancer.

PERSPECTIVE

Bruce Pyenson, FSA, MAAA

discusses the power of collaboration on page 537.

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>Generic (Brand)</th>
<th>Stage</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2018</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/19/2018</td>
<td>Osimertinib (Tagrisso)</td>
<td>IV</td>
<td>First-line for metastatic NSCLC with <em>EGFR</em> exon 19 deletions or exon 21 L858R mutations</td>
</tr>
<tr>
<td>2/16/2018</td>
<td>Durvalumab (Imfinzi)</td>
<td>III</td>
<td>Unresectable stage III disease that has not progressed following concurrent platinum-based chemotherapy and radiation</td>
</tr>
<tr>
<td>1/12/2018</td>
<td>Afatinib (Gilotrif)</td>
<td>IV</td>
<td>First-line for metastatic NSCLC with nonresistant <em>EGFR</em> mutations</td>
</tr>
<tr>
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<tr>
<td><strong>2017</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/6/2017</td>
<td>Alectinib (Alecensa)</td>
<td>IV</td>
<td>Regular approval for <em>ALK</em>-positive metastatic NSCLC</td>
</tr>
<tr>
<td>6/22/2017</td>
<td>Dabrafenib (Tafinlar) + trametinib (Mekinist)</td>
<td>IV</td>
<td>Regular approval; administered in combination for metastatic NSCLC with <em>BRAF</em> V600E mutation</td>
</tr>
<tr>
<td>5/26/2017</td>
<td>Ceritinib (Zykadia)</td>
<td>IV</td>
<td>Regular approval for <em>ALK</em>-positive metastatic NSCLC</td>
</tr>
<tr>
<td>5/10/2017</td>
<td>Pembrolizumab (Keytruda)</td>
<td>IV</td>
<td>Accelerated approval in combination with pemetrexed/carboplatin for previously untreated metastatic nonsquamous NSCLC</td>
</tr>
<tr>
<td>4/28/2017</td>
<td>Brigatinib (Alunbrig)</td>
<td>IV</td>
<td>Accelerated approval for <em>ALK</em>-positive metastatic NSCLC that has progressed on or is intolerant of crizotinib</td>
</tr>
<tr>
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<tr>
<td><strong>2016</strong></td>
<td></td>
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<td></td>
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<tr>
<td>10/24/2016</td>
<td>Pembrolizumab (Keytruda)</td>
<td>IV</td>
<td>Metastatic NSCLC with tumors expressing PD-L1</td>
</tr>
<tr>
<td>10/18/2016</td>
<td>Atezolizumab (Tecentriq)</td>
<td>IV</td>
<td>Metastatic NSCLC that has progressed during or following platinum-containing chemotherapya</td>
</tr>
<tr>
<td>3/11/2016</td>
<td>Crizotinib (Xalkori)</td>
<td>IV</td>
<td>Metastatic NSCLC with <em>ROS1</em>-positive tumors</td>
</tr>
<tr>
<td>2/26/2016</td>
<td>Everolimus (Afinitor)</td>
<td>IV</td>
<td>Adult patients with progressive, well-differentiated, nonfunctional neuroendocrine tumors of gastrointestinal or lung origin, with unresectable, locally advanced, or metastatic disease</td>
</tr>
<tr>
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<tr>
<td><strong>2015</strong></td>
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<td></td>
</tr>
<tr>
<td>12/11/2015</td>
<td>Alectinib (Alecensa)</td>
<td>IV</td>
<td>Accelerated approval for metastatic NSCLC that has progressed on or is intolerant to crizotinib</td>
</tr>
<tr>
<td>11/24/2015</td>
<td>Necitumumab (Portrazza)</td>
<td>IV</td>
<td>First-line metastatic squamous NSCLC in combination with gemcitabine/cisplatin</td>
</tr>
<tr>
<td>11/13/2015a</td>
<td>Osimertinib (Tagrisso)</td>
<td>IV</td>
<td>Accelerated approval for metastatic <em>EGFR</em> T790M-positive NSCLC that has progressed on or after <em>EGFR</em> tyrosine kinase inhibitor therapy</td>
</tr>
<tr>
<td>10/9/2015</td>
<td>Nivolumab (Opdivo)</td>
<td>IV</td>
<td>Metastatic NSCLC with progression on or after platinum-based chemotherapya</td>
</tr>
<tr>
<td>10/2/2015</td>
<td>Pembrolizumab (Keytruda)</td>
<td>IV</td>
<td>Accelerated approval for metastatic NSCLC with tumors expressing PD-L1 and disease progression on or after platinum-containing chemotherapy</td>
</tr>
<tr>
<td>7/13/2015</td>
<td>Gefitinib (Iressa)</td>
<td>IV</td>
<td>Metastatic NSCLC with <em>EGFR</em> exon 19 deletion or exon 21 (L858R) substitution mutations</td>
</tr>
<tr>
<td>3/4/2015</td>
<td>Nivolumab (Opdivo)</td>
<td>IV</td>
<td>Metastatic squamous NSCLC with progression on or after platinum-based chemotherapy</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2014</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/12/2014</td>
<td>Ramucirumab (Cyramza)</td>
<td>IV</td>
<td>Metastatic NSCLC in combination with docetaxel for disease progression on or after platinum-based chemotherapy</td>
</tr>
<tr>
<td>4/29/2014</td>
<td>Ceritinib (Zykadia)</td>
<td>IV</td>
<td><em>ALK</em>-positive metastatic NSCLC with disease progression on or intolerance to crizotinib</td>
</tr>
</tbody>
</table>

---

*Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapies for these aberrations before receiving treatment with this agent.

*Regular approval was granted on 3/30/2017.

*EGFR* = epidermal growth factor receptor; FDA = US Food and Drug Administration; NSCLC = non–small-cell lung cancer; PD-L1 = programmed death ligand 1.
level in terms of dollars per quality-adjusted life-year gained. In the United States, clinical pathways are becoming the norm in an attempt to standardize decision making and to improve therapeutic selection and care delivery. While data show pathways can help decrease costs in lung cancer, it is likely that US authorities will also implement some form of value-based pricing in the years ahead to help control drug price escalation.

## Cost of Care: Just How Bad is the Problem?

### Increasing awareness about therapy pricing

Most physicians do not know the cost of the drug therapies they prescribe. Even fewer know how much their patients are responsible for paying. The first step in reducing financial toxicity for both patients and the country as a whole is to increase awareness of drug costs. Two of the fastest growing drug classes in cancer are tyrosine kinase inhibitors (TKIs) and checkpoint inhibitors, both of which have seen new drug approvals or new indications for lung cancer (Table 1). The cost of these therapies is highly variable and dependent on the payer. For example, the price paid by a private practice oncology clinic for pembrolizumab differs from the price paid by a 340B drug pricing program–eligible clinic.

Although it may have limitations, and potentially represents the high end of the drug price range, the average wholesale price (AWP) can serve as a starting point for oncologists seeking to become better informed about drug prices. The AWP is readily available to the medical community and can often assist with price comparisons among agents within a drug class. Table 2 and Table 3 list the AWPs of commonly prescribed drugs for the treatment of lung cancer.

### Table 2. Cost Comparison of Targeted Therapies for the Treatment of NSCLC

<table>
<thead>
<tr>
<th>Drug Therapy (Generic [Brand])</th>
<th>Cost$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (Iressa)</td>
<td>$9,254.10</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>$10,141.80</td>
</tr>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>$9,785.70</td>
</tr>
<tr>
<td>Osimertinib (Tagrisso)</td>
<td>$17,539.80</td>
</tr>
</tbody>
</table>

**FDA-Approved Drugs for the Treatment of Metastatic EGFR-Mutated NSCLC**

<table>
<thead>
<tr>
<th>Drug Therapy (Generic [Brand])</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>$19,267.20</td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>$11,947.50</td>
</tr>
<tr>
<td>Alectinib (Alecensa)</td>
<td>$17,414.40</td>
</tr>
<tr>
<td>Brigatinib (Alunbrig)</td>
<td>$18,639.60</td>
</tr>
</tbody>
</table>

*Note that costs are based on a 30-day supply of the usual FDA-approved starting dose and are based on the Average Wholesale Price as reported by Lexicomp online. Available at: http://www.crlonline.com/lco/action/home. Accessed October 5, 2018.

**FDA-Approved Drugs for the Treatment of Metastatic ALK-Positive NSCLC**

<table>
<thead>
<tr>
<th>Drug Therapy (Generic [Brand])</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>$7,551.60</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>$11,159.12</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>$10,499.20</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi)</td>
<td>$5,888.26</td>
</tr>
</tbody>
</table>

*Note that costs are calculated using the usual US Food and Drug Administration–approved starting dose, assuming a patient weight of 70 kg for weight-based therapies; they are based on the Average Wholesale Price as reported by Lexicomp online. Available at: http://www.crlonline.com/lco/action/home. Accessed October 5, 2018. Fixed doses were used as per the package insert for nivolumab, pembrolizumab, and atezolizumab.

**NSCLC = non—small-cell lung cancer.**

### Table 3. Cost Comparison of Immunotherapies for the Treatment of NSCLC

<table>
<thead>
<tr>
<th>Drug Therapy (Generic [Brand])</th>
<th>Cost per Cycle$</th>
<th>Cost for 6 weeks of Therapy$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>$7,551.60</td>
<td>$22,654.80</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>$11,159.12</td>
<td>$22,318.24</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>$10,499.20</td>
<td>$20,998.40</td>
</tr>
</tbody>
</table>

*Note that costs are calculated using the usual US Food and Drug Administration–approved starting dose, assuming a patient weight of 70 kg for weight-based therapies; they are based on the Average Wholesale Price as reported by Lexicomp online. Available at: http://www.crlonline.com/lco/action/home. Accessed October 5, 2018. Fixed doses were used as per the package insert for nivolumab, pembrolizumab, and atezolizumab.

**NSCLC = non—small-cell lung cancer.**

### At-risk populations

One particularly vulnerable patient population is Medicare beneficiaries: precisely the demographic most often diagnosed with lung cancer. In our experience, few oncologists understand Medicare Part D drug coverage. In addition, policies that have been created to help address out-of-pocket expenses for Medicare beneficiaries have not been as successful as intended. For example, the Affordable Care Act mandated the closing of the Part D coverage gap, better known as the “doughnut hole,” by decreasing patient cost-sharing from 100% in 2010 to 25% in 2020 for drug spending above $2,960, until the patient reaches $4,700 in out-of-pocket spending. While this might sound
like a win for patients, an analysis of patient costs for oral anticancer therapies revealed that out-of-pocket costs will remain high after the hole closes, with an average of $5,663 annually across anticancer drugs.[5]

As one example, the estimated out-of-pocket expenditure for a Medicare Part D beneficiary (who does not qualify for low-income subsidies) prescribed crizotinib in 2010 was $9,120. After the gap closes in 2020, the annual out-of-pocket expense is estimated at $6,552, representing a savings of $2,568. This is based on the assumption that drug prices remain relatively stable, which is unlikely. If drug prices increase by 50% from 2014 to 2020, the estimated savings after closure of the gap in 2020 is reduced to just $203. [5] Given financial burdens, such as the scenario illustrated above with crizotinib, it is not surprising that financial toxicity is of real concern to patients prescribed oral anticancer therapies, and it deserves our attention.

Lung cancer patients prescribed oral therapies are not the only at-risk population, however. Individuals with Medicare Part B coverage receiving intravenous drug therapy for the treatment of their cancer may also face potentially high out-of-pocket expenses, especially those who do not have a supplemental or Medigap plan or do not qualify for low-income subsidies. Medicare Part B plans allow for cost-sharing, with patients responsible for 20% of the Medicare-approved amount. As drug costs rise, the complexity of regimens increases, and patients live longer, the cumulative cost of care grows. The most recent National Comprehensive Cancer Network (NCCN) guidelines for NSCLC give a category 1 recommendation to the regimen of atezolizumab, bevacizumab, carboplatin, and paclitaxel for the treatment of patients with advanced adenocarcinoma and an ECOG performance status score of 0–1.[6] This was based on the results of the IMpower150 trial.[7] This regimen costs approximately $20,500 for one cycle, and could have an estimated out-of-pocket cost as high as $4,100 per cycle for a Medicare Part B patient with no supplemental insurance. While adherence to intravenous therapy can be directly observed, a patient may need to make significant financial sacrifices in other aspects of his/her life in order to pay for this therapy.

### Adverse consequences of cost-sharing

Recent data exploring the subjective financial toxicity to cancer patients found that 20% of 254 evaluated individuals reported taking less than the prescribed amount of medication due to concerns about cost.[8] Additionally, another 19% filled only part of a prescription, and 24% avoided filling the prescriptions at all as a strategy to cope with the cost of cancer care expenses. Although this patient cohort included predominantly breast cancer patients, it illustrates the unintended adverse consequences of cost-sharing that could...
ultimately result in higher healthcare costs downstream.

Approaching Value in Cancer Care
Follow the evidence

With costs of cancer care increasing precipitously, what can oncologists do? Several simple and practical solutions can help maximize the clinical benefit of therapy at an affordable price.[9] First, physicians should do only what is backed by robust clinical evidence. For tests or procedures, ask, “Will the results from this test or procedure change the treatment that is offered for my patient or significantly reduce symptoms or pain/suffering?” In other words, ensure that the pursuit is not purely academic.

In the treatment of lung cancer, a relevant example is the role of next-generation sequencing (NGS) panels, several of which are currently available in the United States. These testing platforms can identify mutations in more than 300 genes in tumor DNA, as opposed to limited-panel polymerase chain reaction–based tests, which evaluate mutations in a single gene. At the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, researchers reported that using NGS to test for all known lung cancer–related gene changes (EGFR, ALK, ROS1, BRAF, MET, HER2, RET, and NTRK1) at the time of diagnosis was less costly and faster than sequentially testing one or a limited number of genes at a time.[10] Commercially available treatment options exist for lung cancer patients with EGFR, ALK, ROS1, and BRAF mutations, and NCCN guidelines currently recommend treatment with oral therapies that are directed against these mutations.[6] Ongoing clinical trials for other mutations, including MET, HER2, RET, and NTRK1, are underway to test investigational agents against these targets. The authors of the study reported that their model estimated a potential savings of as much as $2.1 million for Medicare and more than $250,000 for commercial insurance providers. In addition, patients initiated appropriate therapy > 2.5 weeks sooner when mutations were found by NGS vs sequential or exclusionary testing.[10]

Another appropriate use of mutation testing is prior to considering osimertinib for the treatment of EGFR-mutated metastatic NSCLC progressing on a first- or second-generation EGFR TKI. The data currently support the use of osimertinib when the T790M mutation is detected and is believed to be the driver of progression on current therapy. When T790M is found, the response rate to second-line osimertinib is 71%, and the median PFS is 10.1 months.[11] However, if T790M is not detected, the response rate to osimertinib is 21% (median PFS, 2.8 months), and this is largely driven by patients who received chemotherapy in the interim.[12] Patients who went directly from a first- or second-generation EGFR TKI to osimertinib with no detectable T790M mutation had a response rate of 11% vs 36% if the therapy immediately prior to osimertinib was not an EGFR TKI. One could make the argument that, for T790M-negative patients, $17,539.80 per month of therapy for an 11% response rate is not a good value. Instead, these patients may be better served by enrolling in a clinical trial or starting chemotherapy.

Inappropriate use of NGS panels includes testing of patients with a low probability of detecting a targetable mutation, such as patients with squamous histology and an extensive smoking history, as well as those with performance status scores that preclude further active treatment. Without specialization in a given disease state within oncology, it can be difficult to interpret the results of molecular testing, and more difficult still to make treatment decisions for a given patient as it pertains to the use of a targeted therapy, with little to no evidence of efficacy in the patient’s disease.

Engage the patient

Physicians should involve patients in the discussion of value and cost. This initiative, established by ASCO over a decade ago, was only recently well defined in the ASCO Value Framework.[13] Conversations with patients should include expected outcomes in terms of median PFS, as well as toxicities that are likely to occur and their associated morbidity. As much as possible, the oncologist should also include costs—both total and out-of-pocket—that are likely to be incurred from the chosen treatment, as well as those associated with alternative treatments.

It is important to remember that additional months of PFS is not always the endpoint most valued by the patient. Patient-defined value incorporates the needs, values, and preferences of the patient.[14] For example, a young lung cancer patient with children approaching college may not want to incur additional costs of therapy, at the expense of reducing money available for his or her children’s higher education, if life expectancy is unlikely to differ by more than a few months regardless of the chosen treatment. Similarly, another patient may
refuse a treatment that will require him to tap into retirement funds because he prefers to use available funds to travel with his spouse.

One major factor limiting the utility of these discussions is the lack of data on patient-reported outcomes and quality of life, which can help oncologists better consider the factors most important to patients.[14] Knowing which cancer-related symptoms are likely to improve with a given therapy and then assessing the global change in quality of life, which is affected by the toxicity of a treatment, can give patients valuable insights into the benefit of a prospective treatment.

Tips for cost-of-care discussions
Incorporating cost-of-care conversations into clinical practice may seem daunting, but it can become routine with a few simple strategies. First, take action by initiating such a discussion with patients. Research has shown that cost conversations may not be as harmful as previously thought. [15] A bigger threat to the patient-physician relationship is pretending that cost of care does not matter. Additionally, a recent study challenges the notion that such conversations are too time-consuming; the median duration of a cost-of-care discussion at a breast oncology clinic was 33 seconds, out of a median appointment time of 12 minutes and 2 seconds.[16]

Do your homework
Secondly, do a little homework. If you know that a clinic visit will focus on pain management, ask a support staff member to provide a list of formulary agents for a given patient’s insurance plan prior to the visit. Formularies are available online, and obtaining a copy of a patient’s most updated medical and prescription insurance card should be a common practice for all new patients. Make this information available to patients during the discussion; it does little good to discuss a therapy that may be financially unobtainable. If your clinic has financial counselors, this may be a good time to utilize such services in order to offer the most value possible. For example, you might ask the counselors to prepare a quick financial comparison of the direct costs associated with two proposed intravenous treatment regimens, which you can then share with the patient. For practices with onsite specialty pharmacies, this can be done for oral therapies as well.

As one example of the potential impact these steps can have, we recently ran test claims for both oral topotecan and oral temozolomide for a patient with relapsed/refractory small-cell lung cancer. Because this patient had Medicare Part B with no supplemental insurance, he was responsible for 20% coinsurance, and the out-of-pocket cost for a cycle of topotecan was nearly 10-fold higher than that of temozolomide (> $1,000 for topotecan vs. $100, respectively). Both options, along with a discussion of the expected treatment benefit, toxicities, and dosing schedules, were presented to the patient during the clinic visit. Resources from several manufacturers are available, even to small practices with no onsite pharmacy, to assist with benefits investigations and to enroll patients in copay or financial assistance programs. Two such programs are AstraZeneca Access 360™ (https://www.myyaccess360.com/patient/patient-unbranded/home.html) and Takeda Oncology 1Point™ (https://www.takedaoncology1point.com/patient/home). Make applicable forms available to patients during the first encounter in which drug recommendations take place. While it is not realistic to be able to identify all financial pitfalls, it is important to let patients know that alternatives to any treatment choice are available. Make sure your patients know that they can notify the care team if they encounter financial hurdles.

Finally, clinicians should incorporate periodic self-assessments into their practice to provide feedback on prescribing patterns and outcomes. These assessments could include denials from insurance companies, the frequency of chemotherapy/immunotherapy/targeted therapy administration in the last 2 weeks of life, and the rates of toxicities that result in hospitalization or loss of life. The latter cannot be understated, as clinical trial outcomes differ from real-world experience when patients who might not be perfect fits for clinical trial inclusion are treated off-protocol. For example, an oncologist might evaluate the incidence of hospitalizations for immune-related adverse events in her practice and ask, “Are patients being adequately screened for consideration of immunotherapy, such as identification of preexisting autoimmune conditions?” One area of interest in our practice is the incidence of pneumonitis in the real world (outside of the PACIFIC trial) when treating patients with durvalumab as consolidation following curative-intent concurrent chemoradiation. In our case, we asked, “How can we better identify patients who are developing pneumonitis, educate these patients, and initiate prompt treatment with

As the primary advisor to the patient, the oncologist has an important role in providing a comparative assessment of the various treatment options available; in the spirit of shared decision making, the patient should have transparent information about the clinical impact that can be expected from the different options presented and their relative financial implications.

steroids to avoid unnecessary morbidity and mortality?" When self-assessment is incorporated into practice, oncologists can improve outcomes for patients and reduce healthcare expenditures.

**A Brief Word on Clinical Pathways**

The IOM estimates that approximately 30% of all healthcare dollars are spent on unnecessary tests, procedures, and doctor visits.[17] Clinical pathways are one proposed way to streamline patient management and reduce costs. Pathways are a subset of guidelines designed to standardize care with best evidence, while reducing unwarranted variability and cost. [18] Developers of clinical pathways claim that a given pathway is chosen based on three factors: efficacy, toxicity, and cost. However, in lung cancer, it is rare for therapy options to have equal efficacy and toxicity, such that the sole deciding factor is cost. One of the best-known studies supporting the use of clinical pathways performed in NSCLC comes from the US Oncology Network. In this study, researchers reported no difference in overall survival for patients treated in the adjuvant or in the first- or second-line metastatic setting when treated on or off their level one pathway; however, costs were reduced by 35% in those treated on vs off their pathway.[19] Little data exist to determine whether clinical pathways make care more affordable for patients.

Despite their shortcomings, clinical pathways have the potential to improve patient care in lung cancer. Standardization of diagnostic procedures, including imaging and molecular testing, could streamline the screening for patients eligible for clinical trials. Pathways might also serve as a springboard for discussions with patients. Many patients are influenced by direct-to-consumer advertising by drug manufacturers, and nearly all patients with lung cancer ask their oncologist whether they are a candidate for immunotherapy. As an academic medical center seeing a fair share of second-opinion referrals from the community, we have seen several EGFR mutation–positive metastatic lung adenocarcinoma patients with intermediate to high programmed death ligand 1 (PD-L1) expression who are started on single-agent immunotherapy off-trial in the first-line setting. This practice is not evidence-based, and it potentially confuses assessment of toxicity when EGFR TKI therapy is initiated. In addition to being costly, this practice could also limit the patient’s clinical trial options in the future.

**Conclusion**

While the future of reimbursement paradigms in the United States remains uncertain, it is undeniable that the current state of escalating healthcare costs, especially in lung cancer, is unsustainable. The Affordable Care Act contained a number of government programs that are attempting to bend the cost curve by incentivizing providers to deliver high-quality care in a cost-effective manner. Among these programs is the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), which includes the Quality Payment Program (QPP), made up of the Merit-based Incentive Payment System (MIPS) and Alternative Payment Models (APMs). These programs seek to enhance the quality of care, while improving patient outcomes and cost efficiency. Starting in 2019, US physicians will receive more or less reimbursement from the Centers for Medicare and Medicaid Services (CMS), depending on how they compare with their peers in quality and in value. Clinicians who adopt a quality-driven practice model now, regardless of the timelines imposed by the CMS, will be better prepared for the changes to come.

Change is hard, and harder still when the mentality of many patients has been, and continues to be, to do everything possible to prolong life, no matter the cost. Engaging patients in candid discussions about quality and cost throughout the spectrum of cancer care will lead to greater patient satisfaction, and lay the foundation for a more value-conscious healthcare culture. Returning healthcare to a patient-centered approach in the United States requires a commitment on the part of physicians to ask and to listen. This is especially important in the rapidly evolving field of lung cancer, where it can be difficult to keep abreast of and assimilate new data. As stewards of some of the most expensive therapies in healthcare, oncologists are ideally suited to lead the way.

*Cost is based on the AWP as published by Lexicomp Online (accessed July 9, 2018) with the following assumptions: body surface area, 1.8 m²; weight, 70 kg; and creatinine clearance by means of Cockcroft and Gault equation, 100 mL/min. Prices for generic medications are an estimate of the AWP, as multiple prices are available and depend on the generic manufacturer used. One cycle of therapy represents atezolizumab 1200 mg, bevacizumab 15 mg/kg, paclitaxel 200 mg/m², and carboplatin dosed at an area under the curve (AUC) of 6 using the Calvert formula. Cycle length is 21 days.

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*For references visit cancernetwork.com/lung-cancer-costs*
ONCOLOGY Contributors at ASH

ONCOLOGY is proud of our board members and our authors, and we applaud their contributions to our journal each month. We would never want to miss an opportunity to recognize their achievements and contributions not just to our pages, but to the wider oncology landscape as well. The following board members, authors, and collaborators—both past and present—will be appearing this December at the 60th American Society of Hematology Annual Meeting & Exposition in San Diego. Below is a summary of sessions they will be participating in along with links to their recent articles in ONCOLOGY. Don’t miss this opportunity to hear their presentations and talk to these great folks in person.

EDITOR IN CHIEF
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Friday Satellite Symposia: Integrating CAR T-Cell Therapy Into the Treatment of Lymphoma, Myeloma, and Leukemia: Strategies for Maximizing Patient Outcomes, Friday, November 30, 12:30 pm to 4:30 pm, San Diego Convention Center (SDCC) Room 30
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How to Decide Which DLBCL Patients Should Receive CNS Prophylaxis CancerNetwork.com/DLBCL-CNS-prophylaxis

CONTRIBUTORS
Ranjana H. Advani, MD
Education Program: Hodgkin Lymphoma: Beyond ABVD for Everyone, Saturday, December 1, 2 PM to 3:30 PM, SDCC Room 6A, or Monday, December 3, 7 AM to 8:30 AM, SDCC Room 6A
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Carl E. Allen, MD, PhD
Scientific Program: Scientific Committee on Blood Disorders in Childhood: A MAP(K) to Pediatric RASopathies (Acquired Hematologic Disorders of RAS-MAPK Activation), Saturday, December 1, 9:30 AM to 11 AM, SDCC Hall AB, or Monday, December 3, 10:30 AM to 12 PM, SDCC Room 6A
Langerhans Cell Histiocytosis: Emerging Insights and Clinical Implications CancerNetwork.com/langerhands-cell-histiocytosis

Jennifer R. Brown, MD, PhD
Education Program: The Future of Chronic Lymphocytic Leukemia (CLL) Therapy, Saturday, December 1, 9:30 AM to 11 AM, SDCC Hall AB, or Monday, December 3, 10:30 AM to 12 PM, SDCC Room 6A
Using Targeted Inhibitors in the Management of Chronic Lymphocytic Leukemia: Are We There Yet? CancerNetwork.com/targeted-inhibitors-CLL

James N. George, MD
Education Program: The Molecular Maelstrom of Myelodysplastic Syndromes (MDS), Saturday, December 1, 4 PM to 5 PM, SDCC Room 6A, or Sunday, December 2, 1 PM to 2 PM, SDCC Room 25C
Incremental Gains and a Long Road Ahead in MDS CancerNetwork.com/MDS-long-road

Andre Goy, MD
Friday Satellite Symposia: Exploring the Present and Future of BTK Inhibition in B-Cell Malignancies: Expert Insights on Practical Implications for Patient Management, Friday, November 30, 7 AM to 11 AM, SDCC Room 31B
Role of Stem Cell Transplantation in Mantle Cell Lymphoma CancerNetwork.com/stem-cell-mantle-cell-lymphoma

Ruben A. Mesa, MD, FACP
Education Program: As If Myeloproliferative Neoplasms Weren’t Already Challenging Enough (Advancing Treatments for Advanced Phase MPNs), Sunday, December 2, 7:30 AM to 9 AM, Room 6A, or Monday, December 3, 2:45 PM to 4:15 PM, SDCC Room 6A
Myeloproliferative Neoplasms: Translating New Discoveries Into Better Outcomes and Quality of Life CancerNetwork.com/myeloproliferative-discoveries

David P. Steensma, MD
Education Program: The Molecular Maelstrom of Myelodysplastic Syndromes (MDS), Saturday, December 1, 4 PM to 5 PM, SDCC Room 6A, or Sunday, December 2, 9:30 AM to 11 AM, SDCC Room 6A
Systemic Malignancies as a Cause of Unexpected Microangiopathic Hemolytic Anemia and Thrombocytopenia CancerNetwork.com/system-malignancies-thrombocytopenia
Introduction
There is considerable interest in making lifestyle changes, including dietary changes, among cancer patients and survivors.[1] Both the American Cancer Society (ACS) [2] and the American Institute for Cancer Research (AICR) have clinical dietary guidelines specific to cancer patients. These guidelines are evidence-based reviews of dietary intake on decreasing the risk of, and mortality from, cancer. Numerous large prospective epidemiological studies have shown that a high level of adherence to the ACS and AICR dietary guidelines significantly decreases the incidence of cancer, from 17% to over 50%, depending on cancer site, and decreases cancer-specific mortality by 20% to 30%.[4-8]

Cancer patients and survivors, however, rarely use dietary guidelines to inform their dietary choices. Instead, surveys among cancer patients and survivors have indicated that “special diets,” such as vegan and macrobiotic diets, are among the most commonly used integrative therapies, with as many as 48% of cancer patients or those at increased risk of cancer adopting these diets.[9-14] In contrast to the ACS and AICR nutrition guidelines, there is limited research on the impact of these popular diets on cancer-specific outcomes, such as incidence, mortality, and quality of life. This leaves clinicians with scarce information on how to advise their cancer patients on the use of these diets.

The purpose of this review is to help oncology providers gain knowledge about the content, rationale, and science of the diets that are popular among cancer patients. Specifically, we examine five of these popular diets: the alkaline, Paleolithic, ketogenic, vegan, and macrobiotic diets, using three different frameworks. The first framework is a series of three questions proposed by nutritionist Marion Nestle about how to evaluate the pros and cons of dietary strategies popular among cancer patients.
any diet. These three questions are: 1) “What is it?” 2) “Is the rationale behind it logical?” and 3) “Does it promote health?”[15] The second framework is to determine what, if any, scientific evidence supports these popular diets for cancer patients, and the third framework is to determine to what extent these special diets concur with the ACS and AICR clinical dietary guidelines.

Alkaline Diet

Proponents of the alkaline diet believe that most cancers are caused by an acidic environment in the body and that the primary cause of this presumed acidosis is acid-forming foods (see Table).[16] The Western diet is characterized by high intake of animal products and refined carbohydrates, with limited consumption of fruit and vegetables, and is thus considered to be highly acid-forming. In contrast, the alkaline diet, designed to provide more alkaline ions after digestion, is rich in fruits and vegetables, with limited protein; it decreases acid load; and it helps to reduce strain on acid-detoxification systems.[17,18] Proponents assume that it will raise systemic pH and that its effects can be assessed by monitoring urine pH. Indeed, a clinical trial in healthy adults comparing an alkaline diet vs an acidic one found that, when urine pH increased by 1.02 units, systemic pH had a significant increase of 0.014 units, indicating that urine pH may be a valid indicator of systemic pH.[19]

Only two studies have investigated the role of dietary acid load and cancer. One prospective cohort study examined the association between bladder cancer risk and urine pH in 27,096 male smokers enrolled in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. The relative risk (RR) for developing bladder cancer was not significantly associated with urine pH (RR, 1.15; 95% CI, 0.86–1.55) when comparing the highest to the lowest urine pH. However, in men who had smoked for longer than 45 years, there was suggested increased risk with lower urine pH levels (RR, 1.72; 95% CI, 0.96–3.10; P = .08).[20] Another small open-label study examined use of an alkaline diet in 11 advanced or recurrent non–small-cell lung cancer patients who were receiving an EGFR tyrosine kinase inhibitor. While patients had longer than expected median progression-free survival (19.5 months; range, 3.1–33.8 months) and overall survival (28.5 months; range, 15.4–46.6 months), there was no control group; thus, findings are difficult to interpret.[21] In sum, the logic behind the alkaline diet is faulty, and evidence is lacking. Despite this, the alkaline diet is highly congruent with dietary recommendations for cancer patients and survivors. As such, it may be appropriate for cancer patients, but for reasons different than those given by proponents (See Figure).

Paleolithic Diet

The Paleolithic diet attempts to replicate the dietary pattern of Stone-Age humans, featuring foods readily available to hunter-gatherers, including fruits, vegetables, nuts, meat, and eggs, while excluding grains, legumes, dairy products, and all processed foods (see Table).[22] The diet's rationale is based on the idea—known as the “evolutionary discordance hypothesis”—that humans evolved for millennia with a relatively consistent diet, and that chronic diseases such as cancer arise from the consumption of foods available only after the agricultural revolution, which humans are not genetically equipped to digest.[23] Proponents of the diet assume that human genes have not changed significantly since the Paleolithic period ending about 10,000 years ago, that there is an understanding of prehistoric diets, and that the foods available historically are equivalent to modern foods. Each of these assumptions is, however, contradicted by anthropological evidence that there is no single Paleolithic diet; that grains have been processed and consumed in Europe for more than 40,000 years; that humans have recently evolved to eat foods prominent in their environment, as evidenced by the development of lactase persistence in Europe and Africa; and that foods available today have been considerably altered by human agricultural practices and are thus substantially different than those foods available historically.[24-27] Moreover, cancer is a disease that tends to occur late in life, after one has passed prime reproductive age, and thus does not exert selection pressure in a population for a lower incidence of cancer.

Evidence for the Paleolithic diet in cancer prevention or treatment is limited to two case-controlled studies. In one study, the highest adherence to a Paleolithic dietary pattern compared with the lowest adherence was associated with reduced all-cause mortality (hazard ratio [HR], 0.72; 95% CI, 0.55–0.95; P = .03).[28] In a similar study, the odds of colorectal adenoma were lower among those in the highest quintile of adherence to Paleolithic dietary pattern when compared with disease-free controls (adjusted odds ratio, 0.71; 95% CI, 0.50–1.02; P = .02).[29] The Paleolithic diet has an emphasis on fruit, vegetables, nuts, and seeds, while restricting refined carbohydrates, processed meats, and alcohol. However, the diet opposes AICR dietary guidelines by being high in saturated fat and low in legumes and cereal grains, a combination associated with worsened colorectal cancer survival.[30] In conclusion, the Paleolithic diet shares characteristics with other healthy diets, but strict adherence may eliminate...
Despite prolonging their life spans, cancer survivors have a substantially reduced quality of life due to symptoms from both malignancies and their treatments, and they are at an elevated risk of premature mortality and serious morbidity. Clear evidence supports the benefits of optimal nutrition in this population, which range from relieving symptoms and treatment-related side effects to improving survival and quality of life. However, cancer survivors’ nutritional intake remains inadequate: their adherence to the Dietary Guidelines for Americans is poor, and their intake patterns are worse when compared with the general population.[1]

While many cancer patients and survivors are highly motivated to seek information about dietary changes to improve their long-term health, nutrition care is largely lacking in the current delivery model of outpatient oncology.[2] In the United States, about 70% of cancer survivors reported that they had never received nutrition advice from their providers.[3] As a result, they often seek nutrition information on the internet, or adopt a popular dietary strategy—such as the alkaline, Paleolithic, ketogenic, or vegan diet—that is not supported by strong scientific evidence.

Cancer patients and survivors report a strong desire to receive nutrition advice from their healthcare providers. The gap between such an aspiration for improved health and their poor dietary intake highlights the need for adequate nutrition support for this vulnerable population. Clinicians must play a larger role in advising patients to follow evidence-based nutrition recommendations. Effective strategies to integrate nutrition into oncology care need to be identified, evaluated, and implemented to close this gap. It is also important to recognize that cancer patients and survivors may encounter barriers that may prevent them from adhering to nutrition recommendations. In addition, some patients may prefer dietary strategies that are consistent with their cultural and ethnic backgrounds. At the end of the day, nutrition recommendations need to be patient-centered to achieve success.

FINANCIAL DISCLOSURE: Dr. Zhang has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Dr. Zhang is an Associate Professor at the Tufts University Friedman School of Nutrition Science and Policy, Boston, Massachusetts.

For references visit cancernetwork.com/dietary-strategies-cancer

Ketogenic Diet

Ketogenic diets are high-fat, low-carbohydrate, adequate-protein diets with a macronutrient ratio of 3–4:1 of fat to protein and non-fiber carbohydrates. Sixty-five percent or more of calories come from fat, while carbohydrate intake is restricted to 20 to 60 grams per day (see Table).[31] This macronutrient composition forces the body to metabolize lipids rather than carbohydrates or proteins, and shifts the body’s primary energy substrate from glucose to ketones. Per the Warburg effect—the phenomenon that cancer cells rely on glycolysis to fuel growth even in the presence of oxygen—proponents hypothesize that cancer cell growth will be hampered by a shift to ketone metabolism.[32] Evidence suggests that some cancer cells appear less able to metabolize ketones compared with healthy cells, while other experiments show that some tumor cells are able to use ketones for energy.[33]

More recently, however, preclinical research suggests that the potential mechanism of ketosis on cancer cells does not rely solely on the Warburg effect. The spectrum of altered growth, metabolism, and signaling metabolites incurred by ketosis may result in a cancer cell–specific induction of oxidative stress, thereby potentiating the effect of chemotherapy and radiation.[34,35] Additionally, ketogenic diets may have a protein-sparing effect that preserves lean body mass in the setting of cancer cachexia.[36] In animal models, ketogenic diets decrease the initiation, progression, and metastasis of cancer.[37]

Evidence in human clinical trials is limited to cases and small open-label studies, typically as salvage therapies, which confirm the feasibility and safety of ketogenic diets. These studies suggest that ketogenic diets are safe, and do not negatively impact quality of life. They are, however, difficult to adhere to, and many patients do not reach desired levels of ketones in the urine. [35,38-41] The bottom line is that ketogenic diets may have utility in certain individuals, especially in combination with other conventional therapies, but there is currently no reliable way to predict which patients might respond. They are exceedingly difficult to implement without professional dietary counseling. Moreover, poorly implemented ketogenic diets incur risk for micronutrient deficiency; are very high in saturated fat; are typically low in fiber; may include processed foods; and may exclude entire food groups, such as fruits, legumes, and many vegetables, which have been shown
to be beneficial for cancer prevention and mortality (See Figure).

**Vegan Diet**
A vegan diet entails abstinence from the consumption of animal products, such as meat, fish, eggs, dairy, and honey (see Table).[42] This is in contrast to plant-based diets, which consist mostly of fruits, vegetables, legumes, nuts/seeds, and whole grains, as well as small amounts of eggs, dairy, fish, fowl, and red meat. Vegan diets are often adopted for ethical or philosophical reasons focused on animal welfare or environmental conservation. Eating a vegan diet is thought to increase intake of so-called “cancer-fighting” foods, such as berries, greens, whole grains, nuts, and seeds, while eliminating foods such as dairy products and red and processed meats that may increase cancer risk.[43,44] A meta-analysis of 24 cross-sectional studies and 4 prospective cohort studies found that vegan diets were associated with a 15% risk reduction in total cancer incidence (RR, 0.85; 95% CI, 0.75–0.95), although no difference was observed for mortality.[45] Also, several small randomized clinical trials in men with low-risk prostate cancer showed benefits of a low-fat (~10% total fat) vegan diet in decreasing prostate-specific antigen levels,[46] lengthening telomeres,[47] positively impacting prostate gene expression,[48] and improving quality of life.[49] The vegan diet, however, was delivered along with exercise, stress reduction, and social support, making it hard to determine how much the diet itself contributed to results.

It is also unclear whether avoiding all animal products is necessary for obtaining the positive health benefits of a vegan diet. Vegetarian diets were associated with an 8% reduced risk in total cancer incidence.[45] Also, when looking at colorectal cancer incidence in a prospective cohort study (The Adventist Health Study 2) of 96,354 men and women, researchers found that those who ate a vegetable-based diet with the addition of seafood had the lowest risk (43%; HR, 0.57; 95% CI, 0.40–0.82), while vegans and vegetarians had similar risk reductions (19% and 18%, respectively) when compared with non-vegetarians.[50] In addition, the evidence for dairy is contradictory: high-fat dairy (not no- or low-fat) is associated with increased cancer mortality and risk of recurrence in prostate cancer and non-Hodgkin lymphoma, while dairy may be protective against colorectal cancer.[51-55] Vegan diets can be low in calcium and vitamin B12 compared with omnivorous diets, although this can be remedied by appropriate dietary advice (see Table).[56] The bottom line is that vegan diets meet many of the ACS and AICR dietary guidelines and can be fine-tuned for greater concordance (See Figure).

**Macrobiotic Diet**
Macrobiotics encompass a philosophy, a cultural movement, and an eating pattern that is based in large part on Eastern philosophical principles of yin and yang.[57] The macrobiotic diet is predominantly vegetarian and emphasizes unprocessed, organic foods. The diet, by weight, is 40% to 60% whole cereal grains, 20% to 30% vegetables, and 5% to 10% legumes. Fruit, white fish, seeds, and nuts are also occasionally consumed (see Table).[58] Many individuals choose macrobiotic diets for philosophical rather than health reasons alone; nevertheless, for justification, proponents point to the health benefits of a diet high in fiber, legumes, and vegetables, while also devoid of red and processed meat.[59]

There are no research studies on the macrobiotic diet in cancer patients; however, DIANA (Diet and Androgens)-5 is an ongoing randomized clinical trial in 1,208 breast cancer survivors investigating the effect of exercise and a Mediterranean-macrobiotic diet plan on weight loss and cancer recurrence.[60] The macrobiotic diet can be high in whole soy foods such as tofu, raising concerns about hormone-sensitive cancers, particularly estrogen receptor (ER)-positive breast cancer. Though there is no clinical trial investigating the impact of soy foods on breast cancer patients after diagnosis, five cohort studies in 11,206 breast cancer patients found that frequent consumption of whole soy foods (around one to three servings per day) after breast cancer diagnosis was associated with a significant 21% reduction in the risk of breast cancer recurrence; it was also associated with a 15% reduction in breast cancer mortality in both ER-negative and ER-positive cancers.[61]

The macrobiotic diet appears to meet or exceed US dietary recommendations.[62] Moreover, in a nationally representative sample, the macrobiotic diet was found to have a lower percentage of energy from fat, higher total dietary fiber, and higher amounts of most micronutrients than the Recommended Daily Allowance (RDA), with the exceptions of vitamin D, vitamin B12, and calcium, which were lower than the RDA.[62] The bottom line is that macrobiotic diets meet most of the dietary ACS and AICR guidelines, including emphasizing a healthy weight and regular physical activity (See Figure).

**Conclusion**
Changes in diet consistent with evidence-based clinical guidelines can have a significant impact on improving cancer incidence and mortality.[4-8] The dietary guidelines of the ACS and AICR/WCRF are framed such that compliance can be achieved with a variety of dietary patterns, including those strategies popular with cancer patients. However, the degree to which these different popular dietary strategies adhere to the dietary guidelines vary, and it is important to emphasize that there is...
### TABLE Definition of Dietary Patterns, Possible Nutrient Deficiencies, and Nutritional Counseling Tips [22,31,59,64–67]

<table>
<thead>
<tr>
<th>Dietary Pattern</th>
<th>Includes</th>
<th>Limits &amp; Avoids</th>
<th>Possible Nutritional Issues/Deficiencies</th>
<th>Nutritional Counseling Tips</th>
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</table>
| **Ketogenic**   | Meat, poultry, fish, processed meats, some dairy (heavy cream, cheeses), vegetables with low net-carbohydrates (leafy greens, cruciferous vegetables, celery, cucumber, avocado, coconut), fats and oils, nuts, seeds; small amounts (< 1/4 cup) of low net-carbohydrate fruits, such as berries | Variable level of carbohydrate restriction; generally: sugars, grains, legumes, milk, fruit, starchy and low net-carbohydrate vegetables | Inadequate fruit, vegetable, and fiber intake; high saturated fat intake; risk for vitamin D, calcium, and electrolyte insufficiency; risk for kidney stones, esp. if present in family history | • Consider a daily multivitamin and a vitamin D and calcium supplement  
• Emphasize nutrient-dense fruit (suggest berries such as blueberries, raspberries, blackberries, cranberries, cherries)  
• Emphasize dark-green vegetables with every meal  
• Suggest oral citrates (ie, Polycitra K) in cases of family medical history significant for kidney stones  
• Emphasize healthy protein choices: fatty fish such as salmon, tuna, sardines, and anchovies, as well as poultry, wild game, or free-range meat products over conventional red and processed meat  
• Emphasize vegetable-sourced fat choices: olive oil, canola oil, nuts, seeds, coconut oil, coconut cream, and avocados |
| **Macrobiotic** | Whole grains (eg, brown rice, barley, millet, oats, corn rye, buckwheat), white-meat fish, soy products, legumes (eg, adzuki, chickpeas, lentils), vegetables (including carrots, pumpkin, mushrooms, and sea vegetables, eg, kombu, nori), nuts and seeds, green tea | Red meat, pork, poultry, most fish, animal fats, eggs, dairy products, refined sugars and foods containing artificial sweeteners or other chemical additives, alcohol | Risk for vitamin D, B12, and calcium insufficiency | • Emphasize fatty fish (tuna, mackerel, salmon, sardines)  
• Emphasize foods fortified with vitamin D: orange juice, soy milk, cereals  
• Emphasize calcium-rich foods: leafy greens, nuts, seeds, sea vegetables, sardines  
• Emphasize vitamin B12–rich foods: fish, fortified foods (cereals, nut milks) |
| **Paleolithic** | Widely variable, but generally: lean meat and animal products, fish, fruit, and vegetables | Legumes, grains, dairy, sugars, added salt, coffee, alcohol, processed foods (refined oil, preserved meat, cereals, and flours) | Risk for vitamin D, calcium, and iodine insufficiency | • Emphasize healthy protein choices: fatty fish such as salmon, tuna, sardines, and anchovies, as well as poultry, wild game, or free-range meat products over conventional red and processed meat  
• Emphasize minimally processed vegetable-sourced fat choices: olive oil, canola oil, nuts, seeds, coconut oil and coconut cream, and avocados  
• Confirm adequate consumption of fruits and vegetables |
| **Vegan** | Grains, plant oils, nuts, seeds, legumes, fruit, and vegetables | All animal products (meat, poultry, fish, eggs, dairy products, and honey) | Risk for iron, calcium, zinc, vitamin D, and vitamin B12 insufficiency | • Consider a vitamin B12 supplement  
• Emphasize foods fortified with vitamin D (dairy products, orange juice, soy milk, and cereals)  
• Emphasize calcium-rich foods (leafy greens, nuts, seeds, sea vegetables, and sardines)  
• Emphasize vitamin B12–rich foods: fortified foods (cereals, nut milks)  
• Emphasize zinc-rich foods: legumes, whole grains, nuts, and seeds  
• Recommend foods high in iron: leafy greens, nuts, seeds, and whole grains |
| **Alkaline** | 80% of the diet consists of alkaline foods; generally: vegetables (beets, broccoli, cauliflower, celery, cucumber, kale, lettuce, onions, peas, pepper, spinach), low sugar fruits (apples, bananas, berries, grapes, lemons, oranges, melons, peach, pear), some legumes | “Acid-forming food” limited to < 20% of calories; generally: red meat, pork, poultry, fish, eggs, dairy products, corn, wheat, coffee, sugar, and alcohol | Similar, but lower, risks as for vegan diets | • Consider a vitamin B12 supplement  
• Emphasize foods fortified with vitamin D (dairy products, orange juice, soy milk, cereals)  
• Emphasize calcium-rich foods: leafy greens, nuts, seeds, sea vegetables, sardines  
• Emphasize vitamin B12–rich foods: fortified foods (cereals, nut milks)  
• Emphasize zinc-rich foods: legumes, whole grains, nuts, and seeds  
• Recommend foods high in iron: leafy greens, nuts, seeds, and whole grains |
little evidence that any element of a given diet, outside of those in accordance with evidence-based clinical dietary guidelines, will confer survival benefits. Notably, as the overall quality and quantity of evidence on these diets is limited, scientific plausibility, mechanistic evidence, and the balancing of risks and benefits are important considerations when making clinical recommendations. Moreover, many of these popular dietary strategies are chosen as much for their philosophical, cultural, or ethical underpinnings as for any scientific evidence of benefit. As such, negative or contradictory statements about a patient’s diet can lead to defensiveness and lack of trust on the part of the patient. Instead, possible strategies to build trust and encourage evidence-based dietary changes include:

1. Ask about diet, including popular diets, and structure the encounter around the “5 As” (assess, advise, agree, assist, arrange). See the discussion of nutrition counseling in clinical practice by Kahan and Manson.[63]

2. Emphasize positive aspects of these popular diet strategies that concur with ACS and AICR dietary guidelines (see Figure).

3. Refer patients to registered dieticians as needed to help guide choices.

4. Suggest foods that align with patients’ dietary strategies to address any nutrient concerns (see Table).

5. Suggest helpful resources for recipes, meal planning, serving sizes, and general dietary information congruent with ACS and AICR dietary guidelines, such as the US Department of Agriculture’s ChooseMyPlate (https://www.choosemyplate.gov), AICR (http://www.aicr.org), and Harvard T. H. Chan School of Public Health’s Healthy Eating Plate and Healthy Eating Pyramid (https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate) websites.

6. Remind patients that there is no need to adopt a strict diet that deprives them of enjoyment at mealtime to obtain the beneficial effects of dietary changes. Instead, it is helpful to mention that the effect of any diet is cumulative and long-term; thus, eating something “unhealthy” occasionally will not have any significant impact on their health.

In summary, despite limited evidence as a means of treating or preventing cancer, popular dietary patterns may appeal to cancer patients. These patients often choose to follow a diet that, with the help of clinicians, can be consistent with dietary guidelines during cancer care and supportive of overall health.

ACKNOWLEDGEMENT: The authors wish to thank the late Fredi Kronenberg, PhD, for her inspiration in addressing this topic.

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.

For references visit cancernetwork.com/dietary-strategies-cancer

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**DIETS**

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<th>Legumes</th>
<th>Exercise</th>
<th>Achieving &amp; Maintaining a Healthy Weight</th>
<th>Red &amp; Processed Meats</th>
<th>Alcohol</th>
<th>Sugar-Sweetened Beverages</th>
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**KEY**

- Green circle: Meets the recommendations of the American Institute for Cancer Research (AICR) and the American Cancer Society
- Red circle: Does not meet the recommendations of the American Institute for Cancer Research (AICR) and the American Cancer Society
- Black circle: Meets some but not all of the recommendations of the American Institute for Cancer Research (AICR) and the American Cancer
- Brown circle: Not specified in the diet

**FIGURE** Comparison of Popular Cancer Diets From the American Cancer Society and American Institute for Cancer Research Dietary Guidelines (Image by Christina Czuhajewski)

1. American Cancer Society Cancer Prevention Guidelines 2012: 1) Achieve and maintain a healthy weight throughout life. 2) Adopt a physically active lifestyle. 3) Consume a healthy diet, with an emphasis on plant foods. • Choose foods and beverages in amounts that help achieve and maintain a healthy weight. • Limit consumption of processed meat and red meat. • Eat at least 2.5 cups of vegetables and fruits each day. • Choose whole grains instead of refined grain products. 4) If you drink alcoholic beverages, limit consumption.[2]

2. American Institute for Cancer Research Recommendations 2018: 1) Be a healthy weight. 2) Be physically active. 3) Eat a diet rich in whole grains, vegetables, fruits, and beans. 4) Limit consumption of “fast foods” and other processed foods high in fat, starches, or sugar. 5) Limit red and processed meat. 6) Limit sugary drinks. 7) Limit alcohol. 8) Don’t rely on supplements. 9) For mothers, breastfeed your baby.[3]

3. Fermentable soy products such as tempeh and tofu allowed.

4. Only limited amount of vegetables with low net-carbohydrates—mostly leafy greens, celery, cucumber, zucchini, and cruciferous vegetables.

5. Fast foods that were consistent with the specific dietary pattern can be eaten. For instance, meat, poultry, and dairy products in fast and processed foods would be included in the ketogenic diet.
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Role of Temozolomide in the Treatment of Cancers Involving the Central Nervous System

Karisa C. Schreck, MD, PhD, and Stuart A. Grossman, MD

ABSTRACT: Temozolomide has been available to oncologists for over 30 years. During this time, it has become an integral part of standard therapy in patients with high-grade gliomas. Given its ability to traverse the blood-brain barrier, temozolomide has also been evaluated in other cancers that involve the central nervous system (CNS). We review its role in the management of patients with primary brain tumors, brain metastases, leptomeningeal carcinomatosis, and other selected CNS cancers. There is strong evidence that temozolomide is effective in patients with high-grade astrocytomas and oligodendrogliomas. Modest evidence supports its activity in primary CNS lymphomas and aggressive pituitary adenomas. Temozolomide, however, has minimal efficacy in a wide variety of systemic cancers. Given that concentrations of temozolomide in the CNS are only 20% of those in the blood, it is not surprising that it is generally inactive in patients with CNS metastases from solid tumors.

Introduction

Temozolomide was synthesized in the 1980s as a water-soluble imidazotetrazinone that exhibited excellent antineoplastic properties in vitro and in vivo.[1,2] At a pH greater than 7, it spontaneously hydrolyzes to its active form, which is the same active metabolite as in dacarbazine. [3] Its novelty came from the fact that it is an orally bioavailable alkylating agent able to penetrate the blood-brain barrier due to its lipophilic nature.

Temozolomide functions by modifying DNA or RNA through the addition of methyl groups (alkylation) to guanine at the N7 and O6 sites, and to adenine at the O3 site. This causes substitution of thymine for cytosine during DNA replication, which creates a mismatched base pair. This in turn triggers the DNA mismatch repair pathway, which attempts to repair the damage but results in inappropriate DNA crosslinks, G2 arrest, and ultimately, leads to apoptosis (Figure).[4,5] The methyl group temozolomide adds can be repaired by some intracellular DNA repair programs, such as DNA mismatch repair or base excision, or it can be removed by O6-methylguanine-DNA methyltransferase (MGMT), a demethylating enzyme. The amount of methylation temozolomide causes within a cell is important for ensuring catastrophic cell death. Notably, the effect of temozolomide on DNA is independent of whether the cell is irradiated, but temozolomide synergizes with radiation to increase glioma cell death.[6]

Temozolomide received accelerated approval from the US Food and Drug Administration (FDA) in 1999 for treatment-refractory anaplastic astrocytomas.[7] It was later approved by the FDA for newly diagnosed glioblastoma administered concurrently with radiation therapy and for 6 months thereafter based on a phase III study.[8]
CANCERS OF THE CENTRAL NERVOUS SYSTEM

Temozolomide’s Mechanism of Action—

Temozolomide is spontaneously hydrolyzed to its active metabolite, MTIC, which translocates into the nucleus. There, it transfers methyl groups on to guanine, causing double-strand DNA breaks during replication and leading to apoptosis. Its actions are opposed by intranuclear DNA repair mechanisms, including MGMT, MMR, and BER.

Since then, it has been a backbone of treatment for both newly diagnosed and recurrent high-grade astrocytomas and oligodendrogliomas.

Although the toxicities of temozolomide are modest compared with other chemotherapy agents, it can have significant side effects. When combined with brain irradiation, 20% of patients develop significant myelosuppression and some develop severe (grade 3/4) lymphopenia, which is long-lasting and associated with reduced survival and poor response to immunologic interventions.

Use of temozolomide can also result in constipation, fatigue, and malaise and a small risk of secondary malignancies.

Blood-Brain Barrier Penetration of Temozolomide

Currently, 98% of drugs on the market do not penetrate the blood-brain barrier. Temozolomide’s small size (194 Da) and lipophilicity enhance CNS penetration relative to other alkylating agents. Despite this, the concentration of temozolomide in brain tumor tissue is about 20% of plasma levels. When combined with chemotherapy agents, it can have significant side effects. When combined with brain irradiation, 20% of patients develop significant myelosuppression and some develop severe (grade 3/4) lymphopenia, which is long-lasting and associated with reduced survival and poor response to immunologic interventions.

Use of temozolomide can also result in constipation, fatigue, and malaise and a small risk of secondary malignancies.

Effect of MGMT Status on Temozolomide Sensitivity

The efficacy of temozolomide may be influenced by gene expression within tumor cells. The most important of these is MGMT, a gene that encodes the protein O6-alkylguanine DNA alkyltransferase (AGT) and is responsible for removing methyl groups from DNA at the O6 position. Each AGT molecule is able to irreversibly remove one methyl group, after which it releases the DNA strand and is ubiquitinated and degraded. MGMT activity is regulated in part by promoter methylation, which turns off gene expression. Hypermethylation is frequently observed in some cancers causing MGMT silencing, and demethylation is associated with gene activity.

In glioma clinical trials, epigenetic silencing of MGMT through promoter methylation has been associated with increased DNA double-strand breaks and sensitivity to the alkylating agents BCNU [bis-chloroethyl nitrosourea; carmustine] and temozolomide. In fact, MGMT promoter methylation appears predictive of tumor sensitivity to temozolomide and is also an independent prognostic biomarker, because MGMT methylation is associated with improved survival independently of temozolomide.

Although MGMT methylation in gliomas is a predictive biomarker for temozolomide sensitivity and a prognostic biomarker, this does not appear to be the case in other cancers, such as colorectal cancer and non–small-cell lung cancer. The one exception may be diffuse large B-cell lymphoma, in which MGMT methylation may correlate with improved overall survival, although it is not routinely tested in clinical practice and has no effect on treatment selection.

Primary Brain Tumors

Astrocytomas

Glioblastoma (grade 4 astrocytoma) is the most common primary brain tumor in adults, affecting over 11,000 people each year in the United States. This cancer is most often diagnosed in older adults and is associated with a median survival of just over 1 year. Although these tumors may appear localized on magnetic resonance imaging, they are virtually never cured with aggressive surgery because tumor
cells extend well beyond surgical margins. Radiation therapy is the most beneficial postoperative therapy for this disease, but unfortunately it does not have curative potential. Initial efforts to combine chemotherapy with radiation determined that the nitrosoureas, which cross the blood-brain barrier, were most effective. In prospective, randomized studies, however, the addition of these agents did not result in a substantial survival advantage.[32,33] In 2005, the results of an EORTC/NCIC trial that randomized patients with newly diagnosed glioblastoma to receive either radiation alone or radiation with concurrent and adjuvant temozolomide were published.[8] This unconventional adjuvant trial design included patients with extensive residual tumor in a disease for which temozolomide had insufficient efficacy at recurrence for FDA approval.

Despite flouting conventional adjuvant clinical trial design, this trial convincingly demonstrated a survival advantage from the addition of temozolomide in newly diagnosed glioblastoma. Although the median survival of patients eligible for this trial improved from 12 to 14.6 months with the addition of temozolomide, survival improved from 10% to 26% at 2 years and from 0% to 10% at 5 years.[34] Additional analysis demonstrated that patients who are MGMT unmethylated derive much less benefit from the addition of temozolomide than those who are MGMT methylated.[34] More recently, the findings of this study were replicated in patients older than age 65 years with newly diagnosed glioblastoma who were treated with a shorter course of radiation.[35] As of 2018, temozolomide remains the only systemically administered pharmaceutical agent documented to provide a survival advantage to patients with glioblastoma.

The annual incidence of anaplastic astrocytomas (grade 3 astrocytoma) is about 1,300 cases/year in the United States, which is 10 times less frequent than that of glioblastoma.[31] As a result, no large prospective, randomized studies exist documenting the magnitude of benefit from adding temozolomide to radiation in this population. The efficacy of temozolomide in patients with recurrent anaplastic astrocytomas, however, was found to be higher than its efficacy in patients with glioblastoma, leading to an approved indication by the FDA.[7] As a result, many patients with newly diagnosed anaplastic astrocytomas, particularly those who are wild type for the isocitrate dehydrogenase (IDH) gene, receive radiation with concurrent and adjuvant temozolomide, just like patients with glioblastoma.

The treatment of patients with grade 2 astrocytomas is more controversial. These tumors may manifest Temozolomide for Brain Tumors: Building on the Foundation

Temozolomide has held a central role in the treatment of glioma for nearly two decades. While this speaks to its unique brain-penetrant properties, it also underscores the marginal progress that has been made in developing other systemic therapies for central nervous system malignancies. The review by Schreck and Grossman is a timely reminder of the data supporting the use of temozolomide for brain tumors, as well as its toxicities. When a drug has become so engrained in daily practice, and when little else is available, it is easy to forget how it became the standard of care in the first place. More importantly, we may overlook the potential risks. After all, temozolomide is “just a pill,” right?

In fact, myelosuppression due to temozolomide can be severe and long-lasting. This can manifest as profound thrombocytopenia or neutropenia, but also as marked lymphopenia. Severe reductions in CD4 counts in newly diagnosed, high-grade glioma are associated with worse outcomes in patients treated with standard radiation and temozolomide, and may have implications for brain tumor immunotherapy trials. There is also a small, but important, risk of idiosyncratic liver injury from temozolomide, which has caused fatalities in some cases.

In terms of efficacy, the benefit of temozolomide is greatest in glioblastomas harboring a methylated MGMT promoter. However, there is still a small benefit for unmethylated patients. Optimal design of front-line clinical trials for glioblastoma must account for both populations. Integrating novel therapies for newly diagnosed disease requires addressing lymphodepletion and other side effects of temozolomide in MGMT-methylated patients, as well as careful consideration of whether temozolomide should be omitted for unmethylated patients. Although its use feels mundane in the era of immunotherapy and targeted therapy, temozolomide remains the centerpiece of glioblastoma treatment. Its efficacy and toxicities should be respected, both in clinical practice and trial design.

FINANCIAL DISCLOSURE: Dr. Bagley has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Dr. Bagley is an Assistant Professor of Medicine in the Division of Hematology/Oncology at Penn Brain Tumor Center at the University of Pennsylvania’s Abramson Cancer Center in Philadelphia, Pennsylvania.
with seizures in patients who are otherwise doing well. In this setting, low-risk patients are often followed closely after surgery without further treatment until there is clear evidence of tumor progression, which may be years later. High-risk patients typically receive treatment with radiation immediately after diagnosis. Risk factors for a poor outcome include age 40 years or older, preoperative tumor size of 5 cm or more, subtotal resection, lack of IDH mutation, lack of 1p/19q codeletion, and elevated mitotic index. The role of chemotherapy in these patients remains controversial. Studies have documented that the PCV regimen, which consists of procarbazine, CCNU [1-(2-Chloroethyl)-3-Cyclohexyl-1-Nitrosourea; lomustine], and vincristine, improves survival following radiation in low-grade gliomas, but the primary benefit appears to be in patients with high-grade astrocytomas,[36] as is the case in glioblastoma, MGMT promoter methylation status may be a marker for response to temozolomide in low-grade glioma, but convincing data are currently lacking.[43]

### Oligodendrogliomas

Approximately 1,000 patients per year in the United States are diagnosed with oligodendrogliomas, which are defined by the presence of a 1p/19q codeletion based on current criteria from the World Health Organization. Of these, 70% have low-grade (grade 2) oligodendrogliomas, while 30% have anaplastic oligodendrogliomas (grade 3). Randomized, prospective trials have clearly demonstrated that radiation followed by PCV chemotherapy in patients with grade 2 and 3 oligodendrogliomas leads to a 7-year improvement in survival over radiation alone.[36,44,45] Efficacy of temozolomide monotherapy has also been demonstrated in newly diagnosed and recurrent oligodendrogliomas.[37-40] Currently ongoing is a randomized, prospective trial designed to determine whether radiation followed by PCV or radiation with concurrent and adjuvant temozolomide is the best regimen for patients with recently diagnosed oligodendrogliomas (NCT00887146). This study had a temozolomide-only arm that closed early because it was not as effective as the arms that contained radiation.

**Ependymomas**

Ependymomas are rare tumors of the cells lining the ventricular cavity. These tumors can occur anywhere along the neuroaxis, but are typically found intracranially in children or within the spinal canal in adults. Treatment usually consists of maximal safe surgical resection, followed by radiation therapy in many cases. Chemotherapy may be used to avoid early irradiation in very young children,
but otherwise it has a very limited role in the treatment of ependymomas. There are several case reports of individual responses to temozolomide in the setting of recurrent disease; however, larger retrospective reviews have shown very limited responses.[46-48] Although limited in scope, these data are generally in line with what is known about the resistance of ependymomas to chemotherapy and do not support general use of temozolomide in ependymomas.

**Primary CNS lymphoma**

Primary CNS lymphoma (PCNSL) is a rare malignancy that comprises 2% of all brain tumors and 2% of all lymphomas. It diffusely involves the brain, and 20% of the time, it is also present in the eyes or spinal fluid. It generally affects older patients. Due to its rarity, randomized clinical trials have been difficult to undertake and complete in this population. Initial treatment attempts focused on whole brain irradiation. The median survival following radiation was only 1 year, however, and the neurologic complications were significant in patients who lived long enough to experience them. As a result, efforts shifted to studying chemotherapy. Typical chemotherapy regimens for lymphomas are considered in patients who are unable to receive HD-MTX. The most common reason for this is an inadequate creatinine clearance. Whole brain radiation therapy (WBRT) and temozolomide are considered in patients who are unable to receive HD-MTX. Malignant gliomas are very sensitive to high-dose methotrexate (HD-MTX) with an overall response rate of 74%.[49] Resultantly, HD-MTX has become the base for all standard regimens in newly diagnosed patients. A standard regimen often includes rituximab, with the possible addition of cytarabine, temozolomide, or procarbazine/vincristine.[50] It is unclear whether one of these combinations is superior, and the combination of multiple chemotherapeutic agents can increase toxicity, so a patient’s functional status is an important consideration when selecting a therapeutic regimen.[51] The regimen with temozolomide, in particular, involves HD-MTX plus temozolomide and rituximab followed by consolidation with etoposide and cytarabine. It has shown a complete response rate of 66%, but with grade 3/4 toxicities in more than 55% of participants.[52]

In general, treatment regimens for newly diagnosed PCNSL containing temozolomide are considered in patients who are unable to receive HD-MTX. The most common reason for this is an inadequate creatinine clearance. Whole brain radiation therapy (WBRT) and temozolomide can be efficacious, with a complete response rate of 85% in one small study.[53] In elderly patients for whom WBRT has increased side effects,
a retrospective study found HD-MTX plus temozolomide resulted in an overall response rate of 55%, which is comparable to other regimens involving chemotherapy, but with fewer toxicities.[54] Notably, this regimen is associated with a shorter overall survival compared to HD-MTX, procarbazine, vincristine, and cytarabine in a randomized phase II study.[55] This suggests temozolomide may not be the optimal chemotherapeutic agent for PCNSL when other options exist.

Currently, no standard treatment regimen exists for patients with relapsed/refractory PCNSL. Re-treatment typically consists of HD-MTX, if the patient responded to this initially, or WBRT, when possible.[56-58] Several chemotherapy regimens, however, have been used with various efficacy. Temozolomide monotherapy has shown a 31% overall response rate in relapsed/progressive PCNSL using a regimen of 150 mg/m² for 5 days every 4 weeks in an early phase II trial.[59] The combination of rituximab with temozolomide may also be effective in relapsed/refractory PCNSL, with two retrospective series showing response rates of 53% to 100%.[60,61] Unfortunately, a follow-up prospective study of temozolomide and rituximab was closed for poor accrual and found a response rate of only 14%.[62] Although a regimen including temozolomide can be considered in patients for whom radiation or repeat HD-MTX is not preferred, data to support its efficacy are limited.

**Pituitary adenomas/carcinomas**

Pituitary adenomas are generally benign tumors that arise from the anterior pituitary and are treated with surgery or pharmacologic treatment. If this initial treatment strategy fails, radiation therapy is used for recurrent/progressive disease. Rarely, aggressive pituitary adenomas or carcinomas continue to progress after standard treatment, in which setting chemotherapy may be considered. Evidence for the use of temozolomide in recurrent pituitary adenoma/carcinomas is limited to case reports and small single-arm studies, the largest of which included 24 patients.[63] In aggregate, however, the response rate to temozolomide monotherapy in aggressive, recurrent pituitary adenoma is 37% to 41%.[64,65] Given this response rate and the lack of other efficacious chemotherapies, the European Society of Endocrinology recommends temozolomide for aggressive pituitary tumors that have failed standard treatment options.[64] Although no clear consensus has been reached on the optimal duration of therapy, generally 6 to 12 months is administered to patients responding to therapy.

**Metastases to the central nervous system from systemic cancers**

Metastases to the CNS are 10 times more common than primary brain tumors.[66] Approximately 50,000 patients per year in the United States are diagnosed with brain metastases from lung cancer, 9,000 from breast cancer, 3,500 from melanoma, and 1,200 from renal cell cancer. As systemic therapies have improved, the likelihood of relapse within the CNS has increased, due in part to the poor blood-brain barrier penetration of many therapies used in systemic disease. Although WBRT was historically the gold standard for brain metastases, this has changed with the advent of stereotactic radiosurgery and improved neurosurgical techniques. In patients with solitary or oligometastatic disease, surgery in addition to WBRT improves local control and survival over radiation alone.[67] Currently, patients who undergo a surgical resection typically receive stereotactic radiosurgery to their resection cavity rather than WBRT, as survival is similar and the risk of neurocognitive side effects is lower.[68-70] WBRT remains the standard treatment in patients with diffuse brain metastases.

Historically, systemic chemotherapy has been considered inadequate treatment for brain metastases, with only class 3 evidence to support it.[71] Temozolomide is a conceptually attractive cytotoxic chemotherapy for brain metastases given its ability to traverse the blood-brain barrier, potential for synergy with radiation, and relatively benign toxicity profile. As such, it has been studied alone or combined with radiation or other chemotherapies in over 40 clinical trials, primarily in melanoma, lung cancer, and breast cancer. The most promising efficacy data in systemic cancers have been from studies in patients with melanoma with a 13% to 20% response rate.[72,73] This is not unexpected given that temozolomide is an imidazotetrazine derivative of dacarbazine, which has been used extensively in patients with metastatic melanoma. Small series and case reports suggest that the response rate to single-agent temozolomide is less than 10% in neuroendocrine tumors, 5% to 9% in non–small-cell lung cancer, less than 5% in renal cell cancer, and 0% in breast and colon cancer.[74-79]

Given the low response rates to single-agent temozolomide in systemic disease, it is understandable that multiple clinical trials failed to demonstrate significant benefit in brain metastases (Table 1, Table 2). A meta-analysis of seven clinical trials using temozolomide in patients with solid tumor metastasis to the brain demonstrated only very modest effects, and 13 trials evaluating a combination of temozolomide with other antitumor drugs and/or radiation were similarly unimpressive.[80]

The one possible exception is small-cell lung cancer, which is generally more chemosensitive. One single-arm phase II study showed a 22% overall response rate to temozolomide monotherapy in relapsed disease, possibly with more sensitivity in MGMT methylated tumors.[81] Overall, temozolomide has been very disappointing in brain metastases, either alone or in combination with systemic therapies or radiation.

**Leptomeningeal carcinomatosis**

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Bone-Targeted Therapy in Early Breast Cancer

Katarzyna J. Jerzak, MD, MSc, FRCPC, Jacques Raphael, MD, MSc, FRCPC, Danielle N. Desautels, MD, MSc, FRCPC, Phillip S. Blanchette, MD, MSc, FRCPC, Ivan Tyono, BScPhm, RPh, and Kathleen I. Pritchard, MD, FRCPC

ABSTRACT: Aromatase inhibitors (AIs) play an important role in the adjuvant treatment of hormone receptor–positive breast cancer, but they are associated with bone loss and increased fracture risk. Although several guidelines for the management of osteoporosis and osteopenia exist, their algorithms do not account for the use of AIs. In this article, we describe the role of bone-targeted therapies, specifically for managing early breast cancer, by reviewing their bone-specific and cancer-specific benefits.

Introduction

Aromatase inhibitors (AIs) play an important role in the adjuvant treatment of estrogen receptor–positive (ER+) breast cancer. By inhibiting the aromatase enzyme responsible for the peripheral conversion of androgens to estrogens, AIs effectively suppress circulating estrogen levels in women without residual ovarian function.[1] In the postmenopausal population, AIs significantly reduce breast cancer recurrence compared with tamoxifen.[2] As such, AIs are the preferred adjuvant endocrine therapy in postmenopausal women with early breast cancer. However, estrogen deprivation resulting from AI treatment is associated with bone loss and increased fracture risk. Because bone loss is generally asymptomatic until a fracture occurs, increased awareness of this issue is important to prevent progression to osteoporosis and resulting fractures.

Risk of Bone Loss and Fracture in Early Breast Cancer

A number of adjuvant trials on AIs in women with early breast cancer evaluated changes in bone mineral density (BMD) in subsets of the study populations. Among 108 evaluable women randomized to receive anastrozole or tamoxifen in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, those assigned to anastrozole had greater bone loss at the lumbar spine (LS) and total hip (TH) (LS, −6.08%; TH −7.24%) vs the tamoxifen group (LS, +2.77%; TH, +0.74%).[3] Separately, the Intergroup Exemestane Study (IES) evaluated 206 women who received 2 to 3 years of adjuvant tamoxifen for early breast cancer. Those who were randomized to switch to exemestane experienced a decline in BMD (LS, −2.7%; TH, −1.4%) after 6 months, while those who remained on tamoxifen demonstrated no change.[4] Over the following 18 months, BMD continued to decline in the exemestane group, albeit more slowly (additional −1.0% in LS and −0.8% in TH). Lastly, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17 trial randomized 226 women to receive letrozole or placebo after 5 years of adjuvant tamoxifen for early breast cancer. Those who were randomized to switch to letrozole experienced a decline in BMD (LS, −2.7%; TH, −1.4%) after 6 months, while those who remained on tamoxifen demonstrated no change.[5]

Fracture is arguably a more clinically relevant endpoint than bone turnover or asymptomatic decreases in BMD, and several of the original large adjuvant AI trials reported fracture data (Table 1). When evaluating these data, the increased fracture rate associated with AIs is greater in studies comparing an AI vs tamoxifen rather than placebo. In a large meta-analysis of individual data for 31,920 postmenopausal women with ER+ early breast cancer who were randomized to receive either an AI or tamoxifen, the 5-year fracture risk was 8.2% in the AI group vs 5.5% in the tamoxifen group (absolute excess, 2.7%; 95% CI, 1.7%–3.7%).[2] The increased fracture risk appears to be somewhat mitigated by prior tamoxifen use in those studies evaluating “switch” strategies.[4,6,7]

Evidence exists that the increased fracture risk associated with AIs decreases after stopping these medications. For example, the 10-year analysis of the ATAC...
trial found fractures were more frequent during active treatment with anastrozole vs tamoxifen (451 vs 351; odds ratio [OR], 1.33; 95% CI, 1.15–1.55; P < .0001), but not in the post-treatment follow-up period (110 vs 112; OR, 0.98; 95% CI, 0.74–1.30; P = .9). With recent evidence supporting longer durations of adjuvant AI treatment in certain high-risk populations,[9] the implications for fracture risk must be considered. A recent publication-based meta-analysis on the toxicity of extended adjuvant therapy with AIs in early breast cancer found that longer treatment was associated with increased odds of fracture (OR, 1.34; 95% CI, 1.16–1.55; P < .001; number needed to harm, 72).[10]

Bone-Targeted Therapy Prevents Bone Loss, Fractures

Adding adjuvant bisphosphonates and receptor activator of nuclear factor κB ligand (RANKL) inhibitors to endocrine therapy in women with early breast cancer improves BMD from baseline, decreases bone loss risk, and reduces the risk of fracture thereafter. While both agents have shown success in these bone-specific endpoints, no “head to head,” comparisons are available; therefore, their data will be described separately herein.

Bisphosphonates

The risk of fracture in the original large randomized controlled trials on the efficacy of adjuvant AIs ranged from 2.0% to 11.0% (Table 1).[4,6,7,11,12] Bone health and fracture risk were also assessed in the more recent phase III randomized controlled trial AZURE, which evaluated whether adjuvant zoledronic acid reduces fractures in breast cancer patients.[13] This trial is the largest analysis on fracture risk during adjuvant bisphosphonate therapy among women with early breast cancer. A total of 3,360 women with stage II or III breast cancer were randomized to receive the standard of care alone or in combination with zoledronic acid. The zoledronic acid was administered at a dose of 4 mg via intravenous (IV) infusion for 5 years (every 3 to 4 weeks for 6 doses, then every 3 months for 8 doses, then every 6 months for the final 5 doses). After a median follow-up of 84.2 months, 8.3% of women sustained ≥ 1 fracture in the control arm, and 6.2% sustained a fracture in the zoledronic acid arm. The addition of zoledronic acid also increased time to first fracture (hazard ratio [HR], 0.69; 95% CI, 0.53–0.90; P = .0053), with most benefit occurring after a disease-free survival (DFS) event. This brings into question whether bisphosphonates might have the highest yield with respect to fracture prevention in the setting of recurrent disease.

The AZURE study was pooled with 26 additional trials in an Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis of 18,766 individual patients. Data regarding fracture risk were available for 13,341 women with early breast cancer. The risk of fracture was 6.3% among patients who received an adjuvant bisphosphonate vs 7.3% for those who did not (relative risk [RR], 0.85; 95% CI, 0.75–0.97; P = .02). In addition, the 5-year fracture risk was reduced from 6.3% to 5.1%, with little effect in years 0 to 1 and most of the gain occurring in years 2 to 4. These results reflect various bisphosphonate regimens, including clodronate and amnobisphosphonates (Table 2). Although the relative efficacy of these regimens was not reported for the outcome of fracture incidence, the majority of individual patient data (97%) studied the use of adjuvant bisphosphonates for 2 to 5 years.

RANKL inhibitors

The ABCSG-18 clinical trial provides the most evidence to date on the use of denosumab in the adjuvant treatment of early breast cancer.[15] ABCSG-18 was a prospective, placebo-controlled, dou-

---

**Table 1: Clinical Fracture Rates in Original Major Randomized Adjuvant AI Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Al</th>
<th>Control</th>
<th>Prior Endocrine Therapy</th>
<th>Duration of Therapy</th>
<th>Duration of Follow-Up</th>
<th>N of Fractures/N of Patients (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>None</td>
<td>5 yr</td>
<td>68 mo</td>
<td>340/3,092 (11.0%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Letrozole</td>
<td>Tamoxifen</td>
<td>None</td>
<td>5 yr</td>
<td>51 mo</td>
<td>211/2,448 (8.6%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IES</td>
<td>Exemestane</td>
<td>Tamoxifen</td>
<td>2–3 yr of tamoxifen</td>
<td>58 mo</td>
<td></td>
<td>162/2,362 (6.9%)</td>
<td>.003</td>
</tr>
<tr>
<td>ABCSG 8/ ARNO 95</td>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>2 yr of tamoxifen</td>
<td>28 mo</td>
<td></td>
<td>34/1,602 (2.1%)</td>
<td>.015</td>
</tr>
<tr>
<td>NCIC CTG MA-17</td>
<td>Letrozole</td>
<td>Placebo</td>
<td>4.5–6 yr of tamoxifen</td>
<td>30 mo</td>
<td></td>
<td>137/2,572 (5.3%)</td>
<td>.25</td>
</tr>
</tbody>
</table>

AI = aromatase inhibitor; ATAC = Arimidex, Tamoxifen, Alone or in Combination; IES = Intergroup Exemestane Study; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group.
ble-blind, multicenter, phase III clinical trial of 3,425 postmenopausal women with early-stage, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who underwent treatment with an AI between 2006 and 2013. Denosumab was administered at 60 mg subcutaneously (SC) every 6 months, with a median of 7 doses administered in the placebo and denosumab arms. Patients who received denosumab had a significant delay in time to first clinical fracture vs placebo (HR, 0.50; 95% CI, 0.39–0.65; \( P < .0001 \)).[15] At 7 years following randomization, the clinical fracture rate in the denosumab arm was 11.1% (95% CI, 8.1%–14.1%) vs 26.2% in the placebo arm (95% CI, 15.6%–36.8%), and the benefits of therapy were seen across all subgroups. The fracture rate among patients in the placebo arm was estimated to be 10% at 3 years, 16% at 5 years, and 26% at 7 years. Significant variations in the rates of fracture seen in ABCSG-18 vs the EBCTCG meta-analysis[14,15] can likely be explained by differences in patient characteristics, type and/or duration of therapy, clinical monitoring for fractures, and study design. Fracture events were not collected as a primary endpoint for the EBCTCG meta-analysis, so the incidence of fractures may be underestimated. Conversely, the ABCSG-18 trial—which had a primary endpoint of clinical fracture—may have reported less severe fractures not captured in other trials. This is due partly to regular x-ray monitoring for the presence of vertebral fractures in the ABCSG-18 trial. Further real-world, population-based evidence is needed to investigate the true burden of osteoporotic fractures in patients on endocrine therapy, as well as the potential benefit of adjuvant bone-targeted therapy or early osteoporosis intervention in this setting.

### Fracture Risk Assessment

Evaluation methods to assess fracture risk are not in the scope of this article; however, some adjuvant trials evaluating the use of bone-targeted agents excluded women with low BMD, prior fracture, and those who previously received or are currently receiving these agents.[16] As recently reviewed by Black and Rosen in the *New England Journal of Medicine*,[16] organizations in Canada,[17] the United Kingdom,[18,19] and the United States[20] offer tools for the assessment of fracture risk, as well as guidelines for both pharmacologic and nonpharmacologic therapy. However, anticancer agents that accelerate bone loss are not included as risk factors in these algorithms, and methods to incorporate the use of AIs to quantitatively assess fracture risk are lacking.

### Reducing the Risk of Breast Cancer Recurrence and Death With Bone-Targeted Therapy Bisphosphonates

The benefit of bisphosphonates, including reducing the risk of breast cancer recurrence and death, varies in the literature. Older studies assessing the role of adjuvant oral clodronate in early breast cancer suggested a survival benefit, specifically among those who developed bone metastases.[21-23] However, a meta-analysis of three adjuvant clodronate trials did not confirm this survival benefit, possibly due to varying patient populations across the included studies and a lack of analyses by menopausal status.[24] Other studies examining the role of adjuvant zoledronic acid in pre- and postmenopausal women also showed varying results. For example, the AZURE trial found no association between the use of adjuvant zoledronic acid and either DFS or overall survival (OS).[13] However, in a prespecified subgroup analysis of postmenopausal women, a statistically significant survival benefit was noted.[13] In the ABCSG-12 trial of premenopausal women who received ovarian suppression with goserelin along with tamoxifen or anastrozole, an improvement in DFS (HR, 0.77; 95% CI, 0.60–0.99) was reported, but there was no OS benefit (HR, 0.66; 95% CI, 0.43–1.02).[25] This increases the possibility that any disease-related benefit of bisphosphonates may be limited to those women who are functionally postmenopausal. Indeed, preclinical evidence suggests that reproductive hormones may antagonize the efficacy of bisphosphonates against cancer cells in the bone.[26] Therefore, the

### TABLE 2 Bisphosphonates Used Within the EBCTCG Meta-Analysis of Clinical Trials[14]

<table>
<thead>
<tr>
<th>Up to 1 Year of Treatment</th>
<th>Studies With Data Received</th>
<th>N of Patients</th>
<th>Percentage of All Received Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year of clodronate</td>
<td>1</td>
<td>72</td>
<td>0.4%</td>
</tr>
<tr>
<td>&lt; 1 year of an aminobisphosphate</td>
<td>3</td>
<td>40</td>
<td>0.2%</td>
</tr>
<tr>
<td>1 year of an aminobisphosphate</td>
<td>1</td>
<td>448</td>
<td>2.6%</td>
</tr>
<tr>
<td>2–5 Years of Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years of clodronate</td>
<td>3</td>
<td>3,912</td>
<td>20.8%</td>
</tr>
<tr>
<td>3–5 years of clodronate</td>
<td>1</td>
<td>1,069</td>
<td>5.7%</td>
</tr>
<tr>
<td>2 years of an aminobisphosphate</td>
<td>8</td>
<td>3,514</td>
<td>18.7%</td>
</tr>
<tr>
<td>3–5 years of an aminobisphosphate</td>
<td>9</td>
<td>9,711</td>
<td>51.7%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>26</td>
<td>18,766</td>
<td>-</td>
</tr>
</tbody>
</table>

EBCTCG = Early Breast Cancer Trialists’ Collaborative Group.
Bone-Targeted Agents in Early Breast Cancer: Part of Standard Practice?

When we consider the use of oral bisphosphonates, intravenous bisphosphonates, or denosumab for early-stage breast cancer, we must ask ourselves two questions. First, do these agents prevent bone loss resulting from aromatase inhibitor (AI) use in a clinically meaningful manner? Second, do these agents prevent breast cancer recurrence in the bone?

To answer the first question, osteopenia, osteoporosis, and bone fracture are clear and significant complications of AI use. When looking at all trials on adjuvant AI use, the degree of osteoporotic fracture stands out to me: it is in excess of 5% in some trials, and appears to increase the longer the AI is given. Both bisphosphonates (in any form) and denosumab have been shown to clearly maintain and improve bone mineral density in women on AIs, and denosumab clearly prevents fractures, even in women with normal bone density. Therefore, it is clear that a bone-targeted agent should possibly be considered for fracture prevention in postmenopausal women on an AI, and definitely in women at a higher risk of osteoporotic fracture.

In answer to the second question, it is clear from many trials to date, as well as a meta-analysis, that bisphosphonates clearly prevent bone metastasis and improve breast cancer–specific survival and overall survival when given as adjuvant therapy to postmenopausal women. As long as 2 years of any bisphosphonate are given, absolute gains in the 10-year overall survival rate approach 3.3%. This comes close to reaching the gains seen from other interventions in this setting, which form the standard of care. Interestingly, denosumab did not improve 5-year disease-free survival in the D-CARE study, and the reason for the difference observed between bone-targeted agents in this setting is of intense interest. I agree with Jerzak et al that these agents should be reserved for women at higher risk of recurrence. Additionally, emerging new markers, such as lack of MAF amplification, may soon guide us as to which women, both pre- and postmenopausal, would benefit from a bone-targeted agent to prevent bone metastasis.

## RANKL inhibitors

The data on the use of adjuvant denosumab to improve breast cancer survival rates remain immature and uncertain. The ABCSG-18[15,27,28] and D-CARE[29] trials are the only studies to report breast cancer–specific outcomes with the adjuvant use of denosumab. The preliminary results of ABCSG-18, presented at the 2015 San Antonio Breast Cancer Symposium, showed a 7-year DFS benefit among women receiving denosumab (83.5%) vs placebo (80.4%), in addition to an increase in the primary endpoint of time to first clinical fracture (HR, 0.816; 95% CI, 0.66–1.00; P = .051). Additional data were presented at the 2018 American Society of Clinical Oncology.

FINANCIAL DISCLOSURE: Dr. Brufsky serves as a consultant to Amgen, Novartis, and Sandoz.

Dr. Brufsky is a Professor of Medicine and serves as the Associate Division Chief for the Division of Hematology/Oncology at the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. He is also the Medical Director of the Magee-Women’s Cancer Program and Associate Director for Translational Investigation at the UPMC Hillman Cancer Center, as well as Co-Director of the Comprehensive Breast Cancer Center, all at the University of Pittsburgh.
Bisphosphonates are a class of medicines used to treat patients with abnormal bone densities or those with a history of abnormal fractures in the hip, arm, wrist, or spine. These agents work by damaging or killing osteoclasts, cells in the body responsible for removing old bone. By halting this activity, bisphosphonate medications are able to preserve bone strength.

—Source: The American College of Rheumatology

(ASCO) Annual Meeting. In the intention-to-treat analysis of 3,425 postmenopausal women, the use of adjuvant denosumab was associated with improved DFS (HR, 0.82; 95% CI, 0.69–0.98; P = .025 by the logrank test) after a median follow-up of 72 months.[28] At 8 years, the DFS rate was 80.6% for denosumab vs 77.5% for placebo (absolute risk reduction, 3.2%). Given the significantly reduced risk of a first clinical fracture, patients were given the option in 2016 to unblind and cross over to the denosumab arm. This may have underestimated the true effect of denosumab on recurrence and survival outcomes.

In the D-CARE clinical trial, 4,509 women were randomized to receive either placebo or denosumab. Those randomized to denosumab received a more aggressive dose of 120 mg SC once a month for 6 months followed by 120 mg SC every 3 months for the next 4.5 years.[29] The HR for the primary endpoint of bone metastasis–free survival (BMFS) was 0.97 (95% CI, 0.82–1.14; P = .70 by the logrank test), with a similar effect seen in both pre- and postmenopausal women. Denosumab did not improve secondary endpoints, including DFS in the overall population, DFS in the postmenopausal subgroup, or OS. Among seven exploratory endpoints, only the time to bone metastasis as a first recurrence (P = .031) and time to first symptomatic bone metastasis (P = .024) improved with the use of denosumab.

The differing results in the ABCSG-18 and D-CARE studies is quite striking and may be related to the different patient populations. Notably, ABCSG-18 enrolled only postmenopausal women, whereas D-CARE included a mixed population of both pre- and postmenopausal women.[28,29] Patients enrolled in ABCSG-18 also had lower-risk breast cancers than those enrolled in D-CARE, with the majority having lymph node–negative disease (71.2% vs 5.8%) and the minority requiring neoadjuvant chemotherapy (24.7% vs 95.9%).[28,29] It is also notable that ABCSG-18 enrolled only women with hormone receptor–positive disease, most of whom had HER2-negative tumors (93.5%), whereas D-CARE included a broader representation of breast cancer molecular subtypes.[28,29] It is also possible that ABCSG-18 results were more favorable when compared with D-CARE because less frequent and lower doses of denosumab are more effective among patients with early breast cancer.

Timing, Duration, and Choice of Bone-Targeted Therapy

Several trials have shown that the immediate initiation of bisphosphonate therapy is better than initiation at the time of BMD decrease, in terms of bone loss prevention. [30-33] The duration of treatment has varied across studies, from 1 year up to 5 years, but most of the data support the use of adjuvant bone-targeted therapy for 2 to 5 years. Further, with increasing use of extended adjuvant endocrine therapy, most clinical guidelines suggest a 3- to 5-year course of a bone-targeted agent.

Notably, in the SUCCESS-A trial, women with high-risk early breast cancer who were randomized to either a 5-year or 2-year duration of adjuvant zoledronic acid had similar OS, DFS, and bone recurrence rates at a median follow-up of 3 years.[34] The majority of women (> 70%) had hormone receptor–positive disease; 58% were postmenopausal, and all of them received adjuvant chemotherapy.[34] Therefore, the population didn’t optimally reflect patients who typically benefit from bisphosphonate therapy (ie, postmenopausal women with hormone receptor–positive breast cancer). Further, it is unclear how many patients received extended adjuvant endocrine therapy and whether bone-specific outcomes differed between the treatment groups. Regardless, longer follow-up will be required to increase confidence in these results.

To date, adjuvant bisphosphonates and denosumab have not been compared “head to head.” Among the trials within the EBCTCG meta-analysis, no significant heterogeneity was found between the effects of various bisphosphonate regimens on bone recurrence. Notably, similar benefits were found in patients who received the non-aminobisphosphonate clodronate (n = 5,053) vs those who received the aminobisphosphonates zoledronic acid or ibandronate (n = 9,290 and 3,072, respectively); however, no benefit was found in the smaller group of 933 women receiving pamidronate. [14] Unfortunately, the efficacy of these agents was not compared for other clinical outcomes in the EBCTCG meta-analysis.[14] Whether pamidronate truly has different effects on bone recurrence than other aminobisphosphonates is unclear based on this exploratory subgroup analysis. However, the increased efficacy of zoledronic acid is biologically plausible given that it is 100 times more...
potent than pamidronate.\[35,36\] Given that adherence to treatment may be improved with IV zoledronic acid vs oral bisphosphonates, with an associated cost savings,\[37\] the preferential use of zoledronic acid may be considered among women with early breast cancer (Table 3). While denosumab has demonstrated excellent efficacy for fracture prevention, the differing breast cancer–specific outcomes seen in ABCSG-18 and D-CARE suggest that some caution should be used when considering its use in the adjuvant setting for early breast cancer. Although D-CARE enrolled a broader and higher-risk population than ABCSG-18 (Table 4), a lack of efficacy was still observed in postmenopausal, lymph node–negative, and hormone receptor–positive subgroups that was more akin to the ABCSG-18 population.\[28,29\]

Cancer Care Ontario’s 2016 Program in Evidence-Based Care, in collaboration with ASCO guidelines, recommends zoledronic acid at 4 mg IV every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/day for 2 to 3 years for women in whom adjuvant bisphosphonate therapy is being considered.\[38\] However, these guidelines acknowledge that different durations of therapy may be employed.\[34\] Recommendations from other organizations, such as the St. Gallen International Expert Consensus guidelines\[39\] and the European Society for Medical Oncology\[40\] guidelines, were summarized by Hadji et al in 2017.\[41\]

As illustrated in the Figure, we propose that women with an intermediate-to-high clinical risk of breast cancer recurrence and/or those with an intermediate-to-high risk of fracture who are treated with an AI receive a bone-targeted agent.

**TABLE 3 Costs Associated With the Administration of Bone-Targeted Therapies for the Treatment of Patients With Early Breast Cancer**

<table>
<thead>
<tr>
<th>AZURE (5 yr)</th>
<th>ABCSG-18 (5 yr)</th>
<th>D-CARE (5 yr)</th>
<th>SUCCESS-A</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid 4 mg IV q3–4 wk × 6, then q3mo × 8, then q6mo × 5</td>
<td>Denosumab 60 mg SC q6mo</td>
<td>Denosumab 120 mg SC q1mo × 6, then q3mo × 18</td>
<td>Zoledronic acid 4 mg IV q3mo × 8 (2 yr)</td>
<td>Zoledronic acid 4 mg IV q3mo × 8, then every 6 mo × 6</td>
</tr>
<tr>
<td>21 doses</td>
<td>10 doses</td>
<td>24 doses</td>
<td>8 doses</td>
<td>14 doses</td>
</tr>
<tr>
<td>$3,831.45\text{a}$</td>
<td>$4,461.20\text{b}$</td>
<td>$17,114.40\text{b}$</td>
<td>$1,459.60\text{a}$</td>
<td>$2,554.30\text{b}$</td>
</tr>
</tbody>
</table>

\(\text{a}\text{Based on the 2017–2018 Cancer Care Ontario CCO Systemic Treatment–Quality-Based Procedure funding bands for treatment delivery cost plus drug cost.}\)

\(\text{b}\text{Retail pharmacy cost (may vary from retailer to retailer).}\)

IV = intravenously; SC = subcutaneously.

**TABLE 4 Comparison of Denosumab Dosing and Patient Populations in the ABCSG-18 and D-CARE Studies\[28,29\]**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABCSG-18</th>
<th>D-CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of denosumab</td>
<td>60 mg every 6 mo</td>
<td>During AI therapy</td>
</tr>
<tr>
<td>Total duration of denosumab</td>
<td>54 mo</td>
<td>54 mo</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N of patients randomized</td>
<td>3,425</td>
<td>4,509</td>
</tr>
<tr>
<td>Total N of patients randomized</td>
<td>3,425</td>
<td>4,509</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>64 (38–91)</td>
<td>51 (NR)</td>
</tr>
<tr>
<td>Lymph node–positive</td>
<td>28.3%</td>
<td>94.2%</td>
</tr>
<tr>
<td>Treatment with chemotherapy</td>
<td>24.7%</td>
<td>95.9%</td>
</tr>
<tr>
<td><strong>Breast Cancer Subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-positive</td>
<td>100%</td>
<td>77.4%</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>6.3%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>0%</td>
<td>15.2%</td>
</tr>
<tr>
<td><strong>Clinical Trial Design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Time to first clinical fracture</td>
<td>Bone metastasis–free survival</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>72 mo</td>
<td>67 mo</td>
</tr>
</tbody>
</table>

AI = aromatase inhibitor; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; NR = not reported.

**Monitoring Bone Health**

Few data exist on the ideal schedule for monitoring BMD in women on AIs. The supplemental 2013 National Comprehensive Cancer Network (NCCN) guidelines recommend dual energy x-ray absorptiometry (DXA) scans at least every other year\[42\];
A more refined algorithm was proposed in 2008 by the UK Expert Group. All women on AIs with a T-score of $<-1$ are considered “high risk.” A bisphosphonate is recommended for all patients in this category. Even while on a bone-targeted agent, the group recommends that the BMD of women on bisphosphonate therapy be monitored every 24 months. “Medium risk” patients with a T-score $>-1$ are recommended to undergo BMD testing at a similar time interval.[45]

We propose a modified, more flexible approach for monitoring bone health in postmenopausal women on adjuvant AIs (Figure). First, we recognize that fracture risk is reflected not only by BMD results, but also by established risk factors, such as advanced age, low body mass index, fracture history, and steroid use, as assessed using the Fracture Risk Assessment Tool (FRAX). Hence, women at a low risk of breast cancer recurrence with a T-score $>-2$ may remain off bone-targeted agents with BMD monitoring every 1 to 2 years, depending on individual risk factors for fracture, rate of yearly bone loss, and preference based on the risks vs benefits of bisphosphonates.

In postmenopausal women on adjuvant AIs who already receive a bone-targeted agent, we recommend that BMD be monitored every 2 to 3 years; more frequent monitoring is unlikely to change management. This schedule may help identify women with declining BMD due to nonadherence, secondary causes of osteoporosis, and/or lack of efficacy of bone-targeted therapy. If reduced BMD is not adherence-related, referral to a bone health specialist is advised for evaluation of secondary causes of osteoporosis. If alternate causes are not found, switching the type of bone-targeted agent and/or endocrine therapy to tamoxifen (which strengthens the bone) may be considered.

We acknowledge that various methods for monitoring bone health in women taking adjuvant AIs are based on expert opinion, and FRAX score has not been validated in a breast cancer population.

**Toxicity Considerations**

Bisphosphonates and denosumab have a low risk of atypical fractures and osteonecrosis of the jaw (ONJ). The risk of ONJ in D-CARE was 5.4%; no confirmed cases of ONJ were reported in ABCSG-18.[28,29] A pooled risk of ONJ was not determined in EBCTCG, but a risk of up to 2% was reported.[14] Since bisphosphonates are cleared renally, renal function must be monitored to detect nephrotoxicity. Generally, women with a creatinine clearance $<30$ mL/min should not receive bisphosphonates; denosumab may be utilized safely since it is not renally cleared. Calcium levels should be monitored before each treatment for both classes of bone-targeted therapy due to a risk of hypocalcemia.[34] Oral bisphosphonates may cause esophageal/gastric irritation or pain. Loss of vision or ocular pain due to inflammatory eye conditions may occur, and require prompt evaluation by an ophthalmologist.[34,46,47] Although data are limited, the toxicity of zoledronic acid and pamidronate appears to be similar.[48] The incidence of grade $\geq 3$ events was comparable in multiple myeloma patients receiving zoledronic acid and pamidronate.
systemic cancer is typically treated with radiation, with or without intrathecal or systemic chemotherapy. Temozolomide has been evaluated for leptomeningeal disease given the paucity of cytotoxic agents with CNS penetration. Several case reports have noted response to temozolomide alone, with other chemotherapy, or combined with radiation and chemotherapy.[82-90]

A nonrandomized phase II study of temozolomide in adults with leptomeningeal carcinomatosis was stopped early due to slow accrual, however, and showed only two patients with partial response (11%) and one with stable disease (5%).[91] This lack of response is probably explained by the fact that breast and lung cancers, which are resistant to temozolomide, are the most common tumors involving the leptomeninges.

Conclusion
Temozolomide has been evaluated as monotherapy or in combination for a broad range of systemic and CNS cancers. Despite this, the only FDA-approved indications for it are for high-grade primary astrocytomas. Extensive investigation in other cancers has produced very low response rates with minimal effect on survival. Because only a fraction of the systemic drug concentration penetrates the blood-brain barrier, it is understandable that temozolomide is minimally effective for brain metastases from systemic cancers that are not sensitive themselves.

Although temozolomide is currently the only effective chemotherapy agent for patients with gliomas, its efficacy in other tumor types and metastatic disease to the brain has been disappointing. As a result, alternative approaches are generally preferred when treating metastatic CNS cancers.

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.

For references visit cancernetwork.com/role-temozolomide-cns
ABSTRACT: As the world population ages, we can expect to care for an increasing number of older cancer patients. Prostate cancer is inherently a condition that affects patients of advanced age. In caring for these patients who have advanced prostate cancer, it is important to first assess the health status of the patient and his goals of care. As this is established, likely through a geriatric assessment, this will inform how to modify or mold the treatment plan to fit a patient's needs and vulnerabilities. These vulnerabilities may surface as patients undergo treatment such as androgen deprivation therapy—the backbone of systemic therapy for advanced disease. Androgen deprivation therapy leads to long-term adverse effects; therefore, providers should carefully consider its use and proactively manage toxicity. It is important to assess patients before starting treatment and to adjust the choice of therapy, or supportive services, in order to maximize benefit and minimize potential harms.

Introduction
Prostate cancer is predominantly a disease of the elderly, with peak incidence occurring at just over 70 years old.[1] Given the breadth of prostate cancer and its therapies, this article focuses on advanced hormone-sensitive disease only. This population is increasing as longevity rates rise and more patients present with advanced disease.[2] Most patients with prostate cancer are over the age of 65 years, and are thus considered part of the cancer population of older adults for which there are specific guidelines on care.

Geriatric Assessment
As in any older patient with cancer, one must first define the patient's general health and fitness with a geriatric assessment. Screening tools, such as the G8, are readily accessible, validated, and referenced in the National Comprehensive Cancer Network Older Adult Oncology guidelines.[3] Screening allows for consideration of how the overall health status of a patient may influence treatment tolerance. Any major findings may lead to a more complete geriatric assessment, which can be performed in conjunction with a geriatric health provider. This approach allows for the identification of patients in whom treatment could cause significant toxicity, or patients who may tolerate therapy if given with additional supportive interventions. By defining a patient's geriatric health and fitness, the oncology team can adjust the care plan or work with supportive care providers to intervene for areas of vulnerability, such as medication adjustment or mobility therapy.

As part of these initial steps, it is also vital to assess the patient's goals of therapy and overall priorities. If the patient is not able to participate in these discussions due to cognitive dysfunction, then physicians must speak with the medical decision maker in order to best align care with the
patient’s values. The diagnosis of prostate cancer might not be more impactful for some patients than that of a chronic condition. Patients with advanced prostate cancer may still have an estimated life expectancy of 4 to 6 years, and as such, understanding how this diagnosis fits into his overall health picture is paramount. For example, an 83-year-old man in excellent health may have an average life expectancy of 8 to 9 years, while a 73-year-old man in poor overall health may have the same life expectancy. Thus, the initial approach to the care of an older patient with metastatic hormone-sensitive prostate cancer should include an estimate of the patient’s age-matched life expectancy with an adjustment for health status, and how this compares with prognosis due to cancer.

With this preliminary evaluation pooling together the physiologic age of the patient and his ability to participate in care planning, as well as the general goals of such planning, disease biology should also be considered. The sites of metastatic disease, the presence or absence of symptoms, and the rate of disease progression inform the remainder of the care-planning discussion. Overall, patients may be assessed as fit, frail (problems that may be reversible), disabled (nonreversible problems that may be adapted), or so ill that only supportive care should be considered.

**Hormone Therapy in Older Patients**

The backbone of prostate cancer treatment is hormonal therapy, which aims to limit the activation of the androgen receptor (AR) with testosterone. This limitation of AR activation may occur through agents that decrease circulating testosterone, such as gonadotropin-releasing hormone (GnRH) agonists or antagonists. The use of these agents also decreases testosterone precursors and other off-target effects of testosterone. Agents such as nonsteroidal anti-androgens block AR activation and yet preserve circulating testosterone levels.

Providers must carefully consider the toxicities of androgen deprivation therapy (ADT) in a physiologically older population. These patients have less reserve to absorb additional imbalances or conditions that will impact their current steady state. In general, agents that result in a hypogonadal state can lead to toxicities within the following domains: metabolic and body composition; sexual health; and mood and central nervous system (CNS) symptoms (Table 1).

### Metabolic and Body Composition

Patients may experience changes in metabolic parameters and body composition, such as bone mineral density loss and sarcopenic obesity.[4,5] These changes occur naturally through the aging process and are accelerated with the use of ADT. The risk of osteoporosis development is important to keep in mind because geriatric syndromes (such as fall risk, delirium, and incontinence) can predispose patients to osteoporotic fractures. Men who suffer an osteoporotic fracture have a higher mortality risk compared with women.[6,7] As such, preventing bone mineral density loss may in turn prevent a fracture and the associated morbidity and mortality risk of such an event. In order to modify this risk, all patients on ADT should take a daily vitamin D and calcium supplement and engage in weight-bearing exercise.

Older patients with prostate cancer who have been initiated on ADT should also undergo baseline bone mineral density testing and should strongly consider bone-modifying agents, as appropriate, to avoid the development of osteoporosis. Providers may also use the Fracture Risk Assessment Tool (FRAX) score, which estimates the 10-year risk of any fracture and specifically hip fractures based on multiple variables.[8] Men should be offered an additional bone-modifying treatment (ie, bisphosphonate therapy) if their FRAX scores include a 10-year risk of hip fracture ≥3% or a 10-year estimated risk of major osteoporotic fracture ≥20%. There are no data to support the use of bone-modifying agents in the treatment of prostate cancer; in the hormone-sensitive setting, these are primarily used as agents to prevent osteoporosis.

Soft-tissue body composition may also change as patients gain fat mass and lose muscle mass—known as sarcopenic obesity—or ADT. In community-dwelling older patients, sarcopenic obesity has been linked to increased risk of morbidity and mortality.[9] The loss of lean body mass impacts balance and mobility, such that these patients may be at increased risk of falls or trouble completing their activities of daily living. It has been noted that these body composition and balance changes can occur as early as 3 months after therapy begins.[10] In order to maintain functional independence, providers should strongly consider referral for prehabilitation or have a low threshold for referral to a cancer rehabilitation program. Patients highly value preserva-
tion of functional independence,[11] so proactively enlisting additional supportive care services is suggested in order to avoid declines while on therapy.

Additionally, patients may experience metabolic consequences, such as decreased insulin sensitivity, elevated cholesterol levels, and hypertension, which contribute to an increased risk of metabolic syndrome and cardiovascular disease in this population. There are no consistent data linking ADT as a causal agent to cardiovascular disease and mortality. However, there are clear relationships between the metabolic changes that occur on ADT and their contribution to cardiovascular disease development.[12] Further analysis is likely needed to better understand different inflammatory responses to ADT. Prospective investigations have not shown a difference in cardiovascular event rates with GnRH agonists vs antagonists. However, a pooled retrospective analysis has shown a difference in the incidence of cardiovascular events between GnRH agonists and antagonists. [13] This warrants further investigation and could be considered in patients with a high risk of cardiovascular events who would benefit from systemic therapy.

Mood and CNS Effects

Other adverse reactions involve changes in mood, cognition, sleep patterns, and vasomotor skills.[14,15] The relationship between use of ADT and cognition requires clarification, but patients do report changes in emotion regulation and focus. These changes are significant in a population already at risk for cognitive decline, and they considerably impact a patient’s ability to function independently. Patients may also experience labile mood and depressive symptoms that could alter quality of life. [16] In addition, use of ADT can contribute to sleep disturbances, in a population already affected by urgency and nocturia in conjunction with the aging-related changes to sleep patterns. This may worsen mood, focus, and function. There are supportive medications that can be used, but should be looked at with caution in an older population sensitive to medication changes. Avoidance of polypharmacy and consideration of altered metabolism of pharmacologic agents are basic tenants of geriatric medicine.

Alterations in the ADT Prescription

Large studies have supported the use of continuous ADT, as opposed to intermittent dosing, in the treatment of metastatic prostate cancer. However, follow-up meta-analyses have opened the door for use of intermittent ADT therapy,[17] which may improve quality of life and decrease the risk of resultant long-term toxicities for individual patients. Improved knowledge of these toxicities has caused providers to rightly consider the potential benefit and harms prior to prescribing ADT. ADT is a highly effective therapy and should not be ignored for patients who may benefit. In patients with limited life expectancy, in which quality of life is prioritized above longevity, consider the use of intermittent ADT. In addition, patients too frail to tolerate standard testosterone-lowering treatment may undergo treatment with nonsteroidal anti-androgen monotherapy. This treatment is inferior to continuous ADT in terms of survival outcomes,[18] yet is active enough to potentially offer some short-term disease control or palliation of symptoms. In some patients, the risk of loss of muscle mass or potential cognitive changes on ADT may outweigh the potential benefit of therapy, and single-agent anti-androgen therapy might be considered. Other options include monthly dosing of ADT in order to monitor toxicity and to allow a quicker potential recovery of testosterone if treatment must be interrupted due to side effects. These decisions to alter the standard course of ADT should be carried out in conjunction with the patients and their supportive network. Considering patient priorities when discussing the potential risks and benefits of these approaches is necessary, as with any important medical decision.

Addition of Other Therapies in the Hormone-Sensitive Setting

Addition of Other Therapies in the Hormone-Sensitive Setting Docetaxel

As in many other malignancies, we have learned that combination therapy at the outset of treatment improves long-term disease control and survival outcomes. Both docetaxel and abiraterone acetate in the hormone-sensitive setting have demonstrated a survival benefit when added to standard ADT (Table 2). Based on these data, most providers should offer, or at least consider, additional therapies to treat patients at this stage. Certainly in a frail patient population, one must continue to assess the overall fitness of a patient. Any patient already thought of as fit should be offered unaltered therapy. Those found to be vulnerable or frail could be considered based on the ability to reverse at-risk conditions.

Two large studies have evaluated the use of docetaxel and found a survival benefit in those with high-volume metastatic disease.[19,20] These studies enrolled patients in their mid-60s, representing a slightly younger, more fit population than a “real-world” patient. Templeton et al have investigated the use of docetaxel in a real-world setting[21] and found increased toxicities in comparison with
the registry trials[19,20]; additional data suggest an increased incidence of febrile neutropenia if docetaxel is used prior to the development of castrate levels of testosterone.[21,22] In many cases, patients on clinical trials do not reflect the patient population we see in the clinic, especially in the case of older adults. In order to help navigate this, a geriatric screen and the use of a chemotherapy toxicity calculator, such as that validated by Hurria et al.[23] can provide useful information in estimating the potential for toxicity due to chemotherapy. Many older men with prostate cancer tolerate chemotherapy, but it is important to maximize pretreatment planning.

**Abiraterone acetate and prednisone**

Recent data support the use of abiraterone acetate for the treatment of metastatic hormone-sensitive prostate cancer.[24,25] This agent inhibits the adrenal production of androgens, and as such, further decreases available testosterone for AR activation. The use of abiraterone acetate has significantly improved overall survival, with tolerable side effects.[24,25] Abiraterone has been approved by the US Food and Drug Administration for the treatment of metastatic castration-resistant disease, and evaluation of the geriatric cohorts in a registry trial revealed excellent efficacy and tolerability.[26] This post-hoc analysis of fit patients in the chemotherapy-naive setting looked at differences in efficacy and toxicity among patients older (346 patients) and younger (736 patients) than 75 years old. Among the patients over 75 years old treated with abiraterone acetate plus prednisone, the survival benefit was similar compared with the younger group. Of note, the study enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (a fairly fit population). One must recall that the ECOG score is fairly insensitive in older adults, and thus may overestimate their functional status and fitness for therapy.[27] The geriatric screen may help identify areas of disability not uncovered with the ECOG score.

The patients enrolled in the LATITUDE and STAMPEDE-abiraterone trials were generally older (median age, 67 years; range, up to 85 years in STAMPEDE), with ECOG scores of 0–2 compared with the CHAARTED and STAMPEDE-chemotherapy cohorts. Of note, patients being treated with abiraterone must take a low-dose corticosteroid to avoid mineralocorticoid excess, which results from alteration of adrenal function. In addition, patients may not have the means to pay for this costly agent, since older patients usually have a fixed income. Overall, there is little need for dose interruptions or reductions of abiraterone, and it should be considered for a broad group of older patients with newly diagnosed metastatic hormone-sensitive prostate cancer.

### Summary

In summary, the first steps in care planning for older patients with prostate cancer are the most crucial. A thorough assessment of a patient’s cognitive function, goals of therapy, and geriatric health through a geriatric assessment will guide decision making. The treatment of advanced prostate cancer is likely to continue to change with ongoing exploration of additional agents; these should be offered to fit older men, and considered in those with some vulnerabilities.

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**TABLE 2** Comparison of Populations Treated With Abiraterone and Docetaxel in the Hormone-Sensitive Setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Drug</th>
<th>HR for Death</th>
<th>Median Age (range)</th>
<th>ECOG Performance Status</th>
<th>Grade 3–5 Toxicities (Rx vs ADT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATITUDE</td>
<td>100% metastatic</td>
<td>Abiraterone</td>
<td>0.62</td>
<td>68 (33–92)</td>
<td>0–2</td>
<td>63% vs 48%</td>
</tr>
<tr>
<td>(N = 1,199)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAMPEDE</td>
<td></td>
<td>Abiraterone</td>
<td>0.63</td>
<td>67 (39–85)</td>
<td>0–2</td>
<td>47% vs 33%</td>
</tr>
<tr>
<td>(N = 1,917)</td>
<td>28% node-negative</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>20% node-positive</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>52% metastatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAARTED</td>
<td>100% metastatic</td>
<td>Docetaxel</td>
<td>0.61</td>
<td>64 (36–91)</td>
<td>0–2</td>
<td>30% vs NR</td>
</tr>
<tr>
<td>(N = 790)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>STAMPEDE</td>
<td></td>
<td>Docetaxel</td>
<td>0.76</td>
<td>65 (40–84)</td>
<td>0–1</td>
<td>52% vs 32%</td>
</tr>
<tr>
<td>(N = 2,962)</td>
<td>24% node-negative</td>
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<tr>
<td></td>
<td>15% node-positive</td>
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<tr>
<td></td>
<td>61% metastatic</td>
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</table>

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NR = not reported; Rx = treatment.
Introduction
Bruton tyrosine kinase (BTK) inhibitors are a class of anticancer agents that have recently helped change the landscape of available therapies for lymphoid malignancies. Ibrutinib, the first-in-class oral BTK inhibitor, is approved by the US Food and Drug Administration for chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), and chronic graft-vs-host disease (GvHD) following allogeneic stem cell transplant.[1] Acalabrutinib (Calquence), currently approved for only MCL, is also of clinical interest due to its specificity for BTK, pharmacodynamic properties in limit resistance, and favorable adverse effect profile.[2,3] Of specific concern with both of these agents, however, are cardiac adverse effects, including hypertension, atrial fibrillation, and an increased propensity for bleeding.

Association Between BTK Inhibitors and Atrial Fibrillation
In the pivotal RESONATE and RESONATE-2 trials of ibrutinib in CLL, atrial fibrillation was noted in only 3% of relapsed/refractory patients and 6% of patients treated in the frontline setting. [4,5] The PCYC-1104-CA trial found a similar rate of atrial fibrillation (4.5%) among MCL patients treated with ibrutinib,[6] Unfortunately, as the data have matured, atrial fibrillation has proven more prevalent than the signal during the follow-up seen in the registration trials. An update to the RESONATE-2 trial revealed a 10% incidence of ibrutinib-associated atrial fibrillation at a median follow-up of 29 months; of these events, only 4% were grade 3. Symptom resolution occurred in 64% of patients (complete resolution, 57%; partial resolution, 7%) and was relatively quick (median, 3 days).[7]

Mechanism of action
Atrial fibrillation occurs as a result of a reduction in PI3K-AKT pathway signaling. Inhibition of the alpha isoform of PI3K is thought to occur due to crosstalk between the BTK and PI3K-AKT pathways, or simply as a direct off-target effect. This mechanism has been validated by animal cardiac myocyte models, which found that ibrutinib administration was associated with an inhibition of PI3K-AKT signaling, leading to prolonged and abnormal action potentials within cardiac tissue.[8,9]

Acalabrutinib is considered to be an attractive alternative to ibrutinib, at least in part due to its enhanced specificity for BTK, which thereby reduces the potential for off-target effects.[10] This is supported by results of ACE-LY-004, a phase II, open-label registration study of acalabrutinib in MCL, which found no reported cases of atrial fibrillation among 124 patients at a median follow-up of 15.2 months. Among 612 patients across multiple studies, only 3% developed either atrial fibrillation or flutter.[2] However, given the late-onset atrial fibrillation seen with a longer follow-up in individuals receiving ibrutinib, similar precautions should be taken for patients on acalabrutinib until long-term safety data are available.

Comorbidities and risk factors
CLL typically occurs in older individuals who may have existing cardiac comorbidities. However, clinicians should note that a history of atrial fibrillation or other cardiac issues does not necessarily serve

FIGURE Additional Considerations in Prescribing BTK Inhibitors

Ibrutinib may induce hypertension (incidence ≥ 25%). Clinicians should monitor blood pressure in patients with pre-existing hypertension while on ibrutinib to determine if adjustments to antihypertensive therapy are needed.

Warfarin use was prohibited in many clinical trials of Bruton tyrosine kinase (BTK) inhibitors. This was the result of 4 patients with mantle cell lymphoma developing subdural hematomas, all of which were also associated with falls and/or head trauma and in patients either on aspirin or warfarin.

BTK inhibitors should be interrupted for 3 to 7 days for procedures that may place the patient at an increased risk of bleeding.
as an absolute contraindication to either BTK inhibitor. Risk mitigation strategies, including identification and correction of modifiable risk factors, such as obesity, smoking, alcohol consumption, high blood pressure, uncontrolled diabetes, and any existing heart disease, should be utilized in patients with pre-existing atrial fibrillation; a robust cardiac workup and optimization of medications should also be completed.[11-14] In addition, a thorough medication history is crucial in managing potential drug interactions. Both ibrutinib and acalabrutinib rely on metabolism via cytochrome P450 enzyme 3A4 (CYP3A4), and the concentration of these agents increases when administered in conjunction with other CYP3A4 inhibitors, such as azole antifungals (eg, fluconazole, posaconazole), diltiazem, verapamil, amiodarone, and/or citrus-based food or drinks (eg, grapefruit juice, Seville oranges). Interrupting and/or reducing the dose of ibrutinib has not been shown to hasten resolution, but is warranted in hemodynamically unstable patients. [13,14] Published clinical experiences and algorithms are available to assist providers in clinical decision making.

The risk of bleeding further complicates the use of BTK inhibitors in patients who develop atrial fibrillation and are at an increased risk for stroke, based on the widely accepted CHA2DS2-VASc predictive model.[13,14] Like atrial fibrillation, a higher risk of bleeding has more often been associated with ibrutinib than acalabrutinib. Approximately 50% of patients receiving ibrutinib reported some degree of bruising or bleeding; however, rates of grade 3 or higher bleeding have been reported in less than 10% of patients, primarily as a result of direct platelet dysfunction.[11,15-17] Although platelet dysfunction is not observed with acalabrutinib, bleeding and bruising have also been reported with this agent.[2,15] The decision to use anticoagulants and antiplatelet agents must be balanced with this risk; a low-molecular-weight heparin or a direct oral anticoagulant is typically preferred over warfarin due to concerns of a small number of subdural hematomas occurring in early clinical trials of ibrutinib.

Clinical uneasiness surrounding these adverse effects in patients who are otherwise eligible to receive BTK inhibitors is understandable. Performing a thorough evaluation of cardiac risk factors and a review of all concomitant medications, including herbal supplements, is crucial in order to ensure safe prescribing. Patient education should include ways to recognize symptoms and reduce modifiable risks, including avoidance of medications, as well as food and drinks, known to inhibit CYP3A4. If avoiding interacting agents is not possible, a reduction in the BTK inhibitor dose may be indicated. See the Figure for additional considerations when prescribing BTK inhibitors.

While longer follow-up is needed to confirm whether these troubling adverse effects are less common with acalabrutinib, providers may consider this agent to be a safer option for patients with MCL. The ongoing ELEVATE study, a head-to-head noninferiority trial of ibrutinib vs acalabrutinib in CLL patients, may shed more light on the toxicity differences between these agents. Attention should also be paid to BTK inhibitors still in development, including zanubrutinib (BGB-3111) and ONO/GS-4059, particularly regarding their cardiac safety. Nevertheless, should patients taking a BTK inhibitor develop atrial fibrillation, emerging evidence has shown that it is manageable, and multidisciplinary care from both a hematologist and cardiologist is recommended.

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.

For references visit cancernetwork.com/atrial-fibrillation-BTK

Ms. Valla is a Clinical Pharmacy Specialist, Hematology/Oncology/BMT at Winship Cancer Institute of Emory University and Emory University Hospital, Atlanta, Georgia.