American Society of Clinical Oncology Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer


ABSTRACT

Purpose
To update the recommendations on the role of bone-modifying agents in the prevention and treatment of skeletal-related events (SREs) for patients with metastatic breast cancer with bone metastases.

Methods
A literature search using MEDLINE and the Cochrane Collaboration Library identified relevant studies published between January 2003 and November 2010. The primary outcomes of interest were SREs and time to SRE. Secondary outcomes included adverse events and pain. An Update Committee reviewed the literature and re-evaluated previous recommendations.

Results
Recommendations were modified to include a new agent. A recommendation regarding osteonecrosis of the jaw was added.

Recommendations
Bone-modifying agent therapy is only recommended for patients with breast cancer with evidence of bone metastases; denosumab 120 mg subcutaneously every 4 weeks, intravenous pamidronate 90 mg over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another. In patients with a calculated serum creatinine clearance of more than 60 mg/min, no change in dosage, infusion time, or interval of bisphosphonate administration is required. Serum creatinine should be monitored before each dose. All patients should receive a dental examination and appropriate preventive dentistry before bone-modifying agent therapy and maintain optimal oral health. Current standards of care for cancer bone pain management should be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. The use of biochemical markers to monitor bone-modifying agent use is not recommended.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for use of bisphosphonates in breast cancer in 2000. ASCO guidelines are updated at intervals determined by an Update Committee of the original Expert Panel. ASCO previously updated these guidelines on bisphosphonates in breast cancer in 2003. In planning the 2011 update, ASCO changed the scope of the guidelines to reflect changes in the field since the previous guideline. Because more research has been published on the use of bone-modifying agents as an adjuvant treatment of breast cancer and in managing treatment-associated bone loss, ASCO decided that the topic of adjuvant bone-modifying agent use in women with breast cancer should become the subject of a separate guideline. This guideline now focuses solely on patients with evidence of bone metastases. An Executive Summary of this 2011 guideline update was published by Journal of Clinical Oncology on February 22, 2011.

Reflecting the Update Committee's anticipation that data on new types of agents, including osteoclast inhibitors, may be available for future updates of this guideline, this guideline uses the term bone-modifying agents. The terminology in Recommendations 1, 2, 4, 6, and 7 has been changed from bisphosphonate to bone-modifying agent. The recommendations within the guideline focus on the
drugs denosumab, zoledronic acid, and pamidronate because they are currently available in the United States.

Six of the recommendations are substantively the same as in the 2003 guidelines for bone-modifying agents for metastatic breast cancer. For each of the recommendations, clinical judgment should also take into consideration the patient’s general performance status, overall prognosis, and goals of care. No additional data identified using the methods of this systematic review are available with regard to the dose, dose interval, or duration of therapy of bone-modifying agents. The current guideline has added a new recommendation regarding osteonecrosis of the jaw (ONJ), a condition recognized after the preparation of the 2003 guidelines. This guideline on metastatic breast cancer also reviews data on a new bone-modifying agent, denosumab.

There are new data on the bisphosphonate ibandronate and no new data on clodronate. However, the US Food and Drug Administration (FDA) has not approved clodronate or ibandronate for use in patients with breast cancer metastatic to the bone as of the publication of this guideline update.

Table 1 provides a summary of the 2003 and 2011 guideline recommendations. Please note that, to improve readability, slight changes have been made in the language of some of the 2003 recommendations, although the changes are not substantive.

### METHODOLOGY

For the 2011 update, an Update Committee composed of members from the full 2003 Bisphosphonate in Breast Cancer Expert Panel was formed to complete the review and analysis of data published since 2003 (Data Supplement 3).

**Consensus Development Based on Evidence**

ASCO convened the Update Committee to lead the 2011 update. The Update Committee met, via three teleconferences, on February 1, February 22, and November 23, 2010, to consider the evidence for each of the 2011 recommendations. A writing group of the Update Committee and ASCO staff drafted the guideline. The guideline was circulated in draft form to the Update Committee. As per standard ASCO practice, the guideline was submitted to *Journal of Clinical Oncology* for peer review. The entire Update Committee, ASCO’s Clinical Practice Guidelines Committee, and the ASCO Board of Directors reviewed and approved the final document.

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**THE BOTTOM LINE**

**ASCO GUIDELINE UPDATE**

**The Role of Bone-Modifying Agents (BMAs) in Metastatic Breast Cancer**

**Intervention**
- Bone-modifying agents (BMAs), including bisphosphonates

**Target Audience**
- Medical Oncologists, Radiation Oncologists, Surgical Oncologists, Palliative Care Providers

**Key Recommendations**
- BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction.
- Denosumab 120 mg subcutaneously every 4 weeks; intravenous (IV) pamidronate 90 mg over no less than 2 hours every 3 to 4 weeks; or IV zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks.
- One BMA is not recommended over another.
- In patients with creatinine clearance >60 mL/min, no change in dosage, infusion time, or interval is required; monitor creatinine level with each intravenous bisphosphonate dose.
- In patients with creatinine clearance <30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.
- All patients should have a dental examination and preventive dentistry before using a BMA.
- At onset of cancer bone pain, provide standard of care for pain management and start BMAs.
- Use of biochemical markers to monitor BMA use is not recommended for routine care.

**Methods**
- Systematic review of medical literature and analysis of the medical literature by the Update Committee of an Expert Panel.

**Additional Information**
- An Executive Summary of this guideline has been published in *Journal of Clinical Oncology* (doi: 10.1200/JCO.2010.32.5209).

The Data Supplement, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/bisphosbreast.
Table 1. Summary of 2011 Recommendations

<table>
<thead>
<tr>
<th>Recommendation Category</th>
<th>2003 Recommendations</th>
<th>2011 Recommendations</th>
<th>Change</th>
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<tr>
<td>Recommendation 1: Indications and time of initiation</td>
<td>For breast cancer patients who have evidence of bone destruction on plain radiographs, IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs. There is insufficient evidence relating to efficacy to support one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient’s general performance status and overall prognosis.</td>
<td>For patients with breast cancer who have evidence of bone metastases, denosumab 120 mg subcutaneously every 4 weeks, IV pamidronate 90 mg delivered over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. Starting bone-modifying agents in women with an abnormal bone scan and an abnormal CT scan or MRI showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs. Starting bone-modifying agents in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended outside of a clinical trial. There is insufficient evidence relating to efficacy to support one bone-modifying agent over another.</td>
<td>Addition of new bone-modifying agent. Term changed from bisphosphonates to bone-modifying agents.</td>
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<tr>
<td>Recommendation 2: Role of bone-modifying agents in the presence of extraskeletal metastases</td>
<td>Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extraskeletal metastases is not recommended. This clinical situation has not been studied using IV bisphosphonates and should be the focus of new clinical trials. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.</td>
<td>Starting bone-modifying agents in women without evidence of bone metastases even in the presence of other extraskeletal metastases is not recommended. This clinical situation has been inadequately studied using IV bisphosphonates or other bone-modifying agents and should be the focus of new clinical trials.</td>
<td>(Unchanged in substance from 2003)</td>
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<tr>
<td>Recommendation 3A: Renal safety concerns</td>
<td>In patients with pre-existing renal disease and a serum creatinine &lt; 3.0 mg/dL (265 μmol/L), no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates among patients with worse function has been minimally assessed. Infusion times &lt; 2 hours with pamidronate or &lt; 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly but there is no evidence upon which to base a recommendation for time intervals. In contrast to multiple myeloma patients, there currently are no data to support routine assessments for albuminuria in patients with breast cancer.</td>
<td>In patients with a calculated serum creatinine clearance &gt; 60 mL/min, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration is required. Use of bone-modifying agents among patients with reduced renal function has been incompletely assessed. The packet insert of zoledronic acid provides guidance for dosing when baseline serum creatinine clearance is ≥ 30 and &lt; 60 mL/min. Infusion times &lt; 2 hours with pamidronate or &lt; 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. The risk of hypocalcemia with denosumab dosed at 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance &lt; 30 mL/min or receiving dialysis. Monitor for hypocalcemia in patients with impaired creatinine clearance. There is no evidence to guide the interval for monitoring serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin with denosumab, pamidronate, or zoledronic acid.</td>
<td>Addition regarding denosumab. A change in serum creatinine clearance threshold. Last sentence of 2003 recommendation taken out. Term changed from bisphosphonates to bone-modifying agents.</td>
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<tr>
<td>Recommendation 3B: ONJ</td>
<td>N/A</td>
<td>ONJ is an uncommon but potentially serious condition associated with the use of bone-modifying agents. The Update Committee concurs with the revised FDA label for zoledronic acid and pamidronate and the FDA label for denosumab and recommends that all patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude the dental assessment. These recommendations should be observed whenever possible. While receiving inhibitors of osteoclast function, patients should maintain optimal oral hygiene and, if possible, avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum. Although most cases of ONJ have occurred in patients treated with IV bisphosphonates and bone-modifying agents who underwent an invasive dental procedure, cases have occurred spontaneously and have been reported in patients treated with other bone-modifying agents, including oral bisphosphonates and direct osteoclast inhibitors.</td>
<td>New recommendation</td>
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### Table 1. Summary of 2011 Recommendations (continued)

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<td><strong>Optimal duration</strong></td>
<td><strong>The Panel suggests that once initiated, IV bisphosphonates be continued until evidence of substantial decline in a patient’s general performance status. The Panel stresses that clinical judgment must guide what is a substantial decline. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.</strong></td>
<td><strong>The Panel suggests that once initiated, bone-modifying agents be continued until evidence of substantial decline in a patient’s general performance status. The Panel stresses that clinical judgment must guide what constitutes a substantial decline. There is no evidence addressing the consequences of stopping bone-modifying agents after one or more adverse skeletal-related events.</strong></td>
<td><strong>(Unchanged in substance from 2003)</strong></td>
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<tr>
<td><strong>Optimal intervals between dosing</strong></td>
<td><strong>For breast cancer patients who have evidence of bone destruction on plain radiographs, IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence relating to efficacy to support one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient’s general performance status and overall prognosis.</strong></td>
<td><strong>For patients with breast cancer who have evidence of bone destruction on plain radiographs, denosumab 120 mg subcutaneously every 4 weeks, IV pamidronate 90 mg delivered over 2 hours, or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended.</strong></td>
<td><strong>Addition of new bone-modifying agent.</strong></td>
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<tr>
<td><strong>Role of bone-modifying agents in pain control</strong></td>
<td><strong>The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and are required by good clinical practice. These standards of care for pain management include analgesics, corticosteroids, interventional procedures, nonsteroidal anti-inflammatory agents, systemic radiopharmaceuticals, and local radiation therapy. Among other therapeutic options, IV pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.</strong></td>
<td><strong>The Panel recommends that the current standards of care for cancer bone pain management be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. This is required by good clinical practice. The standard of care for pain management includes the use of nonsteroidal anti-inflammatory agents, opioid and nonopioid analgesics, corticosteroids, adjuvant agents, interventional procedures, systemic radiopharmaceuticals, local radiation therapy, and surgery. Bone-modifying agents are an adjunctive therapy for cancer-related bone pain control and are not recommended as first-line treatment for cancer-related pain. IV pamidronate or zoledronic acid may be of benefit for patients with pain caused by bone metastases and contribute to pain relief when used concurrently with analgesic therapy, systemic chemotheraphy, radiation therapy, and/or hormonal therapy. Bone-modifying agents have been associated with a modest pain control benefit in controlled trials.</strong></td>
<td><strong>Change in timing of pain management.</strong></td>
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<tr>
<td><strong>Role of biochemical markers</strong></td>
<td><strong>The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care.</strong></td>
<td><strong>The use of the biochemical markers to monitor bone-modifying agent use is not recommended for routine care.</strong></td>
<td><strong>(Unchanged in substance from 2003)</strong></td>
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**Guideline Policy**

ASCO’s practice guidelines reflect expert consensus based on clinical evidence and literature available at the time they are written and are intended to assist physicians in clinical decision making and identify questions and settings for further research. Because of the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline was submitted for publication. Guidelines are not continually updated and may not reflect the most recent evidence. Guidelines address only the topics specifically identified in the guideline and are not applicable to interventions, diseases, or stages of disease not specifically identified. Guidelines cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient’s individual circumstances and preferences. ASCO guidelines describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO guidelines or for any errors or omissions.

### UPDATE METHODOLOGY

**Literature review and analysis**

**Literature search strategy.** For this guideline, computerized literature searches of MEDLINE and the Cochrane Collaboration Library were conducted. Searches of the English-language literature from January 2003 to July 15, 2009, were conducted to address each of the original guideline questions; additional searches on biochemical markers of bone turnover (August 28, 2009) and on ONJ (March 16, 2010) were conducted. A supplemental search limited to randomized controlled trials (RCTs) on efficacy and case-control or cohort studies on adverse events was conducted on November 11, 2010. Search terms

**NOTE.** For each of the recommendations, clinical judgment should also take into consideration the patient’s general performance status, patient preferences, and overall prognosis. Italicized text indicates minor changes. Bolded text indicates substantive changes. Abbreviations: IV, intravenous; CT, computed tomography; MRI, magnetic resonance imaging; FDA, US Food and Drug Administration; N/A, not applicable; ONJ, osteonecrosis of the jaw.
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included the following: “breast neoplasms,” “metastasis,” “bone density conservation agents,” “diphosphonates,” and “biologic markers.” Additional terms included generic and brand names of bone-modifying agents. Searches for efficacy outcomes were limited to published phase III RCTs, systematic reviews, and meta-analyses. For adverse events, the search was broadened to include observational studies because some adverse events of bone-modifying agents are rare. The Update Committee recognized these data as not as significant as data from comparative studies. For biomarker studies, reports were examined of prospective studies or retrospective analyses of prospectively collected samples with prospective aspects. The literature search terms are available in Data Supplement 4. A summary of the literature search results is provided in a QUORUM diagram in Data Supplement 5. Update Committee members provided additional references from personal files.

Inclusion and exclusion criteria. Articles were selected for inclusion if they met the following criteria: participants had metastatic breast cancer and participants were randomly assigned to receive a bone-modifying agent or placebo or an alternative intervention. Outcome measures for efficacy and adverse event studies included at least one of the following: skeletal-related events (SREs) and time to SRE, adverse events, pain, and quality of life (see Definition of Terms).

Data extraction. Relevant articles were selected and reviewed, and one reviewer extracted the data. For each article meeting the inclusion criteria, data were extracted on patient characteristics, study design and quality, intervention, and outcomes. The primary articles and the extracted data were available to the Update Committee and were discussed during the teleconferences.

Study quality and limitations of the literature. The definition of SRE was not uniform across all studies; for example, some studies excluded hypercalcemia of malignancy (HCM). In addition, different efficacy end points were used in different trials. There is a low incidence of some adverse events.

Definition of Terms

SRE. Most clinical trials define an SRE as fracture (pathologic, vertebral, and/or nonvertebral), radiation therapy to bone, surgery to bone, and spinal cord compression. The definition of SREs in a particular study may or may not include HCM. Note that SREs do not include pain, although pain is a skeletal complication of malignancy.

Multiple-event analysis. A multiple-event analysis is an analysis of data on all clinically relevant SREs and time to each event.

Skeletal morbidity rate. The skeletal morbidity rate is the number of SREs per year.1c

Skeletal morbidity period rate. The skeletal morbidity period rate (SMPR) is the number of 12-week periods with new skeletal complications (vertebral and nonvertebral fractures, bone radiotherapy, or bone surgery), divided by the total observational time. This permits assessments of SREs occurring over blocks of time within the study to evaluate the impact that the study interventions may have on the skeletal morbidity rate. The 12-week assessment period includes all complications as a single occurrence, thereby avoiding multiple counting of events, and consequently represents a conservative measure of efficacy. For example, a patient with a pathologic fracture treated with surgery and radiation therapy represents one clinical event, although the patient could be potentially viewed as having three SREs.2,3

Guideline and Conflicts of Interest

The Update Committee was assembled in accordance with ASCO’s Conflict of Interest Management Procedures for Clinical Practice Guidelines (“Procedures,” summarized at www.asco.org/guidelinescoi). Members of the Update Committee completed ASCO’s disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any of these relationships. Disclosure information for each member of the Update Committee is published adjunct to this guideline.

Revision Dates

ASCO guidelines are normally updated every 3 years. At annual intervals, the Update Committee Co-Chairs will determine the need for revisions to the guidelines based on an examination of current literature. If necessary, the entire Update Committee will be reconvened to discuss potential changes. When appropriate, the Update Committee will recommend revised guidelines to the Clinical Practice Guidelines Committee and the ASCO Board for review and approval.

RESULTS

The primary literature search conducted for this update yielded eight RCTs addressing efficacy.1c-8 There were 12 reports of data from these eight RCTs. An additional 11 publications reported efficacy results from studies that were not RCTs, but primarily pooled and subset analyses of RCTs.

Twelve RCTs1c,3,11,15,17 addressed adverse events, reported in 20 publications. Eight publications reported adverse events from cohort studies or other types of studies.12-14,16,18-21 For biomarker reports meeting the inclusion criteria, nine reports were from RCTs of bone-modifying agents, and six reports were from non-RCT studies.

In some cases, there was more than one article reporting on the same trial but reporting outcomes at different time points. Characteristics of the efficacy trials and characteristics of trials reporting on renal adverse events are summarized in Data Supplements 1 and 2.

The Update Committee has evaluated a 2005 Cochrane Collaboration Review and found its conclusions consistent with this ASCO guideline update. Most of the included studies were published before the 2003 ASCO update.

GUIDELINE RECOMMENDATIONS

Note that for each of the guidelines, clinical judgment should also take into consideration the patient’s general performance status, patient preferences, and overall prognosis.

Clinical Question 1

What are the indications for using bone-modifying agents to reduce the risk of SREs in patients with metastatic breast cancer? When is the best time to initiate treatment with bone-modifying agents?
2011 Recommendation 1. For patients with breast cancer who have evidence of bone metastases, denosumab 120 mg subcutaneously every 4 weeks, intravenous (IV) pamidronate 90 mg delivered over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. Starting bone-modifying agents in women with an abnormal bone scan and an abnormal computed tomography scan or magnetic resonance imaging showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs. Starting bone-modifying agents in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, computed tomography scans, or magnetic resonance imaging is not recommended outside of a clinical trial. There is insufficient evidence relating to efficacy to support one bone-modifying agent over another.

Literature update and discussion. This recommendation has been revised since 2003 to include a new bone-modifying agent.

Literature update and discussion: Denosumab. Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor-κ-β ligand, a regulator of osteoclast maturation, differentiation, and survival. Phase I and II clinical trials have demonstrated decreases in bone resorption with denosumab in patients with breast cancer.8,11,22,23 In a Phase III trial published in 2010, patients with metastatic breast cancer involving the bone were randomly assigned to either denosumab 120 mg subcutaneously or zoledronic acid 4 mg IV administered every 4 weeks with corresponding placebo. The primary end point was time to first on-study SRE and demonstrated noninferiority for denosumab (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; P < .001).8 Superiority with time to first on-study SRE, a secondary end point, was met (P = .01) for denosumab. Median time to first SRE was 26.4 months for zoledronic acid and was not reached for denosumab. Grade 3 to 5 adverse events were similar between arms (see Literature update and discussion for Recommendation 3A). ONJ occurred infrequently in both arms (see Literature update and discussion for Recommendation 3B). At the time of the trial’s publication, no statistically significant difference was seen in either disease progression or overall survival between arms.

The suppression of bone resorption and the reduction of SREs with denosumab were demonstrated in patients with breast cancer-related bone metastases in a phase II, randomized, active-controlled (bisphosphonate), multicenter, multidose, parallel group study. In this study, the assigned dose and frequency of administration were blinded for patients receiving denosumab. All doses suppressed urinary N-telopeptide of type I collagen (uNTx)/creatinine (see Literature update and discussion for Recommendation 7 for results from denosumab studies with uNTx end points). SREs measured at 25 weeks occurred in 12% and 16% of patients treated with denosumab and bisphosphonate, respectively.7 Like bisphosphonates, denosumab seems to suppress bone turnover and reduce the risk of SREs in women with metastatic breast cancer to bone.

Literature update and discussion: Zoledronic acid. Since publication of the previous guideline update in 2003, two follow-up studies of a trial reported in that guideline and one new RCT have been published. The new phase III, randomized, placebo-controlled trial of zoledronic acid (4 mg) compared with placebo demonstrated a significant reduction in skeletal complications from metastatic breast cancer (Data Supplement 1).4 At 1 year, the rate of SREs was reduced by 39% in the zoledronic acid group compared with placebo (0.63 v 1.10 events per year). There was an absolute decrease of 20% in the number of patients with at least one SRE in the zoledronic acid group compared with placebo (29.8% v 49.6%, respectively; P = .003). Time to first SRE was significantly delayed for the group treated with zoledronic acid compared with patients on placebo (median, not reached v 364 days, respectively; P = .007). The risk of multiple skeletal events was reduced by 41% in the group treated with zoledronic acid compared with the group on placebo (P = .019). Throughout the study, patients treated with zoledronic acid had consistently reduced composite pain scores, based on the Brief Pain Inventory (BPI), compared with pain scores at baseline and with placebo, although no significant differences between treatment groups were identified with regard to analgesic use (see Literature update and discussion for Recommendation 6).

Follow-up studies of the 2001 RCT of zoledronic acid versus pamidronate found that rates of SREs were not statistically significantly different (46% v 49%12 and 43% v 45%,24 respectively). A multiple-event analysis, which included HCM, favored zoledronic acid 4 mg versus pamidronate (risk ratio, 0.799; 95% CI, 0.657 to 0.972; P = .025).14 A subgroup analysis of women with breast cancer and at least one osteolytic lesion showed that the time to development of an SRE was 178% longer in the zoledronic acid 4 mg arm than in the pamidronate arm (310 v 174 days, respectively; P = .013).24 The subgroup analysis is noteworthy; however, the Update Committee concurs with the 2003 guideline that the data are insufficient to recommend one biphosphonate over another, except in the management of HCM, where zoledronic acid has demonstrated a more rapid normalization and longer duration of maintenance of calculated serum calcium levels.10,11,25,26

The literature search for this guideline found reports on trials of agents that are not FDA approved. Those data are reviewed here but are not incorporated into the recommendations because this guideline focuses on FDA-approved agents. Ibandronate and clodronate are approved for the management of bone metastases from breast cancer in other countries; hence, the guideline will briefly discuss trials of these agents.

Literature update and discussion: Ibandronate. Ibandronate is a highly potent, third-generation aminobisphosphonate developed in both IV and oral formulations. Results of randomized, double-blind, placebo-controlled phase III trials have demonstrated that ibandronate formulations are effective at reducing skeletal complications in patients with metastatic bone disease from breast cancer.

In two prospective trials of women with bone metastases from breast cancer, patients were randomly assigned to treatment with daily oral ibandronate 20 mg or 50 mg or placebo for 96 weeks.2,3 The primary efficacy parameter was the SMRP, which was defined earlier in Definition of Terms. A prespecified pooled analysis of these trials demonstrated a significant reduction in the mean SMPR. The SMPR was statistically significantly reduced with 50 mg of ibandronate compared with placebo (P = .004), and ibandronate reduced the risk of a skeletal event by 38% compared with placebo (Poisson model; hazard ratio, 0.62; P < .001).2 However, the difference in median time to first bone event was not statistically significant between those arms (90.3 weeks with oral ibandronate 50 mg and 64.9 weeks with placebo, P = .089).2

Two randomized, prospective, double-blind, placebo-controlled trials evaluated the efficacy of IV ibandronate. In the first trial of IV ibandronate 2 or 6 mg versus placebo, patients treated with ibandronate 6 mg had a 20% decrease in the mean SMPR compared with the
placebo group (1.19 v 1.48 periods, respectively; \( P = .004 \)). The groups treated with ibandronate (2 or 6 mg) experienced significantly fewer vertebral fractures and events requiring radiation therapy or surgery compared with the group treated with placebo (\( P = .023, P = .012, \text{and} P = .06, \text{respectively} \)). The mean number of new bone events per patient was significantly less in the ibandronate 6 mg treatment group than in the placebo-treated group (2.65 v 3.64 events, respectively; \( P = .032 \)). The time to first new skeletal event was greater in the ibandronate 6 mg group than in both the ibandronate 2 mg group and the placebo group (50.6 v 44.6 v 33.1 weeks, respectively). No major differences in adverse events between the three study arms were identified.

A second trial randomly assigned 150 patients with bone metastases from breast cancer to treatment with placebo or ibandronate 6 mg IV for 24 months.5 The proportion of patients with an SRE was significantly reduced with ibandronate compared with placebo (36% v 48%, respectively; \( P = .027 \)). Furthermore, ibandronate delayed the time to first SRE compared with placebo (median, 457 v 304 days, respectively; \( P = .007 \)). The treatment was well tolerated, and significant renal toxicity was not observed.

A recent review of phase III trials of ibandronate for the treatment of metastatic bone disease from breast cancer concluded that both oral and IV ibandronate reduce the risk of skeletal complications and provide significant relief from metastatic bone pain. Multivariate regression analysis of the data demonstrated a 40% reduction in relative risk with the IV formulation and a 38% reduction in relative risk of progressive skeletal metastases from breast cancer with oral ibandronate.27 Both the IV and oral formulations are approved for use in some countries outside the United States.

There are no new reports on clodronate in the metastatic bone disease setting. Pamidronate was the subject of new study as only a comparator with denosumab in phase II studies.7,11,23,28

**Clinical Question 2**

What is the role of bone-modifying agents in the presence of extraskeletal metastases without evidence of bone metastases?

**2011 Recommendation 2.** Starting bone-modifying agents in women without evidence of bone metastases even in the presence of other extraskeletal metastases is not recommended. This clinical situation has been inadequately studied using IV bisphosphonates or other bone-modifying agents and should be the focus of new clinical trials.

**Literature update and discussion.** This recommendation remains unchanged from 2003. There have been no new clinical trials reported on use of bone-modifying agents for women with extraskeletal metastases who do not have evidence of bone metastases.

**Clinical Question 3A**

What are the renal safety concerns of bone-modifying agent therapy?

**2011 Recommendation 3A.** In patients with a calculated serum creatinine clearance of more than 60 mL/min, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration is required. Use of bone-modifying agents among patients with reduced renal function has been incompletely assessed. The packet insert of zoledronic acid provides guidance for dosing when baseline serum creatinine clearance is \( \geq 30 \) and less than 60 mL/min. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine be monitored before each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. The risk of hypocalcemia with denosumab dosed at 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis. Monitor for hypocalcemia in patients with impaired creatinine clearance. There is no evidence to guide the interval for monitoring serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin in patients on denosumab, pamidronate, or zoledronic acid.

**Literature update and discussion.** Pamidronate and zoledronic acid are associated with renal deterioration, particularly in patients with pre-existing renal impairment and in patients who receive multiple cycles of bisphosphonate therapy. Denosumab has been associated with statistically significantly less renal deterioration than zoledronic acid. In patients with breast cancer with bone metastases, deterioration of renal function was defined as follows: a change in baseline serum creatinine \( \geq 0.5 \text{ mg/dL} \) or \( \geq 2 \times \text{ baseline value in patients with normal baseline serum creatinine (< 1.4 mg/dL)} \); or a change in baseline serum creatinine \( \geq 1.0 \text{ mg/dL} \) in patients with abnormal baseline serum creatinine \( \geq 1.4 \text{ mg/dL} \). The incidence of renal deterioration associated with pamidronate (90 mg) or zoledronic acid (4 mg) ranged between 6.2%14 and 12%.24-29

New dosing guidelines for patients with pre-existing renal impairment were added to the zoledronic acid package insert in January 2005.28 These guidelines recommend a lower initial zoledronic acid dose (ranging from 3.0 to 3.5 mg) depending on the estimated creatinine clearance. The lower doses were calculated to achieve the same area under the curve as that achieved in patients with creatinine clearance of 75 mL/min. No similar dosing guideline exists for pamidronate. Pamidronate and zoledronic acid should be withheld from patients developing renal deterioration, as defined earlier. Once serum creatinine returns to within 10% of baseline, therapy can be resumed. The FDA label states that zoledronic acid therapy should be reintiated at the same dose as that before treatment interruption.

The phase III clinical trial of denosumab versus zoledronic acid required that eligible patients have a creatinine clearance \( \geq 30 \text{ mL/min} \), and there were no denosumab dose adjustments for renal function. In this study, adverse events potentially associated with renal toxicity occurred more frequently with zoledronic acid than denosumab (8.5% v 4.9%, respectively; \( P = .001 \)).8 Osteoclast inhibition may be associated with electrolyte disturbances, and patients with renal impairment may be at increased risk. In the phase III study of denosumab versus zoledronic acid, hypocalcemia occurred in 5.5% of patients in the denosumab arm (grade 3 or 4, 1.6%) and 3.4% of patients in the zoledronic acid arm (grade 3 or 4, 1.2%). The denosumab packet insert states that patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at a greater risk of severe hypocalcemia than patients with normal renal function. The risk of hypocalcemia in patients with a creatinine clearance less than 30 mL/min or receiving dialysis has not been studied in patients receiving denosumab 120 mg every 4 weeks. The Update Committee recommends monitoring of electrolytes and renal function on a regular basis during therapy with bone-modifying agents.

Ibandronate may have a different renal safety profile than pamidronate and zoledronic acid. In randomized placebo-controlled trials, the incidence of renal adverse effects with oral and IV ibandronate was similar to that observed with placebo (approximately 5% in both oral and IV

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trials). The range for renal toxicity with oral ibandronate was 3.5% to 5.2%, and the range with IV ibandronate was 3% to 6%. No definitive conclusions about the comparative safety of ibandronate versus other IV bisphosphonates can be reached from the available data.

Data on the long-term renal safety of bone-modifying agents are limited. A notable increase in serum creatinine was reported in one series of 57 patients with cancer (48 patients with breast cancer) who were treated with either pamidronate or pamidronate plus zoledronic acid every 3 to 4 weeks for more than 24 months (median, 34 months; range, 24+ to 131+ months). In this trial, a significant increase in serum creatinine occurred in seven (12%) of 57 patients. In this trial, bisphosphonates were discontinued in one patient and continued in the remaining six patients. Among the six patients who continued treatment, the serum creatinine returned to normal in two patients and did not increase further in the other four patients.

In an extension of a phase III RCT of IV ibandronate versus placebo, 62 patients either continued or were allowed to cross over to ibandronate for a total of up to 4 years. Six percent of patients in the cross-over arm and 9% in the continuation arm experienced renal deterioration; this compares to a 0.7% and 2.6% increase, respectively, in serum creatinine after the initial phase of the study. A randomized study of 74 patients with metastatic breast cancer involving the bone examined two doses of ibandronate (2 mg infused as a bolus and 6 mg infused over 1 hour). These two ibandronate doses were then compared with a placebo administered monthly over 3 months. During this 3-month period, the renal profiles of both of the ibandronate infusion groups were not associated with impairment of renal function and were similar to the serum creatinine levels in the placebo group. The renal safety profile of ibandronate was also investigated in a randomized, open-label, parallel-group, multicenter, phase II trial comparing ibandronate 6 mg infused over 15 minutes versus 60 minutes every 3 to 4 weeks for up to 6 months; the study included 130 patients. With blood and urine specimens collected before each dose of study drug, the study’s primary end point was percentage of patients whose serum creatinine increased from a baseline of ≥ 44.2 μmol/L (0.5 mg/dL) at any point in the study. Three patients in the 15-minute infusion group experienced an increase in serum creatinine. A central laboratory confirmed this increase in serum creatinine for two patients, but the increase in serum creatinine was considered possibly attributable to concurrent conditions/treatments other than ibandronate in the other patient. No patients in the 60-minute infusion arm had an increase in serum creatinine ≥ 44.2 μmol/L (0.5 mg/dL). Therefore, ibandronate has an acceptable renal toxicity profile.

The Update Committee recommends that clinicians should monitor serum creatinine before each dose of pamidronate or zoledronic acid per FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. The FDA-approved labeling provides no guidance on time intervals for blood chemistry assessment, but it does specify pretreatment creatinine measurement. It is recommended that pamidronate be infused over a period of no less than 2 hours and that zoledronic acid should be infused over a period of no less than 15 minutes every 3 to 4 weeks. Clinicians should not attempt to shorten the infusion time or increase the dose outside of a clinical trial. Reduced intervals between dosing may be considered when treating refractory life-threatening HCM.

Longer follow-up from the zoledronic acid versus pamidronate studies has not changed the 2003 guideline’s conclusion that the safety of the two agents seems to be similar with respect to nonrenal adverse events. Studies of oral ibandronate found slightly higher GI adverse events with ibandronate versus zoledronic acid or placebo and similar rates of myalgia and arthralgia between ibandronate and pamidronate. In a study of IV ibandronate versus placebo, higher rates of arthralgia were observed with ibandronate. The new agent, denosumab, demonstrated similar rates of nausea and vomiting compared with bisphosphonates and lower rates of arthralgia and asthenia. Acute-phase reactions were reported with both bisphosphonates and denosumab, although at lower rates with the latter. In the phase III trial of denosumab versus zoledronic acid, there was a higher rate of acute-phase reactions in the first 3 days of administration of zoledronic acid (27.3% with zoledronic acid vs 10.4% with denosumab).

No new reports of ocular adverse effects were identified within the parameters of this guideline’s literature search. ONJ is discussed in Recommendation 3B. Other postmarketing safety concerns with various uses of bone-modifying agents, including for osteoporosis, have been reported to the FDA. The FDA continues to accept and review these reports. The Update Committee advises clinicians to review the FDA labeling and Web site for updates.

Clinical Question 3B

What are the ONJ safety concerns of bone-modifying agent therapy?

2011 Recommendation 3B. ONJ is an uncommon but potentially serious condition associated with the use of bone-modifying agents. The Update Committee concurs with the revised FDA label for zoledronic acid and pamidronate and the FDA label for denosumab and recommends that all patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude the dental assessment. These recommendations should be observed whenever possible. While receiving inhibitors of osteoclast function, patients should maintain optimal oral hygiene and, if possible, avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum. Although most cases of ONJ have occurred in patients treated with IV bisphosphonates and bone-modifying agents who underwent an invasive dental procedure, cases have occurred spontaneously and have been reported in patients treated with other bone-modifying agents, including oral bisphosphonates and direct osteoclast inhibitors.

Literature update and discussion. ONJ is defined as an area of exposed bone in the maxillofacial or mandibular region that does not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate administered orally or IV and had not had radiation therapy to the craniofacial region. ONJ has been seen in patients treated with denosumab. The exposed bone is necrotic. The population incidence/prevalence and the etiology of ONJ remain unknown. Systems categorizing ONJ have been proposed, but to date, none of these systems has been widely used or has been validated.
ONJ was first reported to the FDA in 2002, the first published reports of ONJ appeared in the dental and medical literature in 2003,3,4 and the first FDA-approved label change appeared in 2004. It is important to note that these early reports of ONJ in patients with cancer treated with bisphosphonates were not based on uniform diagnostic criteria because a working definition of ONJ was not developed until 2006 to 2007.31,32 With the identification of ONJ and its association with bisphosphonate exposure, the FDA labeling of denosumab, pamidronate, and zoledronic acid, the three FDA-approved drugs for the management of bone metastases from breast cancer, advises that patients should maintain good oral hygiene and have preventive dental examinations before initiating therapy, as well as avoid invasive dental procedures whenever possible.25,30,36 Good oral hygiene includes brushing and flossing after meals and use of a fluoride mouth rinse. Although direct evidence of the best way to minimize the risk of ONJ during bone-modifying agent treatment is lacking, it is the expert consensus of the Update Committee to recommend care in line with the FDA-approved labeling.

If an invasive manipulation of the bone underlying the teeth is clinically indicated before starting bone-modifying agent therapy, the Update Committee consensus opinion is that initiation of bone-modifying agent therapy should be ideally delayed for 14 to 21 days to allow for wound healing, if the clinical situation permits. This is based on previous guidelines that have been used for patients with head and neck cancer who are treated with radiation to prevent osteoradionecrosis of the jaw.32 The mechanisms for the development of ONJ in patients treated with bone-modifying agents are under investigation. However, data to support an evidence-based recommendation about the exact waiting period are not available. Therefore, the Update Committee, by consensus, suggests that in the setting of invasive dental procedures, it is advisable, whenever possible, to delay the starting of therapy with bone-modifying agents until the initial bone healing process of the tooth socket bone has taken place.

Several groups have generated position papers on the management of oral health in patients receiving bone-modifying agents, including the American Dental Association, the American Association of Oral and Maxillofacial Surgeons, and the Canadian Consensus Practice Guideline. These documents fall outside the scope of this systematic review. Although it is not the position of the Update Committee to endorse these statements, the Update Committee is in general agreement with the guidance from these groups about dental care before treatment with bone-modifying agents and the recommendation for dental examinations during bisphosphonate treatment, where they are consistent with the FDA-approved label.

The available data on ONJ come primarily from case reports, observational studies, and one systematic review. The incidence of ONJ in patients with metastatic bone disease treated with IV bisphosphonates seems to range between 1% and 10% depending on the specific bisphosphonate, total dose, duration of treatment, and dental history.19,31 The incidence of ONJ specifically in women with breast cancer metastatic to the bone seems to range from approximately 2.5% to 8.8% in cohort studies.21,37,38

Risk factors for ONJ include both bisphosphonate type and duration exposure, with the risk of ONJ increasing with the higher potency drugs (zoledronic acid) and a longer duration of therapy.41 The risk for ONJ occurs with denosumab, pamidronate, and zoledronic acid, whether administered alone or in sequence with other bisphosphonates.8,19,20,37,38 On the basis of a study that included patients with multiple types of cancer, a longer duration of IV bisphosphonate therapy was associated with an increasing risk of ONJ, ranging from 1.5% for patients treated for 4 to 12 months to 7.7% for patients treated for 27 to 48 months.19 ONJ has also been reported in patients receiving oral bisphosphonates31 and denosumab.8,39 In a trial of zoledronic acid and denosumab, the rate of ONJ was not statistically significantly different between the two arms (2% [20 of 977 patients] for denosumab v 1.4% [14 of 985 patients] for zoledronic acid).8

Dental infections and/or extractions, other invasive procedures involving the jaw, and wearing of dentures increase the risks associated with the development of ONJ with bone-modifying agent therapy.8,19,20,31,37,40,41 However, other factors such as comorbid conditions, medications (including bevacizumab), and alcohol and tobacco use have not been consistently correlated with a risk of ONJ with bone-modifying agent therapy. It seems that optimizing oral health may decrease the risk of ONJ during bone-modifying agent therapy.40,41 The Southwest Oncology Group (SWOG) is conducting a registry study to prospectively define ONJ risk factors in patients with metastatic bone disease receiving zoledronic acid (SWOG 0702, NCT00874211). In addition, the Cancer and Leukemia Group B 70604 study (NCT00869206) of patients with metastatic bone disease receiving zoledronic acid dosed either monthly or every 3 months will also generate data on ONJ. Ongoing studies of bisphosphonates for the treatment of metastatic bone disease also now include ONJ as a toxicity end point (NCT00434447 and NCT00320710). In an adjuvant study of bisphosphonates used to decrease the risk of breast cancer relapse, SWOG S0307 (NCT00127205), dental evaluations are performed to gather data on the risk of ONJ in this population. Clinical trials of interventions to treat ONJ are also ongoing and include hyperbaric oxygen therapy (NCT00462098). It has been approximately 10 years since the identification of ONJ, and although much progress has been made to characterize and define the toxicity, much research remains to be performed to better determine and ameliorate risk factors and to offer effective treatment for ONJ associated with bone-modifying agent therapy for breast cancer.

Clinical Question 4

What is the optimal duration of bone-modifying agent therapy for patients with metastatic breast cancer?

2011 Recommendation 4. The Panel suggests that once initiated, bone-modifying agents should be continued until evidence of substantial decline in a patient’s general performance status. The Panel stresses that clinical judgment must guide what constitutes a substantial decline. There is no evidence addressing the consequences of stopping bone-modifying agents after one or more adverse SREs.

Literature update and discussion. This recommendation remains unchanged from 2003. There were no new published prospective clinical trials comparing different durations of bone-modifying agent therapy. In the clinical trials reviewed for this guideline update, durations of therapy ranged from 12 weeks in an early-phase trial of denosumab31 to 96 weeks for the bisphosphonates19,20,37,41 and up to 34 months in the phase III trial of denosumab.8 These studies do not provide data on the impact of either continuing or stopping bone-modifying therapy after a defined time course. In addition, they do not provide sufficient data on the rates of skeletal complications over time to permit estimates on the rate of change in SREs within study groups; however, even with additional details from the existing studies, the
impact of limited versus sustained versus pulsed use of bone-modifying agents could not be assessed.

The median time patients were on study during the phase III clinical trial of denosumab versus zoledronic acid was 17 months, with 45% of patients (> 900 patients) remaining on study at the time of primary analysis, which occurred at approximately 34 months.8 The median time to first on-study SRE was 26.4 months with zoledronic acid and was not reached in the denosumab arm. The 2-year interval from diagnosis of bone metastases to first on-study SRE in the zoledronic acid arm is a marked improvement over the interval seen in earlier phase III studies of zoledronic acid versus pamidronate, where the time to first SRE was approximately 1 year.1c-42

There are no prospective clinical RCT data to support the continued efficacy of bone-modifying agents beyond 1 year. This becomes particularly relevant to patients who are expected to survive beyond 1 year. Patient preference and tolerability of the therapy should also be strongly considered, especially in such cases. The paucity of prospective data addressing long-term toxicities and efficacy of bone-modifying agents does not permit a balanced evaluation of the risk/benefit profile of any long-term bone-modifying agent therapy. Thus, although direct evidence is lacking to show whether or not the benefits of continuing bone-modifying agent therapy beyond 1 year outweigh the risks, the expert consensus of the Update Committee was to continue to support the 2003 recommendation.

Clinical Question 5
What are the best intervals between dosing?

2011 Recommendation 5. For patients with breast cancer who have evidence of bone destruction on plain radiographs, denosumab 120 mg subcutaneously every 4 weeks, IV pamidronate 90 mg delivered over 2 hours, or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended.

Literature update and discussion. Since 2003, there have been three new publications of trials using zoledronic acid. Two studies are further updated analyses of previous trials.1c-24 The first updated analysis is that of the zoledronic acid versus pamidronate trial originally published in 2001 and included in the previous version of this guideline. A 25-month final analysis that used bisphosphonate dose intervals of either every 3 weeks or every 4 weeks evaluated a subset of patients with breast cancer with more than one osteolytic lesion (see Literature update and discussion for Recommendation 1).1c The single new RCT comparing zoledronic acid with placebo used a 4-week dose interval and included 228 participants.9

Concerns exist regarding the dosing interval and duration of therapy. There are limited data on the local (bone surface) bisphosphonate drug concentrations and retention times. These factors are determined by the cellular status of individual bone surfaces, which is affected by the rate of bone turnover, which is influenced by prior bisphosphonate therapy43 and the cancer itself.44,45 There is no new evidence comparing different intervals of administration of either zoledronic acid or pamidronate. Because of a lack of new evidence, the expert consensus of the Update Committee was to continue to support the 2003 recommendation. The Update Committee recognizes that clinical judgment may dictate modifications to dose schedules for a variety of patient-specific indications. As stated elsewhere, research is needed to evaluate this clinical question, and clinical trials are ongoing (NCT00869206 and NCT00320710).

Clinical Question 6
What is the role of bone-modifying agents in control of pain secondary to bone metastases?

2011 Recommendation 6. The Panel recommends that the current standards of care for cancer bone pain management be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. This is required by good clinical practice. The standard of care for pain management includes the use of nonsteroidal anti-inflammatory agents, opioid and nonopioid analgesics, corticosteroids, adjuvant agents, interventional procedures, systemic radiopharmaceuticals, local radiation therapy, and surgery. Bone-modifying agents are an adjunctive therapy for cancer-related bone pain control and are not recommended as first-line treatment for cancer-related pain. IV pamidronate or zoledronic acid may be of benefit for patients with pain caused by bone metastases and contribute to pain relief when used concurrently with analgesic therapy, systemic chemotherapy, radiation therapy, and/or hormonal therapy. Bone-modifying agents have been associated with a modest pain control benefit in controlled trials.

Literature update and discussion. Management of bone pain from cancer may include the use of anticancer therapy for tumor control, systemic or locally directed, as well as medications and interventions to decrease pain. Bone-modifying agents are an adjunctive therapy for pain control. Pain or the manifestation of an SRE is not necessary for the initiation of a bone-modifying agent in a patient with bone metastases from breast cancer. In a new clinical trial of zoledronic acid published since the last guideline, which compares zoledronic acid 4 mg every 3 to 4 weeks with placebo for 1 year, patients treated with zoledronic acid had consistently reduced composite pain scores defined as worst, least, week’s average, and current pain.4 All pain scores were based on the BPI and were compared with baseline levels. Mean pain scores among patients in the placebo arm remained at baseline levels up to week 24 but subsequently increased during the study. Analgesic use was scored on a scale of 0 to 4 (0, no analgesics; 1, minor analgesics; 2, tranquilizers, antidepressants, muscle relaxants, or corticosteroids; 3, mild narcotics; 4, strong narcotics). No significant differences were identified in analgesic use between the placebo and zoledronic acid treatment groups despite higher pain scores and a higher incidence of fractures, need for radiation, and spinal cord compression in the placebo group. Importantly, in the placebo group, 38.9% of patients had a fracture, whereas only 17.7% had radiation, and less than 1% had surgery to the bone. It is not clear how the pain of the nearly 20% of patients who did not have these treatments was managed, and there is a question about whether they received optimal treatment for bone fracture.4

Analyses of bone pain in the follow-up studies of the 2001 RCT of zoledronic acid versus pamidronate showed that the pain levels were similar between groups, indicating that both agents have similar effects on pain.1c,24

In a prospective study of 312 women with metastatic breast cancer to bone, 272 patients were evaluable for pain. At baseline, 247 patients had bone pain, with a mean composite BPI pain score of 3.3. After treatment with zoledronic acid, the pain score (a composite score on the BPI) decreased in 58% of patients, and analgesic use declined in 57% of patients using analgesics at baseline.46 Analgesic use was scored the same as described for the study discussed in the beginning of this section. However, this study lacked a comparison group, making conclusions difficult.
Although ibandronate is not FDA approved in the United States, it is available elsewhere and may have a role in pain control in these settings. Two prospective trials randomly assigned women with bone metastases from breast cancer to placebo or oral ibandronate for up to 96 weeks. In a pooled analysis, bone pain was decreased and maintained below baseline levels throughout the trial in the group treated with oral ibandronate (P = .001 and P = .019, respectively) compared with placebo.47

In a trial of oral ibandronate 20 or 50 mg versus placebo, pain scores were reduced in the 20-mg arm versus placebo, but this reduction was not statistically significant (P = .071). No significant difference in pain scores was observed between the 50-mg dose and placebo arms (P = .201). However, the difference for analgesic use between the 20-mg group and the placebo group was statistically significantly lower in the 20-mg group (P = .066); it approached significance for the 50-mg group (P = .074).4 In another study of oral ibandronate (50 mg/d) versus zoledronic acid (4 mg every 4 weeks), in which pain was a secondary outcome, mean changes from baseline in either pain or analgesic medication use were not significantly different between the two groups, although higher rates of pain were reported in the zoledronic acid group compared with the ibandronate group (12.4% v 5.8%, respectively).4

Oral ibandronate has also been studied for second-line use in a phase II cohort study. All patients had received prior treatment with IV bisphosphonates and also had SREs or progressive bone metastases. The median duration of prior bisphosphonate use was 20 months (range, 3 to 69 months). Almost half of the cohort of 30 patients taking second-line oral ibandronate experienced a palliative response at 8 and 12 weeks, defined as a decrease of ≥ 2 units in the worst BPI score. In addition, there was a statistically significant decrease in several other measures, including the number of pain sites adjusted for on-study analgesic use (baseline, 2.6 sites; 8 weeks, 1.9 sites, P = .037; 12 weeks, 1.5 sites, P = .004).48

One of two randomized, prospective, double-blind, placebo-controlled trials that evaluated the efficacy of IV ibandronate reported on pain outcomes.6 The trial administered either 2 or 6 mg of ibandronate or placebo. Patients in the ibandronate 6 mg group had rapid decreases in their pain scores after the initiation of treatment and significantly improved mean pain scores compared with the patients in the placebo group or ibandronate 2 mg group, who experienced increases in pain.

In a separately published analysis of quality-of-life outcomes from an international ibandronate trial, there was a statistically significant mean decrease in bone pain score for the ibandronate 6 mg arm versus placebo (P < .001). Although the analgesic consumption score (measured on a scale of 0 to 6 as follows: 1, mild analgesic or nonsteroidal anti-inflammatory drug; 2, mild analgesic and nonsteroidal anti-inflammatory drug; 3, moderate analgesic; 4, 5, and 6, opiate use at increasing levels) was decreased in the 6-mg group, this decrease in analgesic consumption was not statistically significant.16

In a review of three phase III trials of ibandronate (both IV and oral formulations), bone pain was reduced below baseline levels for more than 2 years (P = .001) compared with placebo.20 Reports on pain outcomes from the phase III denosumab trial were not available when this guideline update went to press.

Clinical Question 7

What is the role of biochemical markers of bone turnover to guide initiation of therapy in patients without a prior skeletal event, predict treatment response, guide adjustments to bone-modifying agent therapy, or independently predict future fractures?

2011 Recommendation 7. The use of the biochemical markers to monitor bone-modifying agent use is not recommended for routine care.

Literature update and discussion. This recommendation remains unchanged from 2003. Patients with metastatic bone disease and elevated markers of bone resorption may have an increased risk for SREs and poor outcomes.49-51 Markers of bone formation and bone resorption can be measured in the blood or urine (Table 2). Osteoclast inhibition can decrease or normalize the markers of bone resorption. The association between markers of bone metabolism as a surrogate of osteoclast activity and risk of SREs has been investigated. The literature review for bone resorption markers used in bisphosphonate research identified at least two publications on each of the following markers: N-telopeptide of type I collagen (NTX), C-telopeptide of type I collagen (CTX), bone-specific alkaline phosphatase (BALP), osteocalcin, amino-terminal propeptide of type I collagen (PINP), interleukins, deoxypyridinolines, calcium, cystatin C, and vascular endothelial growth factor. In addition, the search yielded single publications on eight additional markers.

Biochemical markers are of interest because it is hypothesized that they could be used for the purposes of diagnosing SREs, predicting SREs and/or the risk of SREs, predicting whether a patient will benefit from receiving a particular bone-modifying agent, aiding selection of a particular agent, and/or monitoring response during treatment. The markers found by this systematic review were investigated for the primary purposes of monitoring, predictive value (including pain reduction), and diagnostic accuracy. Changes in markers of bone metabolism may be able to provide a relatively rapid indication of the balance between bone resorption and formation.52 Excessive bone resorption may be predictive of SREs and cancer progression.49,53,54 To demonstrate clinical utility, an RCT with SREs as a primary end point is necessary. Such evidence is not yet available. The evidence is insufficient to recommend the use of markers of bone turnover outside of a clinical trial. The systematic review focuses on the following five markers with the most robust data: NTX, CTX, BALP, osteocalcin, and PINP.

Literature update and discussion: NTX. Type I bone collagen degradation products, cross-link–associated telopeptides (NTX and CTX) of collagen, are released during osteoclast-mediated bone resorption and can be measured in the blood or urine.55 The systematic review found six publications using NTX that met the search criteria.

Table 2. Biochemical Markers

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<td>Bone-specific alkaline phosphatase (BALP)</td>
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<td>Osteocalcin</td>
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<td>Propeptide of type I collagen (PINP)</td>
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<th>Markers of bone resorption</th>
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<td>C-terminal propeptide of type I collagen (CTX)</td>
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<td>N-terminal propeptide of type I collagen (NTX)</td>
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seven studies measured uNTX,7,8,11,17,28,49,56 and one study measured serum NTX.11 In three studies, NTX was used to monitor response to treatment.7,11,28 One study used NTX as a prognostic factor.49 One study looked at the marker’s correlation with the pain score,86 and one study measured retention of bisphosphonates according to different times of administration.17 Four studies were RCTs with changes in NTX as primary and/or secondary outcomes7,11,17,28 and three were exploratory analyses of clinical trial data.8,49,56 It seems that elevated levels of NTX or NTX levels that do not decrease in response to bisphosphonate therapy are associated with an increased risk of SREs49,51 and studies have measured decreases in NTX secondary to bisphosphonate therapy.

Three trials of denosumab versus bisphosphonate7,11,28 used changes in uNTX as primary end points. In the largest study (see Literature update and discussion for Recommendation 1), at week 13, the median percent changes from baseline were −73% and −79% in the cohorts treated with denosumab and bisphosphate, respectively.7 Among patients with at least one postbaseline measurement of uNTX at week 25, 52% of the patients (109 of 208 patients) treated with denosumab and 46% of the patients (19 of 46 patients) treated with a bisphosphonate had a greater than 65% reduction in uNTX/creatinine.

A small randomized study of patients with either multiple myeloma or breast cancer compared denosumab and pamidronate. In the parallel-dosing phase of the study, levels of uNTX and serum NTX decreased after a single dose of subcutaneous denosumab. The reduction in bone resorption with denosumab was dose dependent, and the duration of treatment effect was at least 84 days.11

Another study randomly assigned 111 patients (46 with breast cancer), after 8 weeks of bisphosphonate therapy, to receive either additional bisphosphonate therapy or denosumab. The primary end point of reducing uNTX levels to less than 50 nmol/L bone collagen equivalents/mM creatinine at week 13 was achieved in 76% of patients with breast cancer in the denosumab group compared with 33% of patients in the bisphosphonate group.28

In a prospective cohort study of patients with metastatic breast cancer involving the bone, the effect of changing from pamidronate or clodronate to zoledronic acid was assessed for changes in uNTX, pain, and quality of life.57 Although the analysis was limited by the small sample size, a decrease in uNTX at 1 week after initiation of bisphosphonates was associated with a decrease in pain score at week 8 (odds ratio, 9.4; 95% CI, 2.28 to 79.8).

In a phase III RCT of denosumab versus zoledronic acid where change in uNTX was an exploratory end point, the percent change from baseline to week 13 was 80% versus 68%, respectively (P < .001).8

At present, there are no published studies in which participants have been assigned to treatment based on NTX status; however, the ongoing Cost-Effective Use of Bisphosphonates in Metastatic Bone Disease: A Comparison of Bone Marker Directed Zoledronic Acid Therapy to a Standard Schedule (BISMARK) trial (NCT00458796) compares bone marker–directed treatment intervals versus standard treatment intervals of zoledronic acid.

Literature update and discussion: CTX. Like NTX, this biochemical marker of bone resorption has been evaluated for monitoring response to osteoclast inhibition therapy. In a phase III study comparing the effect of oral ibandronate versus zoledronic acid on markers of bone metabolism, the two drugs equally decreased the serum CTX and urinary CTX (uCTX) in women with metastatic breast cancer involving the bone.6 In a placebo-controlled study of oral ibandronate versus placebo, there was a dose-dependent decrease in uCTX from baseline in the two ibandronate arms (−39% for ibandronate 20 mg; −55% for ibandronate 50 mg; 34%79 for placebo; P < .001).7 This finding was echoed in a second report of ibandronate (50 mg) versus placebo in patients with metastatic bone disease; uCTX at 96 weeks showed a median change of −77% from baseline with ibandronate therapy.2

Literature update and discussion: Osteocalcin. Osteocalcin is a specific product of osteoblasts and reflects bone formation. In one study, this marker did not show discriminative diagnostic ability for bone metastases but showed a statistically significant difference for patients with more versus less than seven metastases.58 In the study comparing ibandronate with zoledronic acid in patients with bone metastases from breast cancer, there was a decrease of 26% (ibandronate) to 35% (zoledronic acid) in osteocalcin.7

Literature update and discussion: BALP. BALP is also a bone formation marker associated with osteoblasts. In the study of ibandronate versus zoledronic acid, both therapies decreased BALP by 26% (zoledronic acid) to 37% (ibandronate) from baseline. In a study of denosumab versus zoledronic, mean BALP levels decreased 44% versus 37%, respectively (P < .001).8 In an analysis of the three phase III clinical trials investigating zoledronic acid and SREs, an elevated BALP correlated with a higher risk of SREs, although this was not statistically significant for the breast cancer subgroup (relative risk, 1.35; 95% CI, 0.93 to 1.96; P = .109).49

Literature update and discussion: PINP. PINP is product of proliferating osteoblasts and fibroblasts and serves as a bone formation marker. In the study of ibandronate versus zoledronic acid in women with metastatic breast cancer involving the bone, both drugs decreased the PINP by 39% (zoledronic acid) to 47% (ibandronate). In a prospective case-control study, PINP was elevated in patients with more than seven bone metastases. In this small study, PINP tracked with disease status, increasing at progression of disease and decreasing with osseous response to therapy, suggesting that PINP may correlate with response to therapy.58

In summary, although there have been several studies showing decreases in bone resorption or formation markers after administration of bone-modifying agents, the studies’ designs do not permit conclusions about the clinical utility of these markers. Until the time that properly defined markers studies demonstrate clinical utility, the use of biomarkers to guide or monitor bone-modifying agent therapy is not recommended outside of a clinical trial.

Special Commentary on the Role of Vitamin D Deficiency and Bone-Modifying Agents

Vitamin D deficiency is associated with increased breast cancer risk and decreased breast cancer survival after adjustment for tumor- and treatment-related factors.59,60 Vitamin D is essential for promoting calcium absorption in the gut, maintaining adequate serum calcium and phosphate levels, and normal mineralization of bone.61 Although many of the trials of bone-modifying agents have included supplementation of calcium and vitamin D as part of the treatment regimen, there are insufficient data to support a recommendation for a specific level of supplementation. Optimal concentrations of vitamin D for bone health have not been established and are likely to vary at different stages of life and in different clinical settings.
In the absence of definitive data, it is the Update Committee’s expert consensus that if there are no contraindications to calcium and vitamin D supplementation, then patients receiving bone-modifying agents should receive them at doses and schedules similar to those used in the clinical trials of the bone-modifying agents, both to support bone health and decrease the risk of bisphosphonate-induced hypocalcemia. US health authorities generally recommend a minimum consumption of vitamin D of 200 U (5 μg) a day. For the prevention and treatment of osteoporosis in adults, vitamin D 800 U daily is often recommended. Calcium and vitamin D are discussed further in the following section.

**LIMITATIONS OF RESEARCH AND SUGGESTIONS FOR FUTURE RESEARCH**

**Duration**

The optimal duration of bone-modifying agent therapy has not yet been defined. Hypotheses exist in support of either prolonged or limited courses of bone-modifying agent therapy to decrease the risk of SREs. The recommendation (see Recommendation 4) that bone-modifying agent therapy be continued indefinitely is based on the observation that SREs can occur repeatedly over the course of the disease process, given the assumption that the risk of SREs continues over the patient’s life span and that risk may increase with progression of disease in bone. A counterargument to using IV bisphosphonates beyond 1 year of therapy is based on the biochemical property of bisphosphonates accumulating in the skeleton. There is a potential for the bisphosphonates to provide a pharmacologic effect that may persist for long periods of time. It has been proposed that there is continual recycling of bisphosphonate off and back onto the bone surface. This is supported by observations that bisphosphonates can be found in plasma and urine many months after dosing. This has led to the theory of loading the bone at initiation of bisphosphonate therapy and subsequently stopping or altering the interval of dosing the bisphosphonate. It is important to note that components of this strategy are being investigated clinically, but presently, there are no data to address the efficacy of such an approach for any outcomes. Future trials may include investigation of pulse bone-modifying agent therapy. Additional data may enable the development of an index of risk for SREs, and a patient’s individual risk/benefit calculation may guide bone-modifying agent therapy at various points in the management of the cancer. Clinical trials are needed to explicitly explore the risk/benefit profile associated with each approach.

**Intervals**

There is a need for clinical trials that explicitly compare different intervals between treatment with bone-modifying agents to learn the effects on relevant clinical outcomes, such as SREs, time to SRE, pain, and adverse events, evaluated in this guideline. The BISMARK trial (NCT00458796), which randomly assigns participants to different treatment intervals and uses NTX status, may provide data addressing this issue.

**Extraskeletal Metastases**

Currently, there is no evidence to support offering bone-modifying agents to women who do not have evidence of bone metastases, even if they have extraskeletal metastases. Using bone-modifying agent therapy for women with breast cancer in the adjuvant setting has been a focus of recent trials; this topic will be addressed in a separate ASCO guideline update. Currently, limited data from the use of bisphosphonates in the adjuvant setting do not conclusively demonstrate significant impact on the incidence of bone metastases.

The impact of bone-modifying agents in patients with stage IV breast cancer and no bone metastases has not been defined. Therefore, trials specific to whether this population would benefit from initiating bone-modifying agents without evidence of bone metastasis are needed. In addition, the Update Committee suggests including research questions specific to duration and interval of bone-modifying agent administration in future trials.

**Subgroups**

To date, publications of bone-modifying agent trials have not analyzed SRE prognosis or treatment benefit based on subgroups of participants with different demographic and clinical characteristics. Stratification and analysis by such factors as sex, estrogen receptor/progesterone receptor status, human epidermal growth factor receptor 2 status, ethnic and racial status, and whether a given participant has bone-predominant disease versus visceral-dominant disease could help identify whether any of these factors are relevant in selecting the use of bone-modifying agents for patients.

**Denosumab**

Since the publication of the 2003 guideline, phase III clinical trials have studied denosumab, a monoclonal antibody to receptor activator of nuclear factor-κ-β ligand. In addition to trial results discussed in this guideline update, the Update Committee awaits the results of ongoing clinical trials of denosumab.

**Other Bone-Modifying Agents**

Novel therapeutic interventions targeting the bone or the bone microenvironment are in development for their ability to affect bone metastases. These drugs include tyrosine kinase inhibitors such as dasatinib (NCT00410813 and NCT00566618), anti-CCR2 monoclonal antibody MLN1202 (NCT01015560), and cathepsin K inhibitors, as well as others including novel radiopharmaceuticals tagged on a bisphosphonate. The Update Committee awaits the results of investigations of other bone-modifying agents that may be incorporated into future updates.

**Biomarkers**

Markers of bone turnover reflect the status of bone metabolism. There is a need for more research on biochemical markers to incorporate these biochemical signals into directing patient therapy. Biochemical markers of bone turnover may be developed such that they could aid the decision on whether to initiate bone-modifying therapy or perhaps be used to select a specific drug. During therapy, biochemical markers of bone turnover may aid in assessing the efficacy of the bone-modifying agent or in modifying drug dose, drug schedule, duration of therapy, or point to when a change in therapy may be indicated. As bone markers are developed, a given biomarker has to be prospectively attached to a relevant clinical outcome. The ongoing BISMARK study may provide results applicable to this question (NCT00458796). The study is randomly assigning patients to treatment schedules using NTX status.
Vitamin D

Research is needed regarding the optimal dosing of calcium and vitamin D and the role of vitamin D levels in individualizing vitamin D supplementation in patients with metastatic breast cancer who are treated with bone-modifying agents. In the absence of data and with the increasing recognition of the prevalence and the negative health impact of subclinical vitamin D deficiency, higher vitamin D intake is frequently recommended. The Institute of Medicine found insufficient scientific data on which to base recommended daily allowances for vitamin D, so it provided advice on adequate intake levels instead. The tolerable upper intake level of vitamin D for adults is 2,000 U/d. Given studies showing significant differences in vitamin D levels in women with breast cancer, monitoring of vitamin D levels and individualization of vitamin D supplementation to achieve normal levels are considered prudent until further studies are performed. The Update Committee suggests that clinicians consider calcium supplementation for women with low absorption or inadequate dietary intake of calcium. Although the optimal intake has not been clearly established, 1,200 to 1,500 mg of elemental calcium daily is generally recommended for women who are postmenopausal. In women who are premenopausal, the usual recommendation for daily calcium supplementation is 1,200 mg daily.

A recent report suggesting a link between calcium supplements and an increased risk of cardiovascular events has sparked concern. Although some literature has suggested a possible increase in risk, this finding is not uniform, and other studies have not provided evidence of increased risk. The Update Committee suggests that those considering prescribing calcium supplements to their patients be aware of the potential concern about cardiovascular events and stay updated as the data continue to evolve.

Comparative Effectiveness Research and Other Research Needs

Comparative effectiveness research is needed to help determine which subpopulations benefit from treatment and which treatment schedules, including duration of bone-modifying agent therapy, are most beneficial in the treatment of bone metastases from breast cancer. Relevant clinical outcomes include pain relief, defined as a reduction in needed analgesics; improved function; and reduced morbidity from SREs. Comparative effectiveness research also needs to determine how to optimize the use of other modalities, such as radiation therapy, for bone metastases. The physical and personal burdens of therapy on patients and caregivers need to be considered within comparative effectiveness research.

Researchers should consider research on how and when bone-modifying agents should be integrated with other therapies, such as radiotherapy (localized and systemic), for bone metastases from breast cancer, including the following areas: use of systemic therapy with bone-modifying agents, reserving other therapies (surgery and radiotherapy) for the progression of localized bone metastases; multimodal therapy of bone metastases, administering radiotherapy (external-beam radiation) to the symptomatic site while initiating systemic therapy with bone-modifying agents; treating bone metastases only with radiotherapy (external-beam radiation or radiotherapeutics), reserving systemic therapy with bone-modifying agents for progression of bone metastases; timing of bone-modifying agent therapy in the setting of bone healing from orthopedic surgery or pathologic fracture; combining or sequencing bone-modifying agents over the course of patient care; and selecting a bone-modifying agent to attempt synergy with systemic therapy.

Communicating the risks and benefits of treatments, including supportive care, is an important aspect of cancer care. It is also essential that patients are informed about expected outcomes from cancer treatments (eg, extending life, improving quality of life) and that patients have opportunities to assess their treatment values throughout the course of therapy. This update and other peer-reviewed publications of clinical trials provide information to clinicians regarding the consideration of benefits and potential risks of bone-modifying therapy in the setting of metastatic breast cancer. Information from these peer-reviewed publications then must be related to the individual patient’s characteristics by the clinician. A search for publications about clinician-patient communication regarding bone-modifying agent use was conducted separately from the systematic review but did not yield any published results.

Communication needs to include the rationale for bone-modifying agent therapy, and the goals of this therapy need to be established with the patient. The goal of therapy for bone-modifying agents includes the reduction of skeletal morbidity and is not intended to increase survival in this setting. Skeletal morbidity involves both the reduction of fracture rate and avoidance of bone pain. The physician should also relate that the initiation and continued administration of bone-modifying agents, like any therapy, depends on the clinical status of the patient.

The toxicities of therapy, relative to the toxicity and complications of the disease process, are especially important to review. Long-term and short-term toxicities of therapy are relevant because a patient with metastatic breast cancer to the bone may survive for several years. Toxicities and investment of time in therapy are especially important among patients with poor prognoses. With a poor prognosis, each day consumed in therapy and toxicity represents a greater percentage of the patient’s remaining survival. As an ongoing process, it is important for physicians to determine with the patient whether the investment of time and potential toxicities are felt to provide sufficient therapeutic benefit. It is also important that clinicians and patients understand the guidelines related to ONJ and risk of renal toxicity and that they have educational tools to use these guidelines.

As always, information should be conveyed at an educational level that the patient understands. Asking patients to repeat back key pieces of information can be helpful in determining their level of comprehension. ASCO’s Cancer.net “What to Know” guide about this guideline regarding the use of bone-modifying agents in metastatic breast cancer is also an important resource for patients.

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer from minority racial/ethnic groups...
suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor-quality care than other Americans. Many other patients lack access to care because of their geography and distance from appropriate treatment facilities and/or lack of transportation to and from health care facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

A literature search for health disparities related to breast cancer and bisphosphonate use, performed separately from the systematic review, did not yield any published results. However, the primary literature search identified a longitudinal study of pain outcomes by race based on participants in the 2001 zoledronic acid trial and found race predictive of pain. One hundred thirty-three of the 1,124 participants with breast cancer were of a nonwhite race. Patients in the nonwhite group experienced higher risks of pain severity, interference in their daily activities/feeling states as a result of pain, and greater worsening of pain, as measured by the BPI. The analysis did not stratify outcomes by treatment arm and did not assess analgesic adequacy. The authors suggest that early intervention for pain among nonwhite women with breast cancer metastatic to the bone may improve pain outcomes.

**REFERENCES**


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