Guideline Summaries

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

Catherine H. Van Poznak, MD, Jamie H. Von Roenn, MD, and Sarah Temin, MSPH

University of Michigan, Ann Arbor, MI; Lurie Comp Cancer Center of Northwestern University, Chicago, IL; American Society of Clinical Oncology, Alexandria, VA

Journal of Clinical Oncology (*JCO*) recently published ASCO's update to its guideline on the use of bone-modifying agents for patients with breast cancer with bone metastases.[1] A commentary on this guideline appears in this issue of *Journal of Oncology Practice*. ASCO first published evidence-based clinical practice guidelines for use of bisphosphonates in breast cancer in 2000 and updated these guidelines in 2003. In its current update, the scope was narrowed to the use of bone-modifying agents for patients with evidence of bone metastases. The updated guideline uses the term "bone-modifying agents" to encompass both bisphosphonates and newer osteoclast inhibitors. The topic of the use of bone-modifying agents for the adjuvant treatment of breast cancer and in managing treatment-associated bone loss will be covered in a separate guideline update.

The guideline is based on a systematic search and review of the literature. The recommendations on efficacy are based only on phase III randomized controlled trials. The primary outcome of interest in these trials was skeletal-related events (SREs), the definition of which typically includes fracture, radiation to the bone, surgery to the bone, and spinal cord compression and may or may not include hypercalcemia of malignancy.

Six of the eight recommendations are substantively unchanged from the 2003 guideline update. A new recommendation was added regarding osteonecrosis of the jaw, a condition recognized after the preparation of the 2003 guidelines. This guideline on metastatic breast cancer also added a new bone-modifying agent, denosumab (Table 1). 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, duration of therapy of bone-modifying agents, or pain management. These recommendations appear in Table 2. The adverse event recommendations, including the new recommendation for osteonecrosis of the jaw, rely on evidence from randomized controlled trials, case-control, and cohort studies (Table 3).

The guideline reviews data from studies on biomarkers, however, it continues to recommend against their routine use 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, unless the patient is enrolled onto a clinical trial (Table 3). The markers found by this systematic review were investigated for the primary purposes of monitoring, predictive value (including pain reduction), and use as a diagnostic tool.

The guideline includes a special commentary on the role of vitamin D deficiency and bone-modifying agents. Currently, there are insufficient data on which to base a recommendation on the level of vitamin D and calcium supplementation for patients taking bone-modifying agents. It also includes a section on research the Update Committee recommends be conducted to address outstanding questions, including questions on dose interval and duration of therapy of bone-modifying agent therapy.

The tables in this article are reprinted from the recent Guideline Update and provide the updated recommendations. JCO published an Executive Summary of the guideline[1], which presents a brief summary overview of the complete ASCO Clinical Practice Guideline Update and a brief discussion of the relevant literature for each updated recommendation. The complete guideline, including comprehensive discussions of the literature, a description of methodology, all cited references, and a data supplement, which contains the evidence tables used to formulate these recommendations, is available at www.asco.org/guidelines/bisphosbreast, along with a patient guide. As in other ASCO Guidelines, the full Guideline Update includes a discussion of Patient Communication and Health Disparities relevant to this topic. A slide set is provided as an online Data Supplement of this article.

Authors

ASCO Clinical Practice Guideline Update Recommendations on the Role of Bone-Modifying Agents in Metastatic Breast Cancer was developed and written by Catherine H. Van Poznak, MD; Sarah Temin, MSPH; Gary C. Yee, PharmD, Nora A. Janjan, MD, MPSA, MBA, FACP, FAC; William E. Barlow, PhD; J. Sybil Biermann, MD; Linda D. Bosserman, MD, FACP; Cindy Geoghegan, Bruce E. Hillner, MD; Richard L. Theriault, DO; Dan S. Zuckerman, MD; and Jamie H. Von Roenn, MD.

Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314;e-mail: guidelines@asco.org.

Table 1. New Bone-Modifying Agent

Recommendation Category	2003 Recommendations	2011 Recommendations	Change
Indications and time of initiation	For breast cancer patients who have evidence of bone destruction on plain radiographs, IV pamidronate 90 mg delivered over 2 h or zoledronic acid 4 mg over 15 min every 3 to 4 wk are 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.	For *patients with breast cancer* who have evidence of bone **metastases, denosumab 120 mg subcutaneously every 4 wk,** or IV pamidronate 90 mg delivered over no less than 2 h, or zoledronic acid 4 mg over no less than 15 min every 3 to 4 wk 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.	Addition of new bone-modifying agent. Term changed from bisphosphonates to bone-modifying agents.

Note: Bolded text indicates substantive changes. Italicized text indicates minor changes.
Abbreviations: IV, intravenous; CT, computed tomography; MRI, magnetic resonance imaging; h, hours; min, minutes; wk, weeks.

THE BOTTOM LINE

ASCO GUIDELINE UPDATE

The Role of Bone-Modifying Agents 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 IV 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 exam and preventive dentistry before receiving 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, the full guidelines, data supplements including evidence tables, and Clinical Tools and Resources are available at www.asco.org/guidelines/bisphosbreast.

Table 2. Additional Efficacy and Pain Recommendations

Recommendation Category	2003 Recommendations	2011 Recommendations	Change
Role of bone-modifying agents in the presence of extraskeletal metastases	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.	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.	*(Unchanged in substance from 2003)* Term changed from bisphosphonates to bone-modifying agents.
Optimal duration	The Panel suggests that once initiated, intravenous 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.	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.	*(Unchanged in substance from 2003)* Term changed from bisphosphonates to bone-modifying agents.
Optimal intervals between dosing	For breast cancer patients who have evidence of bone destruction on plain radiographs, intravenous pamidronate 90 mg delivered over 2 h or zoledronic acid 4 mg over 15 min every 3 to 4 wk are 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.	For *patients with breast cancer* who have evidence of bone destruction on plain radiographs, **denosumab 120 mg subcutaneously every 4 wk**, IV pamidronate 90 mg delivered over 2 h, or zoledronic acid 4 mg over 15 min every 3 to 4 wk are recommended.	Addition of new bone-modifying agent. The second-to-last sentence of 2003 recommendation is in Recommendation 1 of 2011 recommendations. The last sentence from 2003 recommendation applies to all recommendations.
Role of bone-modifying agents in pain control	The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and is 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.	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.	Change in timing of pain management. Term changed from bisphosphonates to bone-modifying agents.

Note: Bolded text indicates substantive changes. Italicized text indicates minor changes.
Abbreviation: IV, intravenous; CT, computed tomography; MRI, magnetic resonance imaging; h, hours; min, minutes; wk, weeks.

Table 3. Adverse Event Recommendations

Recommendation Category	2003 Recommendations	2011 Recommendations	Change
Renal safety concerns	In patients with *pre-existing renal disease and a serum creatinine less than 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 less than 2 h with pamidronate or less than 15 min 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 is no data to support routine assessments for albuminuria in breast cancer patients.**	In patients with **a calculated serum creatinine clearance > 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 < 60 mL/min.** Infusion times less than 2 h with pamidronate or less than 15 min 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 wk 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 with denosumab, pamidronate, or zoledronic acid.*	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.
Osteonecrosis of the jaw	N/A	**Osteonecrosis of the jaw (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.**	New recommendation
The role of biochemical markers	The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care.	The use of the biochemical markers to monitor *bone-modifying agent* use is not *recommended* for routine care.	*(Unchanged in substance from 2003)* Term changed from bisphosphonates to bone-modifying agents.

Note: Bolded text indicates substantive changes. Italicized text indicates minor changes.
Abbreviations: IV, intravenous; h, hours; min, minutes; wk, weeks.

Accepted for publication on January 19, 2011.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Catherine H. Van Poznak, Amgen (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Catherine H. Van Poznak, Amgen, Novartis **Expert Testimony:** None **Other Remuneration:** None

Author Contributions

Conception and design: Catherine H. Van Poznak, Jamie H. Von Roenn, Sarah Temin

Administrative support: Sarah Temin

Collection and assembly of data: Catherine H. Van Poznak, Sarah Temin

Data analysis and interpretation: Catherine H. Van Poznak, Jamie H. Von Roenn, Sarah Temin

Manuscript writing: Catherine H. Van Poznak, Jamie H. Von Roenn, Sarah Temin

Final approval of manuscript: Catherine H. Van Poznak, Jamie H. Von Roenn, Sarah Temin

DOI: 10.1200/JOP.2011.000212

Reference

1. Van Poznak CH, Temin S, Yee GC, et al: American Society of Clinical Oncology executive summary of the clinical practice guideline update recommendations on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol doi:10.1200/JCO.2010.32.5209

Commentary: Role of Bone-Modifying Agents in Metastatic Breast Cancer

By Gabriel N. Hortobagyi, MD, FACP

Bone is the most frequent target of metastatic breast cancer, and although bone metastases are not life threatening, some of the complications (spinal cord compression, hypercalcemia) can be.[1] More important, bone metastases and their complications can be substantially disabling, require multiple interventions, and are costly to the patient and the health care system. Until about 1990, there were no approved drugs for the management of bone metastases, although there was much interest in agents to control hypercalcemia (calcitonin, vitamin D, mithramycin, etc). In the latter part of the 1980s, exciting reports indicated that bisphosphonates were effective in control of hypercalcemia, and a number of clinical trials were initiated to determine the benefit of these agents in the management of patients with bone metastases. Clinical trials demonstrated that both clodronate and pamidronate had some analgesic effect and reduced the risk of bone-related complications (skeletal-related events), such as pathological fractures, hypercalcemia, and spinal cord compression, while reducing the need for palliative radiotherapy and surgery.[2-5] As a result, these agents were rapidly incorporated into the treatment of patients with bone metastases, first in breast cancer and multiple myeloma and subsequently other cancers that targeted bone. Ibandronate and zoledronic acid followed, with clinical trials demonstrating that the latter was significantly more effective than earlier generation bisphosphonates for control of bone metastases and reduction of skeletal-related events.[6-7] Bisphosphonates were shown to be more effective and/or easier to use than previously existing agents (calcitonin, mithramycin) or newer agents with established activity (gallium nitrate). Over a short period of time, bisphosphonates became part of the standard of care for metastatic cancers, and clinical trials were initiated to determine their contribution to curative treatment of primary malignancies. It is clear that the addition of bisphosphonates to multidisciplinary treatment strategies has dramatically altered the clinical course of bone metastases. Hypercalcemia has decreased drastically in incidence and severity, as have bone pain, pathological fractures, and the need for palliative radiotherapy and surgery. This is an important achievement, as patients with bone metastases live longer than those with metastases to other organs and therefore, their symptoms are present for a longer time, as is the disability they cause.

Although well tolerated, bisphosphonates do have a few adverse effects: infusion-related reactions and hypocalcemia are occasionally seen, although they are self-limited and reversible.[6] Of greater concern, reports of osteonecrosis of the jaw (ONJ) started to appear and were eventually linked to longer term administration of bisphosphonates.[8] Renal function impairment was also observed, requiring renal function monitoring with these agents. It was also apparent that bisphosphonates worked for many, but certainly not all, patients with bone metastases and that there were no biomarkers to select those patients most and least likely to benefit. These circumstances set the stage for the development of additional, perhaps better bone-targeting agents. During the development of bisphosphonates, multiple research laboratories markedly expanded our understanding of bone physiology and molecular biology, and indicated novel targets for developing effective therapeutics.[9] The receptor activator of NFκB (RANK) and its natural ligand (RANKL) are at the epicenter of this signaling network. Thus, a humanized soluble receptor (osteoprotegerin) was developed to compete with the ligand, and subsequently, a monoclonal antibody against RANKL (denosumab).[10] Clinical trials have thus far shown that denosumab is somewhat more effective than zoledronic acid in metastatic cancers, although neither agent delays progression of bone metastases per se. The denosumab trials have also raised concerns about potential increases in infectious complications and new malignancies in patients taking this drug. This deserves close monitoring over the upcoming years, as rare events tend to accumulate when drugs are used for common indications. It is also important to monitor these events because denosumab, like third-generation bisphosphonates, is going to be tested as part of adjuvant systemic therapy of breast and perhaps other cancers. ONJ was also reported in the denosumab trials, although the more limited experience with this drug does not allow precise quantitation of risk. Certainly, the lessons learned about bisphosphonates

and ONJ should serve us well for minimizing the risk of ONJ in association with denosumab: patients should have a good dental assessment and hygiene before initiating bone-directed therapy.

There have been a few reports of midshaft fractures unrelated to metastatic lesions in patients receiving chronic bisphosphonate therapy, including the administration of bisphosphonates for treatment of osteoporosis.[11] It is uncertain whether this represents a causal relationship, and additional, well-designed studies are needed to determine the nature of this association, as well as its pathophysiology. In the meantime, careful monitoring for these rare events is clearly indicated.

The ASCO guidelines group has recently completed the monumental task of updating "The Role of Bone Modifying Agents in Metastatic Breast Cancer."[1] This is an important service to the community of patients and physicians alike, because this is an evolving field and there have been multiple publications since the most recent iteration of these guidelines. It is important to pause here to point out how the ASCO guidelines differ from guidelines developed by other organizations. ASCO has an established, validated process that starts with a comprehensive review of the literature, following a pre-established protocol to identify those studies that contain the appropriate information with which to formulate evidence-based guidelines. That review is distilled into the final group of studies that satisfy the definitions, the results are tabulated, discussed, decisions are made regarding the impact new data have on the standard of care or previous guidelines, and a writing committee develops the guideline document, including the Executive Summary and the practical aids associated with each guideline. The ASCO process takes many months and by nature tends to be conservative in its recommendations. This process differs from that followed by other organizations that base some or all of their guidelines on the consensus of a group of experts, weaving into the discussion those studies that the same experts consider of value. Such guidelines might be developed in a day, and the document to summarize them might be completed in a few additional days. When you read the ASCO guidelines, you need to consider these differences, as well as the differences emanating from basing the literature review on a predefined period of time, and excluding from consideration data that become available after the closing date.

The updated guidelines included denosumab on the basis of controlled trials that have demonstrated the relative efficacy of this drug compared with zoledronic acid. This is a good addition to the guidelines and our armamentarium, although additional monitoring of its effects will be welcome. The guidelines also included a clear statement about ONJ and its prevention and management. There is much more research to be done in this field: the optimal timing of onset and discontinuation of bone-modifying agents; the optimal dose and schedule, especially for chronic administration; development of biomarkers that identify patients who will (and those who will not) benefit from these drugs; and elucidation of the pathophysiology of the more serious adverse effects and complications, as well as methods to prevent their development. We know these drugs improve bone density; their effects on bone strength have been poorly documented. We think of these drugs as "targeted therapies"; yet, we have no biomarkers to use in assessing which populations to target. Finally, all these agents work in up to 50% of patients with bone metastases; we need to understand why they don't work on the rest, and what strategies can be used to better control bone metastases for all patients.[12-13] The fate of patients with bone metastases has improved significantly over the past couple of decades thanks to bone-modifying agents. Our choices are becoming more complex, and we must make sure we use these drugs most effectively while limiting the risks of chronic and serious adverse effects.

Gabriel N. Hortobagyi, MD, FACP, is Professor and Chair, Department of Breast Medical Oncology at The University of Texas M. D. Anderson Cancer Center, P.O. Box 301439, Houston, TX 77230-1439. Contact him at ghortoba@mdanderson.org/.

Accepted for publication on January 13, 2011.

Author's Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Gabriel N. Hortobagyi, Novartis (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Gabriel N. Hortobagyi, Novartis **Expert Testimony:** None **Other Remuneration:** None

DOI: 10.1200/JOP.2011.000218

References

1. Coleman RE: Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. Cancer Treatment Rev 27:165-176, 2001

2. Elomaa I: Treatment of skeletal disease in breast cancer: A controlled clodronate trial. Bone 8:S53-S56, 1987 (suppl 1)

3. Hortobagyi GN, Theriault RL, Porter L, et al, for the Protocol 19 Aredia Breast Cancer Study Group: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone lesions. N Engl J Med 335:1785-1791, 1996

4. Theriault RL, Lipton A, Hortobagyi GN, et al, for the Protocol 18 Aredia Breast Cancer Study Group: Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: A randomized, placebo-controlled trial. J Clin Oncol 17:846-854, 1999

5. Lipton A, Theriault RL, Hortobagyi GN, et al: Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: Long term follow-up of two randomized, placebo-controlled trials. Cancer 88:1082-1090, 2000

6. Coleman RE: Bisphosphonates: Clinical experience. Oncologist 9:14-27, 2004 (suppl 4)

7. Rosen LS, Gordon DH, Dugan W Jr, et al: Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 100:36-43, 2004

8. Hoff AO, Toth BB, Altundag K, et al: The frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Min Res 23:826-836, 2008

9. Kingsley LA, Fournier PG, Chirgwin JM, et al: Molecular biology of bone metastasis. Mol Cancer Ther 6:2609-2617, 2007

10. Stopeck AT, Lipton A, Body JJ, et al: Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. J Clin Oncol 28:5132-5139, 2010

11. Odvina CV, Levy S, Rao S, et al: Unusual mid-shaft fractures during long-term bisphosphonate therapy. Clini Endocrinol (Oxf) 72:161-168, 2010

12. Onishi T, Hayashi N, Theriault RL, et al: Future directions for bone-targeted therapy for metastatic breast cancer. Nat Rev Clin Oncol 7:641-651, 2010

13. Hortobagyi GN: Systemic therapy for bone metastasis: Past, present, and future. Am Soc Clin Oncol Ed Book, 1-7, 2010