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

Summary of 2011 Recommendations

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

<table>
<thead>
<tr>
<th>Category</th>
<th>2003 Recommendations</th>
<th>2011 Recommendations</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<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 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</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.</td>
<td>Addition of new bone-modifying agent. Term changed from bisphosphonates to bone-modifying agents.</td>
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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.

**Recommendation 2**

**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.

**Recommendation 3A**

**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 hours with pamidronate or less than 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.

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 hours with pamidronate or less than 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

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.
In contrast to multiple myeloma patients, there currently is no data to support routine assessments for albuminuria in breast cancer patients. 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 with denosumab, pamidronate, or zoledronic acid.

### Recommendation 3B

**Osteonecrosis of the Jaw**

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 which 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.

### Recommendation 4

**Optimal Duration**

The Panel suggests that once initiated, IV bisphosphonates be continued until evidence of substantial decline in a patient’s general performance status. The Panel suggests that once initiated, bone-modifying agents be continued until evidence of substantial decline in a patient’s general performance status. The (Unchanged in substance from 2003)
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.

**Recommendation 5**  
**Optimal intervals between dosing**

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 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 breast cancer patients 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.

**Recommendation 6**  
**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 non-opioid** 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.

Recommendation 7
The role of biochemical markers

<table>
<thead>
<tr>
<th>The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care.</th>
<th>The use of the biochemical markers to monitor bone-modifying agent use is not recommended for routine care.</th>
</tr>
</thead>
</table>

(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; CT, computed tomography; MRI, magnetic resonance imaging; FDA, US Food and Drug Administration; N/A not applicable; ONJ, osteonecrosis

This is Table 1 in the ASCO Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer. The practice guideline and this table are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This summary does not recommend any particular product or course of medical treatment. Use of the practice guideline and this summary is voluntary. The practice guidelines and additional information are available at http://www.asco.org/guidelines/bisphosbreast. Copyright © 2011 by the American Society of Clinical Oncology. All rights reserved.