American Society of Clinical Oncology

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

The guideline update - resources

- Executive Summary– JCO publication (http://jco.ascopubs.org/misc/specialarticles.dtl)
- Full Text Guideline (www.asco.org/guidelines/bisphosbreast)
- Clinical Tools & Resources (www.asco.org/guidelines/bisphosbreast)

INTRODUCTION

- ASCO guideline on bisphosphonates for people with breast cancer was published in 2000
- Previously updated in 2003
- For 2011 update, scope was made specific to people with metastatic breast cancer
- Use of bone-modifying agents (BMAs) for adjuvant treatment will be addressed in a separate guideline

Guideline Methodology: Systematic Review

- The Update Committee completed a review and analysis of the medical literature available from January 2003 to July 2009. Additional searches were conducted in November 2010.
- Databases searched:
  - ✓Medline
  - ✓Cochrane Collaboration Library

Study Quality and Limitations of the Literature

- The definition of skeletal-related events (SREs) was not uniform across all studies; for example, some excluded hypercalcemia of malignancy. In addition, different efficacy endpoints were used in different trials. There is a low incidence of some adverse events.

The Bottom Line

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; IV pamidronate, 90 mg over no less than 2 hours every 3-4 weeks; or IV zoledronic acid, 4 mg over no less than 15 minutes every 3-4 weeks
- One bone-modifying agent 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 i.v. 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

The Bottom Line, cont'd

Key Recommendations, continued:

- All patients should have a dental exam and preventive dentistry prior to 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

- The recommendations, clinical questions, and a brief summary of the literature and discussion are in the Executive Summary published in the *Journal of Clinical Oncology*
- **The full guideline, with comprehensive discussions of the literature, methodology, full reference list, evidence tables, and clinical tools and resources, can be found at www.asco.org/guidelines/bisphosbreast.**

Clinical Questions

1. What are the indications for using bone-modifying agents to reduce the risk of skeletal-related events (SREs) in patients with metastatic breast cancer? When is the best time to initiate treatment with bone-modifying agents?
2. What is the role of bone-modifying agents in the presence of extra-skeletal metastases without evidence of bone metastases?
3. What are the prominent safety concerns of bone-modifying agent therapy?
    - 3A. Renal safety concerns?
    - 3B. Osteonecrosis of the Jaw (ONJ) concerns?

Clinical Questions

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?

Note:

- For each of the recommendations, clinical judgment should also take into consideration the patient's general performance status and overall prognosis

Recommendations

Recommendation 1: Indications and time of initiation

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.

Recommendations

Recommendation 1, cont'd

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.

Recommendations

Recommendation 2: Role of bone-modifying agents in the presence of extra-skeletal metastases (unchanged in substance from 2003)

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.

Recommendations

Recommendation 3A: Renal safety concerns

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.

Recommendations

Recommendation 3A , cont'd

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.

Recommendations

Recommendation 3A , cont'd

The risk of hypocalcemia with denosumab dosed at 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance < 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.

Recommendations

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.

Recommendations

Recommendation 3B, cont'd

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. While 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.

Recommendations

Recommendation 4: Optimal Duration (unchanged in substance from 2003)

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.

Recommendations

Recommendation 5: Optimal intervals between dosing

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.

Recommendations

Recommendation 6: Role of bone-modifying agents in pain control

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.

Recommendations

Recommendation 6, cont'd

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.

Recommendations

Recommendation 7: The role of biochemical markers (unchanged in substance since 2003)

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

Special Commentary on the Role of Vitamin D Deficiency and Bisphosphonates

- Trials of bone-modifying agents have included supplementation of calcium and vitamin D as part of the treatment regimen
- Insufficient data to support recommendation on optimal concentrations
- Based on expert consensus, in absence of definitive data:
  - If no contraindications
  - Use doses and schedules like those used in the clinical trials of the bone-modifying agents

Suggestions for Future Research

- The Update Committee suggests research be conducted in the areas of:
  - Duration
  - Intervals
  - Role of bone-modifying agents for those with extra-skeletal metastases
  - Subgroups (e.g. sex, ER/PR status, HER2 status, ethnic and racial status)
  - Biomarkers

Suggestions for Future Research, cont'd.

- Role of Vitamin D
- Comparative Effectiveness
- Role of bone-modifying agents integrated with other therapies
- Completion of research on other bone-modifying agents

Guideline Methodology: Update Committee Members

Update Committee Members	Affiliation/Institution
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Additional ASCO Resources

- The Executive Summary, Full Text guideline, this slide set, and additional clinical tools and resources can be found at: http://www.asco.org/guidelines/bisphosbreast
- A patient guide, “What to Know” about this guideline, is available at: http://www.cancer.net/whattoknow

ASCO Guidelines

This resource is a practice tool for physicians based on an ASCO® practice guideline. The practice guideline and this presentation 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 presentation does not recommend any particular product or course of medical treatment. Use of the practice guideline and this resource is voluntary. The full practice guideline and additional information are available at http://www.asco.org/guidelines/bisphosbreast.