



American Society of Clinical Oncology

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The Role of Bisphosphonates in Multiple Myeloma: 2007 Update

Clinical Practice Guideline

Introduction

- ASCO convened an Update Committee to review and update the 2002 recommendations for the role of bisphosphonates in multiple myeloma.
- The Update Committee used an evidence-based strategy and expert consensus to inform the 2007 recommendations.
- New to the 2007 Update is the expanded scope of the guideline to include recommendations concerning the association of osteonecrosis of the jaw and bisphosphonate therapy.

Guideline Methodology: Literature Analysis

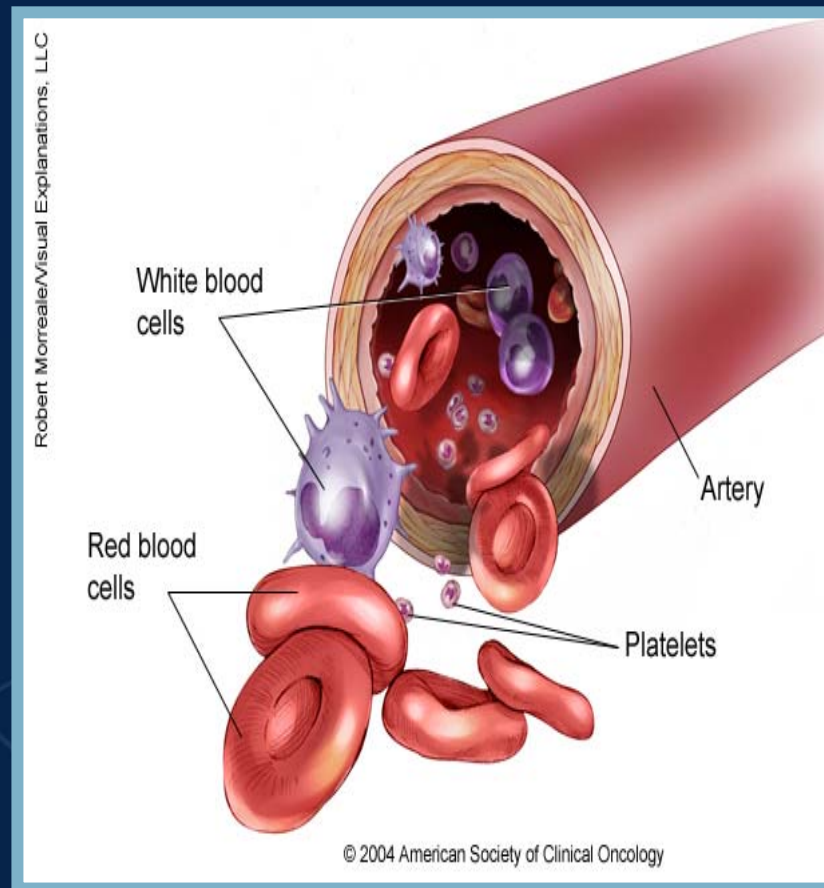
- The Update Committee completed a review and analysis of data published from 2002 to January 2007:
 - ✓ MEDLINE
 - ✓ Cochrane Database of Systematic Reviews
- For the recommendations related to osteonecrosis of the jaw, the Update Committee considered data and reports from the following sources:
 - Manufacturers of bisphosphonates
 - Governmental agencies
 - Other dental and medical professional societies

Guideline Methodology (cont ' d): Panel Members

- Kenneth Anderson, MD, *Co-Chair* Dana Farber Cancer Institute
- Robert Kyle, MD, *Co-Chair* Mayo Clinic
- Patrick J. Flynn, MD Minnesota Oncology Hematology P.A
- Sundar Jagannath, MD St Vincent's Comprehensive Cancer Center
- Susan Halabi, PhD Duke University Medical Center (DUMC)
- Robert Orłowski, MD, PhD University of North Carolina at Chapel Hill
- David Roodman, MD VA Pittsburgh Healthcare System
- Patricia Twilde Patient Representative
- Gary C. Yee, Pharm D University of Nebraska Medical Center

Background

- Multiple myeloma, a cancer of the plasma cells that may develop in multiple sites of the bone marrow, is a common hematologic malignancy.
- Increased osteoclast activity within the myeloma bone marrow leads to loss of bone structure, pathologic fractures, hypercalcemia, and pain.
- Patient quality of life is optimized by reducing morbidity and skeletal involvement by the disease.



Background (cont ' d)

- In 2002 bisphosphonates were a new class of agents shown to reduce bony complications associated with multiple myeloma. That same year the U.S. Food and Drug Administration (FDA) approved the use of zoledronic acid for the treatment of patients with multiple myeloma and other metastatic bone disease.
- Bisphosphonates have an affinity for bone and are preferentially delivered to sites of increased bone formation or resorption. Once deposited on the surface of bone, bisphosphonates are ingested by osteoclasts that are engaged in bone resorption.
- There are seven bisphosphonates on the market:
 - Etidronate
 - Clodronate
 - Tiludronate
 - Pamidronate
 - Alendronate
 - Ibandronate
 - Zoledronic Acid

2007 Update Recommendation Topics

- Lytic Disease on Plain Radiographs
- Monitoring
- Duration of Therapy
- Myeloma Patients with Osteopenia Based on Normal Plain Radiograph or Bone Mineral Density Measurements
- Patients with Solitary Plasmacytoma, or Smoldering or Indolent Myeloma Without Documented Lytic Bone Disease
- Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS)
- Biochemical Markers
- Role in Pain Control Secondary to Bony Involvement
- Osteonecrosis of the Jaw (ONJ) *NEW!*

Lytic Disease on Plain Radiographs

- For multiple myeloma patients who have on plain radiograph(s), lytic destruction of bone or compression fracture of the spine from osteopenia:
 - Pamidronate i.v. 90 mg (≥ 2 hours), or
 - Zoledronic acid 4 mg (≥ 15 minutes; every 3-4 wks)
- In light of data from Zervas et al showing a 9.5-fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared to pamidronate, patients may prefer pamidronate to zoledronic acid until more data become available on this adverse effect of bisphosphonate therapy.
- Clodronate is an alternative bisphosphonate approved worldwide except for the United States for either oral or intravenous administration.

Monitoring

- Due to increased concerns over renal adverse events, new dosing guidelines for patients with pre-existing renal impairment were added to the Zometa package insert.
- The new guideline recommends that patients with pre-existing mild-to-moderate renal impairment (estimated creatinine clearance 30-60 mL/min) should receive a reduced dosage of zoledronic acid.
- No changes in infusion time or interval are required.
- Although no similar dosing guidelines are available for pamidronate, the Update Committee recommends that clinicians consider reducing the initial pamidronate dose in patients with pre-existing renal impairment.

Monitoring (cont ' d)

- Pamidronate, 90 mg given over 4-6 hours, is recommended for patients with extensive bone disease and existing severe renal impairment (serum creatinine level > 3.0 mg/dL [$265 \mu\text{mol/L}$] or an estimated creatinine clearance <30 mL/min).
- Zoledronic acid has not been studied in patients with severe renal impairment and is not recommended for use in these patients.
- Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided.

Monitoring (cont ' d)

- The Update Committee recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling.
- In patients who develop renal deterioration during bisphosphonate therapy, zoledronic acid or pamidronate should be withheld. Bisphosphonate therapy can be resumed, at the same dosage as that prior to treatment interruption, when the serum creatinine returns to within 10% of the baseline level.
- Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly, although there is no evidence on which to base a recommendation for time intervals.

Monitoring (cont ' d)

- The Update Committee also recommends intermittent evaluation (every 3-6 months) of all patients receiving pamidronate or zoledronic acid therapy for the presence of albuminuria.
 - In patients experiencing unexplained albuminuria (defined as > 500 mg/24 hours of urinary albumin), discontinuation of the drug is advised until the renal problems are resolved.
 - These patients should be reassessed every 3-4 weeks (with a 24-hour urine collection for total protein and urine protein electrophoresis) and pamidronate re-instituted over a longer infusion time (≥ 4 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline.
 - Although no similar guidelines are available for zoledronic acid, some Update Committee members recommend that zoledronic acid be re-instituted over a longer infusion time (≥ 30 minutes).

Duration of Therapy

- A single randomized clinical trial has shown no benefit of monthly bisphosphonates after a tandem transplant.
- The Update Committee suggests that therapy with bisphosphonates be given monthly for a period of two years. (The French data suggest one year if the patient is in a CR or NCR following a tandem transplant.)
- At two years, the physician should seriously consider stopping bisphosphonates in patients with responsive or stable disease, but their further use is at the discretion of the treating physician.
- There are no data to support a more precise recommendation for duration of bisphosphonate therapy in this group of patients. For those patients in whom bisphosphonates were withdrawn after two years, the drug should be resumed upon relapse with new onset skeletal related events.

Myeloma Patients with Osteopenia Based on Normal Plain Radiograph or Bone Mineral Density Measurements

- It is reasonable to start intravenous bisphosphonates in multiple myeloma with osteopenia but no radiographic evidence of lytic bone disease.
 - **Note:** patients with non-lytic lesions have been included in selected trials but have not been the primary focus of the trial or of sufficient number to be separately analyzed.

Role in Pain Control Secondary to Bony Involvement

- Intravenous pamidronate or zoledronic acid are recommended for patients with pain due to osteolytic disease and as an adjunctive treatment for patients receiving:
 - Radiation therapy
 - Analgesics
 - Surgical intervention to stabilize fractures or impending fractures

Osteonecrosis of the Jaw (ONJ)

- ONJ is an uncommon but potentially serious complication of intravenous bisphosphonates.
- The Update Committee agrees with the recommendations described in the revised FDA label for zoledronic acid and pamidronate, *Dear Doctor* letters, a white paper, and various position papers or statements.
- All cancer patients should receive a comprehensive dental examination and appropriate preventive dentistry prior to bisphosphonate therapy.
- Active oral infections should be treated and sites at high risk for infection should be eliminated. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures, if possible.

Other Nonrenal Adverse Effects

- The safety and frequency of other nonrenal adverse events with zoledronic acid appear to be similar to pamidronate.
- Transient myalgias, arthralgias, and flu-like symptoms with fever tend to occur more often in patients treated with pamidronate or zoledronic acid than placebo.
- These symptoms usually occur only after the first and/or second infusion of pamidronate and are not an indication to discontinue drug treatment.
- Ocular side effects from pamidronate are a relatively rare but well-recognized complication, first reported in 1994. These effects have been reported with zoledronic acid and other bisphosphonates, as well.
- An updated review of case reports found 17 cases of unilateral scleritis and one case of bilateral scleritis, usually within 6 hours to 2 days after intravenous pamidronate. Six patients had positive rechallenge testing with the scleritis occurring again after a repeat drug exposure.

NOT RECOMMENDED

- Patients with Solitary Plasmacytoma, or Smoldering or Indolent Myeloma Without Documented Lytic Bone Disease
 - Starting bisphosphonates for patients with solitary plasmacytoma or smoldering (asymptomatic) or indolent myeloma is not recommended.
- Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS)
 - Starting bisphosphonates for patients with monoclonal gammopathy of undetermined significance (MGUS) is not recommended.
- Biochemical Markers
 - The use of the biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care

Additional ASCO Resources

- The full-text guideline as well as the following resources are available at:

<http://www.asco.org/guidelines/bisphosmyeloma>

- Summary Slide Set
- [Guideline Summary](#)
- [ASCO Patient Guide](#)
- [Revisions Table](#)

ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.