



Complete Summary

GUIDELINE TITLE

American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma.

BIBLIOGRAPHIC SOURCE(S)

Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, Orlovski RZ, Roodman DG, Twilte P, Anderson K. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007 Jun 10;25(17):2464-72. [44 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Society of Clinical Oncology Bisphosphonates Expert Panel. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2002 Sep 1;20(17):1-19.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [May 18, 2005, Aredia \(pamidronate disodium\) and Zometa \(zoledronic acid\)](#). Dental healthcare professionals notified of revisions to the prescribing information to describe the occurrence of osteonecrosis of the jaw (ONJ) observed in cancer patients receiving treatment with intravenous bisphosphonates.
- [March 25, 2005, Zometa \(zoledronic acid\)](#). Revisions to the DOSAGE AND ADMINISTRATION and WARNINGS sections of the prescribing information for the drug, to reflect new safety information on management of patients with advanced cancer and renal impairment.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

SCOPE

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SCOPE

DISEASE/CONDITION(S)

- Multiple myeloma
- Lytic bone disease

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To update the clinical practice guidelines for the use of bisphosphonates in the prevention and treatment of lytic bone disease in multiple myeloma and to expand the guideline to include a discussion of osteonecrosis of the jaw

TARGET POPULATION

Multiple myeloma patients with lytic bone disease or osteopenia

INTERVENTIONS AND PRACTICES CONSIDERED

1. Bisphosphonates, such as pamidronate (Aredia) and zoledronic acid (Zometa), for prevention and treatment of lytic bone disease in multiple myeloma, including consideration of duration of therapy and reduction of pamidronate dosage for patients with renal impairment

Note: Clodronate is an alternative bisphosphonate approved worldwide, except in the United States, for oral or intravenous administration.

2. Monitoring/evaluation
 - Serum creatinine (before each dose of pamidronate or zoledronic acid)
 - Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin (periodically)
 - Albuminuria (every 3-6 months)
 - Biochemical markers to monitor therapy (not recommended)
3. Comprehensive dental examination and preventive dentistry prior to bisphosphonate therapy

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Update Committee's literature review focused attention on available randomized clinical trials, clinical practice guidelines, and systematic reviews of published clinical trials and a meta-analysis report. For the guideline recommendations related to osteonecrosis of the jaw, the Update Committee considered data and reports from manufacturers of bisphosphonates, governmental agencies, and other dental and medical professional societies.

For the 2007 update, a methodology similar to that applied in the original American Society of Clinical Oncology (ASCO) practice guideline for use of bisphosphonates in multiple myeloma was used. Pertinent information published from 2002 to 2007 was reviewed to address each of the original guideline questions and the new topic of osteonecrosis of the jaw. The Medline database (National Library of Medicine, Bethesda, MD) was searched to identify relevant information from published randomized clinical trials, systematic reviews, meta-analyses, and practice guidelines for this update. A series of searches was conducted using the medical subject headings or text words "multiple myeloma" and "bisphosphonates" and variants thereof. Targeted searches using broad inclusion criteria were conducted to identify relevant articles related to osteonecrosis of the jaw. Search results were limited to human studies and English-language articles; editorials, letters, and commentaries were excluded from consideration. The Cochrane Library was searched for available systematic reviews and meta-analyses with words "biphosphonates," "bisphosphonates," and "diphosphonates." Directed searches based on the bibliographies of primary articles were also performed. Finally, Update Committee members and ASCO staff contributed articles from their personal collections. Update Committee members

reviewed the resulting abstracts and titles that corresponded to their assigned section.

The literature search conducted for this update identified several relevant reports, including two articles reporting the results of randomized clinical trials, one clinical practice guideline, one consensus statement, and two systematic reviews of the literature.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

For the 2007 update, an Update Committee composed of members from the full Expert Panel was formed to complete the review and analysis of data published since 2002.

The Update Committee held a single face-to-face meeting to consider the evidence for each of the 2007 recommendations. Additional work to complete the update was completed via teleconferences with the steering group and with the full Update Committee. Representatives from industry attended the Update Committee meeting and provided preprints and reprints of relevant studies.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was circulated in draft form to the Update Committee, American Society of Clinical Oncology's (ASCO's) Health Services Committee and the ASCO Board of Directors also reviewed the final document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Lytic Disease on Plain Radiographs or Imaging

For multiple myeloma patients who have, on plain radiograph(s) or imaging, lytic destruction of bone or compression fracture of the spine from osteopenia, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg delivered over at least 15 minutes every 3 to 4 weeks is recommended. In light of data from showing a 9.5-fold greater risk for the development of osteonecrosis of the jaw (ONJ) with zoledronic acid compared with 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 that has been approved worldwide, except in the United States, for either oral or intravenous administration.

Monitoring

As a result of increased concerns over renal adverse events, new dosing guidelines for patients with preexisting renal impairment were added to the zoledronic acid package insert. The new guidelines recommend that patients with pre-existing mild-to-moderate renal impairment (estimated creatinine clearance, 30 to 60 mL/min) should receive a reduced dosage of zoledronic acid. No changes in infusion time or interval are required. Zoledronic acid has not been studied in patients with severe renal impairment and is not recommended for use in these patients. Pamidronate 90 mg administered over 4 to 6 hours is recommended for patients with extensive bone disease and existing severe renal impairment (serum creatinine level >3.0 mg/dL [265 micromol/L] or an estimated creatinine clearance <30 mL/min). Although no dosing guidelines are available for patients with pre-existing renal impairment, the Update Committee recommends that clinicians consider reducing the initial pamidronate dose in that setting.

Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Update Committee recommends that

serum creatinine should be monitored before each dose of pamidronate or zoledronic acid, in accordance with US Food and Drug Administration–approved labeling. In patients who develop renal deterioration with no other apparent cause during bisphosphonate therapy, zoledronic acid or pamidronate should be withheld. Bisphosphonate therapy can be resumed, at the same dosage as that before 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. The Update Committee also recommends intermittent evaluation (every 3 to 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. When the proteinuria returns to baseline, these patients should be reassessed every 3 to 4 weeks (with a 24-hour urine collection for total protein and urine protein electrophoresis), and pamidronate should be reinstated over a longer infusion time (≥ 4 hours) and at doses not to exceed 90 mg every 4 weeks. The Update Committee supports the use of screening urinalysis for proteinuria but underscores that a 24-hour urine collection for determination of total protein and electrophoresis is required if the screening test is positive. Although no similar guidelines are available for zoledronic acid, some Update Committee members recommend that zoledronic acid be reinstated over a longer infusion time (≥ 30 minutes).

Duration of Therapy

A single randomized clinical trial has shown no benefit of monthly bisphosphonates after tandem stem-cell transplantation. There was no difference in the proportion of skeletal events in the pamidronate-containing regimens (21% and 18%) compared with no maintenance (24%) after 29 months of follow-up. Given these data and the best clinical opinion of the Update Committee, we suggest that therapy with bisphosphonates be administered monthly for a period of 2 years. (One trial suggests 1 year if the patient is in a complete response or near complete response after a tandem stem-cell transplantation.) At 2 years, physicians 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 are withdrawn after 2 years, the drug should be resumed on 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 patients with osteopenia but no radiographic evidence of lytic bone disease. Note, patients with nonlytic 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.

Patients With Solitary Plasmacytoma or Smoldering or Indolent Myeloma Without Documented Lytic Bone Disease

Starting bisphosphonate therapy in patients with solitary plasmacytoma or smoldering (asymptomatic) or indolent myeloma is not recommended.

Patients With Monoclonal Gammopathy of Undetermined Significance

Starting bisphosphonates in patients with monoclonal gammopathy of undetermined significance is not recommended.

Biochemical Markers

The use of biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care because of a lack of prospective studies validating such an approach.

Role in Pain Control Secondary to Bony Involvement

Intravenous pamidronate or zoledronic acid is recommended for patients with pain caused by osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures or impending fractures.

Safety and Adverse Effects: Osteonecrosis of the Jaw (ONJ)

NOTE. The topic of ONJ as an adverse effect is new to the guideline.

ONJ is an uncommon but potentially serious complication of intravenous bisphosphonates. The Update Committee agrees with the recommendations described in the revised US Food and Drug Administration 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 before 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The evidence for the update included two articles reporting the results of randomized clinical trials, one clinical practice guideline, one consensus statement, and two systematic reviews of the literature.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of bisphosphonates in the management of multiple myeloma

POTENTIAL HARMS

Reported complications include:

- Renal toxicity, including albuminuria
- Osteonecrosis of the jaw is an uncommon but potentially serious complication of intravenous bisphosphonates
- Transient myalgias, arthralgias, and flu-like symptoms with fever
- Ocular adverse events

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are 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 result.
- Accordingly, American Society of Clinical Oncology (ASCO) considers adherence to this guideline assessment 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, this guideline describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, Orłowski RZ, Roodman DG, Twilde P, Anderson K. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007 Jun 10;25(17):2464-72. [44 references] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Sep 1 (revised 2007 Jun 10)

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

GUIDELINE COMMITTEE

2007 American Society of Clinical Oncology Bisphosphonates in Multiple Myeloma Guideline Update Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. 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 on the [Journal of Clinical Oncology Web site](#).

Employment: N/A **Leadership:** N/A **Consultant:** Robert A. Kyle, Novartis; David G. Roodman, Amgen, Novartis, Merck, Millennium; Kenneth Anderson, Novartis, Celgene, Millenium **Stock:** N/A **Honoraria:** Robert A. Kyle, Novartis; Gary C. Yee, Novartis; David G. Roodman, Amgen, Novartis, Merck, Millennium; Kenneth Anderson, Novartis, Millenium, Celgene **Research Funds:** Kenneth Anderson, Millenium, Celgene **Testimony:** N/A **Other:** N/A

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Society of Clinical Oncology Bisphosphonates Expert Panel. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2002 Sep 1;20(17):1-19.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#).

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 1900 Duke Street, Suite 200, Alexandria, VA 22314; E-mail: guidelines@asco.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of bisphosphonates in multiple myeloma: guideline summary. *J Oncol Pract* 2007 3:236. Electronic copies: Available from the [American Society of Clinical Oncology Web site](#).

- The role of bisphosphonates in multiple myeloma: 2007 update. Summary slide set. American Society of Clinical Oncology. 2007. Electronic copies: Available from the [American Society of Clinical Oncology Web site](#).

Guidelines are available for Personal Digital Assistant (PDA) download from the [ASCO Web site](#).

PATIENT RESOURCES

The following is available:

- ASCO patient guide: bisphosphonate treatment for multiple myeloma. 2007 May. Electronic copies: Available from the [Cancer.Net Web site](#).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on February 27, 2003. The information was verified by the guideline developer on March 14, 2003. This summary was updated by ECRI on March 28, 2005, following the U.S. Food and Drug Administration advisory on Zometa (zoledronic acid). This summary was updated by ECRI on May 20, 2005, following the U.S. Food and Drug Administration advisory on Aredia (pamidronate disodium) and Zometa (zoledronic acid). This NGC summary was updated by ECRI Institute on July 23, 2007. The updated information was verified by the guideline developer on August 2, 2007.

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