

Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including an abbreviated Data Supplement with new studies, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelineswiki.

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Purpose

To update guideline recommendations on the role of bone-modifying agents in multiple myeloma.

Methods

An update panel conducted a targeted systematic literature review by searching PubMed and the Cochrane Library for randomized controlled trials, systematic reviews, meta-analyses, clinical practice guidelines, and observational studies.

Results

Thirty-five relevant studies were identified, and updated evidence supports the current recommendations.

Recommendations

For patients with active symptomatic multiple myeloma that requires systemic therapy with or without evidence of lytic destruction of bone or compression fracture of the spine from osteopenia on plain radiograph(s) or other imaging studies, intravenous administration of pamidronate 90 mg over at least 2 hours or zoledronic acid 4 mg over at least 15 minutes every 3 to 4 weeks is recommended. Denosumab has shown to be noninferior to zoledronic acid for the prevention of skeletal-related events and provides an alternative. Fewer adverse events related to renal toxicity have been noted with denosumab compared with zoledronic acid and may be preferred in this setting. The update panel recommends that clinicians consider reducing the initial pamidronate dose in patients with preexisting renal impairment. Zoledronic acid has not been studied in patients with severe renal impairment and is not recommended in this setting. The update panel suggests that bone-modifying treatment continue for up to 2 years. Less frequent dosing has been evaluated and should be considered in patients with responsive or stable disease. Continuous use is at the discretion of the treating physician and the risk of ongoing skeletal morbidity. Retreatment should be initiated at the time of disease relapse. The update panel discusses measures regarding osteonecrosis of the jaw. Additional information is available at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

The goal of this update is to provide oncologists, hematologists, other health care practitioners, patients, and caregivers with recommendations regarding the role of bone-modifying agents in multiple myeloma.

ASCO first published evidence-based clinical practice guidelines on the role of bisphosphonates in multiple myeloma in 2002 and an update in 2007.¹ The goal of this 2017 guideline update is to provide oncologists and other clinicians with current

recommendations regarding the role of bone-modifying agents (BMAs) in multiple myeloma. The current 2017 update assesses whether the 2007 recommendations remain valid. A complete list of previous recommendations is available at www.asco.org/hematologic-malignancies-guidelines.


METHODS

Guideline Update Process

ASCO uses a signals² approach to facilitate guideline updating. This approach is intended to

ASSOCIATED CONTENT

 Appendix
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 Data Supplement
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THE BOTTOM LINE

Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update**Guideline Question**

What is the role of BMAs in patients with multiple myeloma?

Target Population

Patients with multiple myeloma.

Target Audience

Medical oncologists, hematologists, radiation oncologists, oncology pharmacists, advanced practice providers, nurses, and other health care providers.

Methods

A systematic review of the literature was performed, and relevant evidence was evaluated for inclusion in this updated clinical practice guideline using the signals approach.

Key Recommendations**Indications to initiate a BMA**

Patients with lytic disease on plain radiographs or other imaging studies. For patients with multiple myeloma who, on plain radiograph(s) or other imaging studies (magnetic resonance imaging or computed tomography Scan), have lytic destruction of the 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. Alternative treatment includes the use of denosumab, a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand.

Patients with osteopenia in the absence of lytic disease. Starting bisphosphonates in patients with solitary plasmacytoma or smoldering (asymptomatic) or indolent myeloma is not recommended.

Adjunct to pain control in patients with pain as a result of osteolytic disease and those receiving other interventions for fractures or impending fractures. Intravenous pamidronate or zoledronic acid is recommended for patients with pain as a result of osteolytic disease and as an adjunctive treatment of patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures or impending fractures. Denosumab is an additional option.

Patients with myeloma with normal plain radiograph or osteopenia in bone mineral density measurements. The Expert Panel supports starting intravenous bisphosphonates in patients with multiple myeloma with osteopenia (osteoporosis), but no radiographic evidence of lytic bone disease.

Patients with monoclonal gammopathy of undetermined significance. Starting bisphosphonates in patients with monoclonal gammopathy of undetermined significance is not recommended, unless osteopenia (osteoporosis) exists.

Dosing and selection of BMAs. As a result of increased concerns over renal adverse events, dosing guidelines for patients with preexisting renal impairment were added to the zoledronic acid package insert. Guidelines recommend that patients with preexisting 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. Recent data that compare denosumab with zoledronic acid has demonstrated fewer adverse events related to renal toxicity with denosumab, and this may be preferred in patients with compromised renal function.

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 μmol/L) or an estimated creatinine clearance of < 30 mL/min. Although no dosing guidelines are available for patients with preexisting renal impairment, the Expert Panel recommends that clinicians consider reducing the initial pamidronate dose in that setting. Infusion times < 2 hours with pamidronate or < 15 minutes with zoledronic acid should be avoided.

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THE BOTTOM LINE (CONTINUED)

Duration of therapy. The Expert Panel suggests that bone-targeting treatment continue for a period of up to 2 years. Less-frequent dosing has been evaluated and should be considered in patients with responsive or stable disease. In patients who do not have active myeloma and are on maintenance therapy, the physician may consider a 3-month interval of bisphosphonate administration. There are no data to support a more precise recommendation for the duration of bisphosphonate therapy in this group of patients. For those patients for whom bisphosphonates were withdrawn after 2 years, the drug should be resumed upon relapse with new-onset skeletal-related events. Denosumab should not be stopped abruptly, given its reversible mechanism of action.

Monitoring. The Expert Panel recommends that serum creatinine should be monitored before each dose of pamidronate or zoledronic acid, in accordance with US Food and Drug Administration (FDA)–approved labeling. Denosumab does not require monitoring of renal function.

In patients who develop renal deterioration without an 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 serum creatinine returns to within 10% of the baseline level. Denosumab requires no dose modification.

Serum calcium should be monitored regularly, and serum vitamin D levels should be evaluated intermittently. Hypocalcemia is an adverse effect of all bone resorptive agents and is more pronounced with denosumab. Patients should be calcium and vitamin D repleted.

The Expert Panel also recommends intermittent evaluation—every 3 to 6 months—of all patients receiving pamidronate or zoledronic acid therapy for the presence of albuminuria on a spot urine sample. In patients who experience unexplained albuminuria, a 24-hour urine collection should be obtained to assess for > 500 mg/24 hours of urinary albumin, and discontinuation of the drug is advised until renal problems are resolved. 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 (\geq 4 hours) and at doses not to exceed 90 mg every 4 weeks when renal function returns to baseline.

The Expert Panel supports the use of screening urinalysis for proteinuria, but underscores that a 24-hour urine collection for the determination of total protein and electrophoresis is required if the test is positive. Although no similar guidelines are available for zoledronic acid, some Expert Panel members recommend that zoledronic acid be reinstated over a longer infusion time (\geq 30 minutes).

Biochemical markers. Use of the biochemical markers of bone metabolism to monitor bone-modifying therapy use is not suggested for routine care.

Osteonecrosis of the jaw. Osteonecrosis of the jaw (ONJ) is an uncommon but potentially serious complication of intravenous bisphosphonates and denosumab. The Expert Panel 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 patients should receive a comprehensive dental examination and appropriate preventive dentistry before bone-modifying therapy. Active oral infections should be treated, and sites that are at high risk for infection should be eliminated. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures, if possible. Continuation of a bone-targeting agent in the setting of ONJ has to be individualized and dependent on a risk–benefit ratio and the severity of bone disease.

Additional resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

identify new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on routine searches of the literature and the expertise of ASCO guideline panel members to identify signals. The Methodology Supplement, available at www.asco.org/hematologic-malignancies-guidelines, provides additional information about the signals approach.

PubMed and the Cochrane Library were searched for randomized controlled trials, systematic reviews, meta-analyses, clinical practice guidelines, and observational studies for the period from January 2007

through July 2017. The disease and intervention search terms used were those that were used for the 2007 guideline. An Expert Panel—members listed in Appendix Table A1, (online only)—was formed in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines, and the panel reviewed the abstracts that were identified on the basis of predefined signals that would suggest the need to change a previous recommendation. Additional information about the results of the updated literature search (Data Supplement 1) and the 2017 search strategy string and results (Data Supplement 2), as well as

a discussion of the ASCO signals approach to guideline updating, are available at www.asco.org/hematologic-malignancies-guidelines and in the 2017 Data Supplement and 2017 Methodology Supplement, respectively. A QUOROM diagram of the updated search and the clinical questions are provided in Data Supplements 3 and 4, respectively.

This systematic review-based guideline product was developed by an Expert Panel with multidisciplinary representation, including patients, and by ASCO guidelines staff with health research methodology experience. The Expert Panel met via teleconference calls to consider the evidence for each of the 2017 recommendations. The guideline was circulated in draft form to the Expert Panel. ASCO's Clinical Practice Guidelines Committee leadership reviewed and approved the final document. All funding for the administration of the project was provided by ASCO.

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Guideline and Conflicts of Interest. The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The search yielded 35 publications.³⁻³⁷ After careful review of the identified publications, the Expert Panel concluded that additional BMAs are now available, and the 2007 guideline recommendations¹

have been updated. The guideline recommendations also provide information to additionally clarify the evidence that supports additional recommendations on duration and complications of BMAs. A bibliography and summary of the results of the updated literature search is provided in Data Supplement 2.

RECOMMENDATIONS

The 2017 recommendations are listed in the Bottom Line Box. These recommendations are consistent with the previous recommendations, with new information on denosumab, a receptor activator of nuclear factor kappa-B ligand inhibitor.³⁶ Additional modifications were made to some of the recommendations on the basis of recent data to better clarify the indications for treatment, duration of treatment, and associated complications of treatment, and these are discussed in greater depth in this section.

The definition of active multiple myeloma that requires therapy has been revised. Hypercalcemia, renal dysfunction, anemia, or bone disease remain indications for treatment. In the absence of these features, patients who have > 60% bone marrow plasma cells, involved free light chain > 100 mg/L with κ/λ ratio > 100-fold, or more than one site of bone disease on magnetic resonance imaging or on positron emission tomography computed tomography scanning are now recommended for treatment. Any patient who receives treatment for active multiple myeloma should receive bisphosphonate therapy. In a large randomized trial that was conducted in the United Kingdom (MRC IX Trial), patients without lytic bone disease also benefitted from bisphosphonate therapy (zoledronic acid) with reduced skeletal-related events at the time of relapse, and there was improvement in progression-free survival, but not overall survival.^{20,21} Clodronate is approved worldwide, except in the United States, for either oral or intravenous administration; however, the recent MRC IX randomized controlled trial demonstrates that intravenous zoledronic acid is superior for avoiding skeletal complications.^{20,21}

Patients With Lytic Disease on Plain Radiographs or Other Imaging Studies

The previous guidelines recommended the use of intravenous bisphosphonates for patients with myeloma with evidence of bone disease.¹ Denosumab was studied in a large, international, randomized, double-blinded, phase III study that evaluated the efficacy and safety of denosumab compared with zoledronic acid for the prevention of skeletal-related events in patients with newly diagnosed multiple myeloma.^{36,37} Patients (N = 1,718) were randomly assigned in a 1:1 allocation ratio to denosumab 120 mg subcutaneously every 4 weeks or zoledronic acid 4 mg intravenously every 4 weeks. Denosumab was noninferior to zoledronic acid in delaying the time to first skeletal-related events. Overall survival for patients who were treated with denosumab was not different than patients who were treated with zoledronic acid. Fewer adverse events related to renal toxicity were reported with denosumab, providing an additional option as a BMA in multiple myeloma.

Denosumab is more expensive than zoledronic acid or pamidronate and must be considered in treatment decisions. [Table 1](#) provides an overview of the estimated cost of these medications in the United States.

Table 1. Estimated Prices for Bone-Modifying Agents in the United States

Agent (route)	Dose (mg)	Schedule	Price Per Dose (US dollars)	Total Price Per 1-Year Treatment Cycle (US dollars)
Bisphosphonate				
Pamidronate (intravenous)	90	Delivered over no less than 2 hours every 3 or 4 weeks	\$30.67*	Every-4-weeks price: \$398.71 (\$30.67 × 13)
Zoledronic acid (intravenous)	4	Delivered over no less than 15 minutes every 12 weeks or every 3-4 weeks	\$53.64†	Every-12-weeks price: \$214.56 (\$53.64 × 4) Every-4-weeks price: \$697.37 (\$53.64 × 13)
Monoclonal antibody				
Denosumab (subcutaneous injection)	120	Every 4 weeks	\$1,995.48‡	Every-4-weeks price: \$25,941.24 (\$1,995.48 × 13)

NOTE. Prices per dose were for a single infusion or per single injection. Prices for drugs reimbursed through Medicare Part B only were identified from the second quarter 2017 Medicare Payment Allowable Part B Drugs Average Sales Price data.³⁹ Drug price may vary by plan and by pharmacy where a medication is filled (eg, preferred or nonpreferred pharmacies). Drug prices are dynamic, and thus the prices listed in the table may not reflect current prices. Bone-modifying treatment continue for a period of up to 2 years. Less-frequent dosing has been evaluated and should be considered in patients with responsive or stable disease. Continuous use is at the discretion of the treating physician and the risk of ongoing skeletal morbidity. Retreatment should be initiated at the time of disease relapse. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures.

*\$10.223/30 mg × 3.

†\$13.411/1 mg × 4.

‡\$16.629/1 mg × 120.

Duration and Frequency of Therapy

The risk of ONJ has prompted the use of less-frequent dosing of zoledronic acid, which may be an option for patients.^{26,38} These two studies were carried out to address the dosing of zoledronic acid every 3 months. To this end, the Z-MARK study evaluated whether patients with 1 to 2 years of prior intravenous bisphosphonate therapy could be treated safely long term with less-frequent zoledronic acid on the basis of markers of bone turnover.²⁶ Patients with urinary N-telopeptide of type I collagen (uNTX) levels < 50 nmol/mmol creatinine received zoledronate 4 mg every 12 weeks versus every 4 weeks for higher levels of uNTX. uNTX levels were monitored over the course of treatment, and the dosing of zoledronic acid was adjusted as a result. In addition, patients who developed a skeletal-related event or who experienced disease progression were treated on the every-4-week schedule thereafter, regardless of uNTX levels. The majority of patients (79 of 121) received the every-12-week schedule throughout the study. Of the 79 patients, only seven patients (8.9%) had a skeletal-related event in year 1 and five in year 2. The low incidence of skeletal-related events overall in this study compared with prior studies with zoledronic acid suggests that less-frequent dosing of zoledronic acid beyond 1 to 2 years may continue to reduce the risk of skeletal-related events. Furthermore, it also suggests more effective treatment of multiple myeloma with novel therapies may have protective effects on the bone.

In another large randomized trial, zoledronic acid that was administered every 12 weeks was compared with that administered every 4 weeks to demonstrate noninferiority.³⁸ This randomized, open-label clinical trial included 1,822 patients with at least one site of bone involvement for a treatment duration of 2 years. Two hundred seventy-two patients in this trial had multiple myeloma. The proportions of skeletal-related events did not differ significantly between the every-4-week dosing group versus the every-12-week dosing group. Among other end points, there was no difference noted in the incidence of ONJ and kidney dysfunction. At the time of relapse, retreatment on the 4-week schedule is recommended.

Although both these studies have used less-frequent dosing, there are several limitations that should be kept in mind. The

Z-MARK study was a single-arm study with only 121 patients included; however, this trial did address patients who received up to 4 years of bisphosphonate treatment. In contrast, the trial by Himmelstein et al was randomized, but only included 272 patients with myeloma. Moreover, in this open-label trial, nearly 40% of patients did not complete the stipulated 2-year duration of the study. Finally, this trial did not address the duration of therapy beyond 2 years. Given these caveats, the guidelines committee has only made these as suggested recommendations.

ONJ

ONJ is a major complication that is increasingly observed when more potent bisphosphonates, such as pamidronate and zoledronic acid, have been used. Although first described with bisphosphonates, ONJ also occurs with denosumab. The Expert Panel 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 patients with cancer should receive a comprehensive dental examination and appropriate preventive dentistry before bone-modifying therapy. Active oral infections should be treated, and sites that are at high risk for infection should be eliminated. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures, if possible. Continuation of a bone-targeting agent in the setting of ONJ has to be individualized and dependent on a risk-benefit ratio and the severity of bone disease. Other notable complications of BMAs include atypical fractures of the femur.¹⁹

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including Data and Methodology Supplements, slide sets, and clinical tools and resources, is available at www.asco.org.

[org/hematologic-malignancies-guidelines](#). Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

Related ASCO Guidelines

- Role of Bisphosphonates in Multiple Myeloma¹ (<http://ascopubs.org/doi/10.1200/jco.2007.12.1269>)
- Management of Chronic Pain in Survivors of Adult Cancers⁴⁰ (<http://ascopubs.org/doi/10.1200/JCO.2016.68.5206>)
- Screening, Assessment, and Management of Fatigue in Adult Survivors of Cancer Guideline Adaptation⁴¹ (<http://ascopubs.org/doi/10.1200/jco.2013.53.4495>)
- Integration of Palliative Care into Standard Oncology Practice⁴² (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)
- Patient-Clinician Communication⁴³ (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Manuscript writing: All authors

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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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