

American Society of Clinical Oncology Clinical Practice Guidelines: The Role of Bisphosphonates in Multiple Myeloma

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Purpose: To determine clinical practice guidelines for the use of bisphosphonates in the prevention and treatment of lytic bone disease in multiple myeloma and to determine their respective role relative to other conventional therapies for this condition.

Methods: An expert multidisciplinary Panel reviewed pertinent information from the published literature through January 2002. Values for levels of evidence and grade of recommendation were assigned by expert reviewers and approved by the Panel. Expert consensus was used if there were insufficient published data. The Panel addressed which patients to treat and when to treat them in the course of their disease. Additionally, specific drug delivery issues, duration of therapy, initiation of treatment and management of treatment of lytic bone disease was reviewed and compared with other forms of therapy for lytic bone lesions. Finally, the Panel discussed patient and physician expectations associated with this therapy for bony metastases, as well as public policy implications related to the use of bisphosphonates. The guidelines underwent external review by selected physicians, by the Health Services Research Committee members, and by the ASCO Board of Directors.

Results: The available evidence involving randomized controlled trials is modest but supports that oral clodronate, intravenous pamidronate, and intravenous zoledronic acid are superior to placebo in reducing skeletal complications. A reduction in vertebral fractures has consistently been seen across all studies. No

agent has shown a definitive survival benefit. Intravenous zoledronic acid has recently been shown to be as effective as intravenous pamidronate. Because there are no direct comparisons between clodronate and pamidronate or zoledronic acid, the superiority of one agent cannot be definitively established. However, the panel recommends only intravenous pamidronate or zoledronic acid in light of the use of the time to first skeletal event as the primary end point and more complete assessment of bony complications in studies evaluating it. Additionally, clodronate is not available in the United States. The choice between pamidronate and zoledronic acid will depend on choosing between the higher drug cost of zoledronic acid, with its shorter, more convenient infusion time (15 minutes), versus the less expensive drug, pamidronate, with its longer infusion time (2 hours).

Conclusion: Bisphosphonates provide a meaningful supportive benefit to multiple myeloma patients with lytic bone disease. However, further research on bisphosphonates is warranted, including the following: (1) when to start and stop therapy, (2) how to integrate their use with other treatments for lytic bone disease, (3) how to evaluate their role in myeloma patients without lytic bone involvement, (4) how to distinguish between symptomatic and asymptomatic bony events, and (5) how to better determine their cost-benefit consequence.

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IN THE UNITED STATES, multiple myeloma is the third most common hematologic malignancy with nearly 14,600 cases estimated for 2002.¹ Bone destruction in multiple myeloma is responsible for the most distressing clinical features of the disease. Interleukin-1, interleukin-6, tumor necrosis factor, and receptor for activation of nuclear factor kappa B–ligand are potent bone resorbing factors.²⁻⁴ These cytokines are produced by the myeloma cells as well as stromal cells of the bone marrow. Therefore, the myeloma bone marrow contains increased osteoclast activity. This leads to a loss of bone structure and often leads to pathologic fractures, hypercalcemia, and pain. Conventional roentgenograms reveal abnormalities consisting of lytic lesions, osteoporosis, or fractures in 79% of patients with multiple myeloma at the time of diagnosis.⁵ The vertebrae,

skull, sternum, ribs, pelvis, and proximal humeri and femora are the most frequent sites of involvement. Pathologic fractures can be devastating, as seen in decreased mobility from femoral fractures or spinal cord compromise with vertebral body collapse. Because most experts believe

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Table 1. Summary of Guidelines

1. Lytic disease on plain radiographs	For multiple myeloma patients who have on plain radiograph(s), lytic destruction of bone, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended.
2. Monitoring	In patients with pre-existing renal disease and a serum creatinine < 265 μ mol/L or < 3.0 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates in 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 intermittent evaluation (every 3 to 6 months) of all patients receiving chronic pamidronate or zoledronic acid therapy for the presence of albuminuria and azotemia. In patients experiencing unexplained albuminuria (defined as > 500 mg/24 hours of urinary albumin) or azotemia (defined as an increase of \geq 0.5 mg/dL in serum creatinine or an absolute value of > 1.4 mg/dL among patients with normal baseline serum creatinine levels), discontinuation of the drug is warranted until the 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 reinstated over a longer infusion time (\geq 2 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline.
3. Duration of therapy	The Panel suggests that, once initiated, intravenous pamidronate or zoledronic acid be continued until there is evidence of a substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide at what point the potential palliative benefits of pamidronate or zoledronic acid are less than the inconvenience of receiving this intravenously administered drug. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.
4. 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 nonlytic lesions have been included in selected trials but have not been the primary focus of the trial and never of sufficient number to be separately analyzed.
5. Patients with solitary plasmacytoma, or smoldering or indolent myeloma without documented lytic bone disease	Starting bisphosphonates for patients with solitary plasmacytoma ⁶ or smoldering or indolent myeloma ^{7,8} is not suggested.
6. Patients with monoclonal gammopathy of undetermined significance	Starting bisphosphonates for patients with MGUS ⁸ is not suggested.
7. Biochemical markers	The use of the biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care.
8. Role in Pain Control Secondary to Bony Involvement	Intravenous pamidronate or zoledronic acid is recommended for patients with pain due to osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures or impending fractures.

Abbreviation: MGUS, monoclonal gammopathy of undetermined significance.

multiple myeloma to essentially be incurable with current treatment, emphasis must be placed on quality of life. Measures to reduce morbidity from skeletal involvement by multiple myeloma are important for optimizing a patient's quality of life.

Bisphosphonates are a new class of agents that have been shown in a variety of studies to reduce bony complications associated with multiple myeloma. Several studies have been performed in myeloma that suggest improvements of important outcomes. To obtain a more precise estimate of such benefits and confirm the conclusions that can be drawn from the total body of evidence on bisphosphonates in myeloma, an evidence-based guideline is warranted.

There are a large number of patients with multiple myeloma who theoretically could be considered candidates for this form of therapy. Thus, the American Society of

Clinical Oncology (ASCO) as a service to patients, to its members, and to practicing physicians in general, convened an Expert Panel under the auspices of its Health Services Research Committee to develop recommendations regarding the use of bisphosphonates for multiple myeloma (Table 1) and, in a separate, already published report for breast cancer.⁹ The following recommendations for use of bisphosphonates specifically do not address the use of bisphosphonates as therapy for hypercalcemia in multiple myeloma or other malignancies.

PRACTICE GUIDELINES

The ASCO Health Services Research Committee uses the following definition: "Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical

circumstances.”¹⁰ Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, multidisciplinary process, review of evidence, and documentation. Utilization of guidelines may improve patient outcomes, improve medical practice, minimize inappropriate practice variation, provide decision support tools for practitioners and points of reference for medical orientation and education, and may provide criteria for self-evaluation and assistance with reimbursement and coverage decisions. However, it is important to realize, that guidelines 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. Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient’s individual circumstances. They cannot be assumed to apply to interventions performed in clinical trials, which are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. In that 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.

METHODS

A methodology similar to that applied in prior ASCO practice guidelines was used.

Panel Composition

A panel of experts composed of medical, radiation, and surgical oncologists, health service researchers, statisticians, and pharmacists with an expertise in metastatic bone disease was convened. A patient representative who was currently taking bisphosphonates for her multiple myeloma was also included. Both academic and community practitioners were included. Panel participants are listed in the Appendix.

Process

Pertinent information from the published literature was retrieved and reviewed for the creation of these guidelines. Computerized literature searches of MEDLINE (National Library of Medicine, Bethesda, MD) were performed through January 2002. Abstracts presented at ASCO Annual Meetings were also included. Key words/phrases included in the literature search were multiple myeloma, diphosphonates/bisphosphonates, bone neoplasms, efficacy, surgery, radiotherapy, pain management/palliative care, spinal cord compression, and patho-

Table 2. Levels of Evidence and Grade of Evidence for Recommendations^{8,9}

Type of Evidence	
Level	
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade for Recommendation	
Grade	
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV and findings are generally consistent
C	There is evidence of types II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

logic fractures. Limits included clinical trials, English language, and human studies.

The entire Panel met twice. The first meeting was intended to identify topics to be addressed by the guideline, to develop a strategy for completion of the guideline, and to do a preliminary review of the initial literature search. A second meeting reviewed work to date and refined assignments for the guideline. Subsequently, a subgroup of the Panel, which included the co-chairs, met primarily by conference telephone calls. These meetings were to review progress to date, to identify other supporting or evolving data, and to refine the initial strategies and scope of the guidelines to facilitate timely completion of the guidelines.

A rating of the evidence was made by consensus of the group, rather than by a specific weighting method. Table 2 lists the definitions used in determining the levels of evidence and the grades of recommendation.^{11,12} These definitions were the same as in prior ASCO guidelines. The guideline was circulated in draft form, and all members of the Panel had an opportunity to comment on the levels of evidence, as well as the systematic grading of the data supporting each recommendation. Subsequently, an external review by individuals (see Acknowledgment) not directly involved in development of the guideline assessed the clarity, utility, and completeness of the document. J.B. and B.H. performed final text editing.

Table 3. Clinical Approval Status

Generic Name	Proprietary Name/Manufacturer	Relative Potency*	Current Status
Etidronate	Didronel/Proctor & Gamble Pharmaceuticals, Cincinnati, OH	1	FDA-O (PO) FDA-HC (IV)
Clodronate	Bonefos, Clotoban, Loron, and Ostac/Roche Pharmaceuticals, Nutley, NJ	10	Ongoing and completed phase III
Tiludronate	Skelid/Sanofi Pharmaceuticals, New York, NY	10	FDA-O (PO)
Pamidronate	Aredia/Novartis Pharmaceuticals, East Hanover, NJ	100	FDA-B&MM (IV) FDA-HC (IV)
Alendronate	Fosamax/Merck & Co, West Point, PA	1,000	FDA-O (PO)
Ibandronate	Bondronat/Rhone-Poulenc Rorer, Collegeville, PA	10,000	Completed phase III
Zoledronic/acid	Zometa/Novartis Pharmaceuticals, East Hanover, NJ	100,000	FDA-B&MM (IV) FDA-HC (IV)

Abbreviations: FDA, Food and Drug Administration—approved for: O, postmenopausal osteoporosis; PO, orally; IV, intravenous; HC, hypercalcemia; B&MM, breast cancer and multiple myeloma patients with lytic bone disease.

*Relative to etidronate.

Guideline and Conflict of Interest

The content of the guidelines and the manuscript were reviewed and approved by the ASCO Health Services Research Committee and by the ASCO Board of Directors before dissemination. All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. No conflicts were identified that required any individual's role to be limited (Appendix).

Revision Dates

At annual intervals, the Panel co-chairs and two Panel members designated by the co-chairs will determine the need for revisions to the guidelines based on an examination of current literature. If necessary, the entire Panel will be reconvened every 3 years to discuss potential changes, or more frequently, if new information suggests that more timely modifications may be warranted. When appropriate, the Panel will recommend revised guidelines to the ASCO Health Services Research Committee and the ASCO Board for review and approval.

BISPHOSPHONATE BACKGROUND

Definition

Bisphosphonates are analogs of endogenous pyrophosphate in which a carbon atom replaces the central atom of

oxygen. This carbon substitution makes these compounds resistant to hydrolysis and allows two additional chains of variable structure. One of these side chains usually contains a hydroxyl moiety, which allows high affinity for calcium crystals and bone mineral. The differences at the other side chain produce marked differences in the antiresorptive potency of different bisphosphonates, as shown in Table 3. In fact, the newer bisphosphonates, such as ibandronate and zoledronic acid, show 10,000- to 100,000-fold greater potency than do the older agents such as etidronate. The clinical approval status of these bisphosphonates is shown in Table 3.

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.^{13,14} Bisphosphonates are potent inhibitors of osteoclastic bone resorption and are effective in treating cancer-induced hypercalcemia of malignancy, Paget's disease of bone, and postmenopausal osteoporosis.¹⁵⁻¹⁹ Therefore, it was logical to explore different bisphosphonates to treat patients with osteolytic bone metastases from multiple myeloma.

The mechanism of action and biochemistry of bisphosphonates have been recently reviewed by Fleisch.²⁰ The bioavailability of bisphosphonates is poor, ranging from a few percent for clodronate, etidronate, and tiludronate, to below 1% for pamidronate and alendronate. In addition, there is high inter- and intraindividual variability that is decreased by drinks such as orange juice and coffee as well as calcium.²¹

Although worldwide seven bisphosphonates (Table 3) are available for various conditions, before 2001 only one agent was approved in the United States for treatment of metastatic bone disease: pamidronate intravenous (IV). In Feb-

ruary 2002, the United States Food and Drug Administration (FDA) approved the use of zoledronic acid for the treatment of patients with multiple myeloma and other metastatic bone disease. Roche Pharmaceuticals (Nutley, NJ), the makers of clodronate, which is available in both IV and oral forms, will soon be seeking FDA approval. In Canada, both pamidronate and clodronate are approved for use in patients with metastatic bone disease.

Whom to Treat

Bony complications are the most important clinical manifestation of multiple myeloma. Ideally, oncologists would like to identify predictors of who will develop serious complications of their bony disease such as fractures, spinal cord compression, or intractable pain. This would assist in the stratification of these patients into who is or is not likely to respond to interventions intended to modify the natural history of bony complications. Such predictors, including biochemical bone markers, are currently not validated but are under investigation. Current evidence has principally used the presence of radiographic evidence of lytic bone disease to stratify risk.

Definition of End Points

The ultimate measures of the clinical value of any intervention are its beneficial effect on the length of disease-free or overall survival and quality of life. Both short- and long-term toxicities of the treatment as well as its cost-effectiveness are important in judging the value of a given clinical intervention. Intermediate outcomes in metastatic bone disease include biomarkers, radiographic criteria for bony response or progression, and, in the adjuvant setting, bone mineral density. Intermediate outcomes have much less value unless they are associated with or can predict clinical outcomes that are important to patients (eg, survival and quality of life).

With the exception of a few subset analyses, all published randomized trials have observed no overall survival benefit in myeloma patients receiving bisphosphonates. A variety of nonfatal skeletal-related complications could occur and be measured as meaningful end points: fractures, spinal cord compression, hypercalcemia, and pain. A change in the frequency of these events should be, in aggregate, associated with an improvement in quality of life. For pathologic fractures, their presence or absence and site are not subject to substantial observer variation. However, measuring their functional consequence and associated pain severity can vary by observer. Subsequent therapeutic action (ie, surgery or radiation) that follow from these events can also vary from one

caregiver to another. Therefore, randomized and double-blind assessments are essential.

In many of the clinical reports reviewed, the Panel could not discern the preplanned primary end point of the various reported end points. Various studies used the number of fractures per person-year, progression of osteolytic lesions per person-year, and a composite end point of skeletal related events (SREs) divided by the time on trial for each patient. The latter composite end point of SREs was chosen in cooperation with the FDA for the intravenous pamidronate trial.^{22,23} An SRE was defined as the patient developing either a pathologic fracture, spinal cord collapse/compression, or requiring surgery or therapeutic radiation therapy for bone pain or a bone-related cause. This definition included SREs that may have resulted from therapeutic interventions such as surgery or radiotherapy without an associated pathologic fracture or spinal cord compression. For example, SREs included prophylactic surgical intervention and/or radiotherapy for patients with impending pathologic fractures or radiation for pain control. As currently used, the SRE definition does not distinguish between symptomatic and asymptomatic events or pathologic fractures that were asymptomatic, but detected by surveillance radiographs. All were counted equally as one SRE.

A recent critical analysis of end points in bisphosphonate trials for patients with metastatic bone disease, presents important information to consider when interpreting results from these studies.²⁴ Many of these trials relied on events-per-person-years analysis in evaluating their end points, which assumes that all patients within each arm of the study experience skeletal complications at the same rate. In fact, the rate of occurrence of bone complications is highly variable among patients with metastatic bone disease, as was observed in the pamidronate studies.^{22,23,25} Thus, this between-patient variation in complication rates means that tests for the effects of bisphosphonates on skeletal complications based on the events per person-year will increase false-positive error rates. Cook and Major's²⁴ simulated analysis projected that false-positive errors rate could increase from the typically assumed level of 5% to up to 20%. The primary statistical reason is that the events of interest (fractures) may not be independent events but clustered events. In the case where the therapy was superior to the control, this would magnify that effect.

A more reliable statistical end point in these types of clinical trials is time to first SRE.²⁶ This eliminates the bias in analyses based on events per person-years. An analysis of the time to first event avoids the problem of clustering of SREs across a treatment arm. As subsequently discussed, a reduction of rates of skeletal complications (events per year)

did not translate into an impact on time to first skeletal event in a breast cancer trial²⁷ and was not reported in the largest clodronate myeloma trial.²⁸ In contrast, the randomized clinical trials showing a delay in time to first skeletal event with bisphosphonate usage have also consistently shown a smaller but statistically significant reduction in skeletal complication rates (ie, number of skeletal events per year).^{22,23,25}

Whereas from a statistical perspective, the time to first SRE is the most effective at detecting a clinical benefit; from a clinical perspective, an aggregate score of symptomatic SREs may be more informative. The clustering of adverse events such as SREs may in total have substantial morbidity and mortality. Solely assessing time to first SRE may underestimate the potential benefits of bisphosphonate therapy in terms of future events prevented by this treatment.

In summary, the panel strongly recommends that investigators and editors of reports for medical conditions where recurrent events are common and anticipated (such as SREs) to require a statistical analysis plan that clearly and distinctly report their data as both the proportion of patients experiencing skeletal events (eg, vertebral fracture) and the time to first event. Reporting of the number of events (fractures) per person per year should be only a secondary end point. Distinguishing between symptomatic and asymptomatic events should also occur.

GUIDELINES FOR THE USE OF BISPHOSPHONATES IN MULTIPLE MYELOMA

In this guideline, recommendations about the indications for using bisphosphonates for bone disease in multiple myeloma are presented in the context of five clinical presentation scenarios for patients with myeloma and other monoclonal gammopathies, including patients with lytic disease, solitary plasmacytoma or smoldering myeloma, only osteopenia, monoclonal gammopathy of undetermined significance, and the presence of bone pain. In addition, recommendations address evidence of the use of biochemical markers to monitor bisphosphonate use and the duration of therapy.

1. Lytic Disease on Plain Radiographs

Guideline: For multiple myeloma patients who have on plain radiograph(s), lytic destruction of bone, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended.

Level of Evidence: II

Grade of Recommendation: B

The Panel based its recommendation on reviewing all the available literature but specifically focused its critical appraisal on the four most relevant studies.^{22,23,28-30} Table 4 provides a detailed comparison of the entry criteria, design, statistical planning, and reporting of results and number of patients needed to treat to avoid one SRE for these trials (number needed to treat).^{31,32}

Pamidronate

There is only one randomized placebo-controlled trial evaluating the use of intravenous pamidronate for patients with myeloma.^{22,23} This prospective study subsequently led the FDA to approve the use of the drug in this setting. Three hundred ninety-two patients with stage III multiple myeloma and at least one lytic lesion were randomized to placebo or pamidronate (90 mg), given as a 4-hour infusion every 4 weeks, for 21 cycles. All patients' antimyeloma therapy had to have been unchanged for at least 2 months before entry into the study. The serum creatinine was less than 5.0 mg/dL. The primary preplanned end points were the reduction of skeletal related events after nine cycles of therapy²² and the evaluation of safety and survival after 21 cycles of randomized treatment.²³ Patients were stratified before randomization based on having received either their first antimyeloma regimen (stratum 1) or having received their second or more antimyeloma regimens (stratum 2). Three hundred seventy-seven patients were assessable for the primary end point (SREs), 179 in the placebo group and 198 in the pamidronate group. Approximately two thirds (n = 247) were on their first antimyeloma regimen (stratum 1). The treatment groups were comparable in terms of age, sex, stratum, number of lytic lesions, and prior antimyeloma regimens. The published reports do not give the preplanned effect size used in calculating the sample size or if an intent-to-treat analysis was used.

At 9 months, the primary time end point, the mean number of SREs per year was reduced from 2.1 in the placebo group to 1.1 in the pamidronate group ($P = .0006$). At further follow-up of 21 months, the number of SREs changed minimally at 2.2 per year in the placebo group and 1.3 per year with pamidronate ($P = .008$). In addition, the median time to the first skeletal event was 10 months in the placebo group and 21 months in the pamidronate group ($P < .001$). At 12 months, 28% of patients in the pamidronate group versus 44% in the placebo group had an SRE ($P = .001$). At further follow-up of 21 months, this difference persisted but narrowed slightly to 38% in the pamidronate group versus 51% in the placebo group ($P = .015$).

Other end points showing a benefit included a lower percentage of patients developing a pathologic fracture or requiring radiation to bone in the pamidronate group. Using

Table 4. Select Trial Characteristics

	Pamidronate 90 mg IV Over 4 Hours Every 4 Weeks	Clodronate 2.4 g Daily Up to 24 Months	Clodronate 1.6 g Daily Until Disease Progression	Zoledronic Acid 4 or 8 mg Every 3-4 Weeks for 12 Months
Author	Berenson et al ^{22,23}	Lahtinen et al ²⁸	McCloskey et al ^{29,31}	Rosen ³²
Design				
Duration, median months	18	24	31	12
Sample size, n	392	350	536	1,648 (513 myeloma, 1,130 breast cancer)
Patients treated when in course of disease	First or second chemotherapy, > 1 osteolytic lesion (prior skeletal event)	First treatment with or without osteolytic bone lesions	First treatment, no pre-planned stratification by osteolytic lesion	First treatment, > 1 osteolytic lesions
Entry				
Osteolytic bone lesions at entry, % of patients	100	66	60	100
Pretreatment x-rays, % of patients	100	100	Unknown	100
Planning				
End point assessment	Beginning at 6 months, x-rays every 3 months	X-ray every 6 months until 24 months	X-rays annually or if symptomatic	3, 6, 9, and 13 months
Preplanned primary end point	Combined SREs at 9 months (path fracture, radiation, or surgery on bone or cord compression)	Progression of osteolytic lesions by 24 months	Death	Combined SREs
Prestudy power calculation	Not stated	30%	Not stated	Noninferiority study to intravenous pamidronate
Prestudy statistical plan	Not stated	Events per person per year	Not stated	Proportion of patients with at least one SRE
Radiographs read blind and independently	Not stated	Yes	Yes	Yes
Intent-to-treat analysis	Not stated	Yes	Yes	Yes
Coded symptomatic v asymptomatic fractures	No	No	No	No
Follow-up				
X-rays completed during follow-up	83%	95% of surviving patients at 24 months	50-52% of survival patients at 12 months	Not stated
Results				
Statistical approach used	Time to first SRE	Events per person per year	Events per person per year	Time to first SRE
Pain score decline	Yes	Nonsignificant change	11% v 20% at 24 months, at other times NS	Yes, equal to pamidronate
Hypercalcemia > 3 mmol	No difference	No difference	5.1% v 10.1% (P = .064)	No difference
Radiographic progression of osteolytic disease	Not reported	12% v 24% (P = .026)	Not reported	Not reported
Time to first skeletal-related event	~12 v 21 months	Not reported	Not reported	Median 12.3 months zoledronic acid v 12.0 months pamidronate
Skeletal-related events per year	28% v 44% at 12 months. 38% v 51% at 21 months	Not reported	Not reported	47% to 49% zoledronic acid v 49% pamidronate
Nonvertebral fractures	15% v 10%	24% v 23%	6.8% v 13.2% (P = .036)	Not reported. Rate per month no different
Vertebral fractures	Not reported	30% v 40%, NS	80 v 146 (P < .001)	Not reported
Vertebral fractures, people	16% v 27%	Not reported	15.5% v 22% by ITT (41 v 60% (P < 0.001) in pts having x-rays)	Not reported
Radiotherapy needed	25% v 34%	Not reported	Not reported	0.47 v 0.71 per year, P = .018
Survival analysis				
Percent at 24 months	~53% v 50%	68% v 60%	61% v 64%	Not reported
End point	Any SRE	Progression osteolytic lesion	Vertebral fracture	N/A
Summary				
RRR	36.4% at 12 months; 25.4% at 21 months	50%	29.50%	N/A
NNT avoid one event	6.2 at 12 months; 7.7 at 21 months	8.3	15.3 all patients; 5.2 with x-rays	N/A

Abbreviations: IV, intravenous; NS, nonsignificant; SRE(s), skeletal-related event(s); NNT, number needed to treat; ITT, intention to treat; RRR, relative risk ratio; N/A, not applicable.

the Radiation Therapy Oncology Group scoring system, patients receiving pamidronate had significant decreases in their pain and required no increase in analgesic drug use. In contrast, the placebo group had no improvement in their pain and required more analgesic drug use during the trial. Quality of life as measured by Eastern Oncology Cooperative Group (ECOG) criteria³³ and the Spitzer quality of life index³⁴ deteriorated only in the placebo-treated patients.

Seventy-eight percent of the patients completed the first nine cycles of randomized treatment. Seventy-five percent of patients continued randomized assignment beyond the first nine cycles, with 41% completing 21 cycles of the study drug. The analysis beyond nine cycles was primarily performed to assess safety and survival. Although survival was not different between the pamidronate-treated group and placebo patients in all randomized patients, a pre-planned subgroup analysis found that stratum 2 patients (those on their second or more antimyeloma regimens) who received pamidronate lived longer than those patients who received placebo (21 months versus 14 months, respectively, $P = .041$).

The benefits of IV pamidronate were principally seen in reductions in skeletal complications, such as pathologic fractures, surgery for fracture or impending fracture, radiation, spinal cord compression, and hypercalcemia.

Another clinical trial evaluated oral pamidronate (300 mg/d) compared with placebo in 300 newly diagnosed myeloma patients who were also receiving intermittent oral melphalan and prednisolone.³⁵ The drug had no effect on either SREs or survival. The results from patient self-assessments were conflicting—significantly fewer episodes of severe pain in the pamidronate group but no benefit in average pain score or analgesic use. Height loss and bone resorption markers improved in the oral pamidronate group. The authors attributed the overall negative results of their study to the low absorption of oral bisphosphonates. These results are consistent with the known poor and erratic absorption of this class of drugs. Although orally administered, even weak, first-generation agents may be effective in the treatment of postmenopausal osteoporosis, the amount of inhibition of bone resorption required to overcome osteoclast activation, and to lead to a clinical benefit for myeloma patients, is much greater.

No clinical trials are known to be in progress to better define the dose, interval, or patient subgroups that may specifically benefit from intravenous pamidronate. However, the second report from the randomized pamidronate trial evaluated specific subgroups of patients.²³ First, pamidronate reduced the proportion of patients developing an SRE regardless of whether or not patients had a skeletal complication before study entry. Second, as a surrogate for

progressive disease during the trial, patients were evaluated based on whether a change in chemotherapy occurred during the trial. Intravenous pamidronate reduced the proportion of patients with an SRE both in those changing their chemotherapy during the trial as well as those showing no change in therapy.

Clodronate

In a placebo-controlled clinical study by Lahtinen et al,²⁸ 350 (336 assessable) newly diagnosed patients who were treated with oral melphalan and prednisolone were randomized to receive either clodronate (2,400 mg/d) or placebo for 2 years.²⁸ The trial's sample size was based on an anticipated effect size of 30% for clodronate in reducing progression of osteolytic lesions or events per person per year. At the primary end point time of 24 months, 95% of patients still alive had received radiographs. Of those who had radiographs at baseline and 24 months, the proportion of patients with progression of osteolytic lesions in the placebo group was double that in the clodronate group (24% v 12%, respectively, $P = .026$). The clodronate group experienced a lower rate of progression of vertebral fractures (30% v 40%), which was not statistically significant. A similar rate of progression in nonvertebral fractures was noted in both groups (clodronate, 24% and placebo, 23%). In addition, the number of patients developing hypercalcemia, the number of changes in pain index, and the use of analgesics was similar between the arms. The need for surgery and radiotherapy was not assessed in this trial.

The use of oral clodronate was the subject of another randomized, double-blind trial from the Medical Research Council (MRC).²⁹ In addition to their chemotherapy, 536 newly diagnosed multiple myeloma patients received either 1,600 mg of clodronate or placebo daily. The trial's pre-planned primary end point was a change in overall survival. After a median follow-up of 8.6 years, there was no overall significant difference in survival between the two groups. ($P = .38$).³¹

The analysis of skeletal complications used the number of skeletal events per patient per year. The primary limitation of the trial was that follow-up radiologic evaluation was performed principally only in symptomatic patients. Only about one half of patients had radiographs at 1-year follow-up.²⁹

Nonvertebral fractures were 13.2% in the placebo group versus 6.8% in the clodronate group ($P = .036$). Vertebral fractures were reduced in those patients having x-rays from 55% in the placebo group versus 38% in the clodronate group ($P < .001$). However, intent-to-treat evaluation (of all randomized patients) reduces the difference to 22% in the

placebo group versus 15.5% in the clodronate group ($P = .05$, χ^2 analysis) (prepared by B.H. for this guideline).

With regard to hypercalcemia, patients treated with oral clodronate experienced the complication only slightly less than those who received placebo. However, severe hypercalcemia (more than 3 mmol/L) was reduced by 50% in those who received clodronate. The drug had no statistically significant effect on pain, except back pain, at a single time point (24 months), and performance status was unaffected except at this time point. Less than 10% of patients had radiotherapy, and its use did not differ between groups.

The time to first nonvertebral fractures or severe hypercalcemia was reported graphically and was reduced by about 8% to 10% ($P < .021$). However, a projection to the time to first vertebral fracture or the other components used in the definition of an SRE used in the pamidronate trial was not reported.

Subset analyses have found different possible effects associated with disease burden. The pamidronate trial had a preplanned subset analysis (J. Berenson, personal communication, April, 2002), which found a survival advantage in those patients receiving pamidronate who had failed prior chemotherapy (stratum 2) compared with first-line chemotherapy (stratum 1).^{22,23} A similar subgroup analysis could not be in the MRC clodronate study because all patients were receiving first-line chemotherapy. However, if having a prior skeletal fracture is an indicator of greater disease burden, than a survival analysis might show an advantage in such patients. In contrast, the MRC clodronate study found that patients with prior skeletal fractures had a poorer (not better) survival with clodronate (hazard rate, 1.6; 95% confidence interval, 1.1 to 2.3).³¹ This inconsistency between the two studies highlights the hazard in drawing conclusions versus hypotheses from such analyses.

Several other randomized studies have been published evaluating oral clodronate but were not further considered in making these guidelines because of their small size³⁶ or lack of a placebo in the control group.³⁷ No direct comparative trials of pamidronate and clodronate have been reported or are in progress. No direct comparisons of any of the oral bisphosphonates, for example, clodronate, to etidronate or alendronate, for multiple myeloma patients are known to be in progress. The only direct comparative study was between intravenous pamidronate and zoledronic acid (see below).

Zoledronic Acid

In February 2002, the FDA approved an expanded indication for zoledronic acid for the treatment of patients with bone metastases that included its use in multiple

myeloma (www.fda.gov/cder/cancer). This new indication is based on a large randomized comparison to pamidronate.

Two randomized trials showed zoledronic acid can be given safely over several minutes and produce similar antiresorptive effects, as assessed by bone resorption markers, as 90 mg of pamidronate.^{32,38} The randomized phase II study, compared this newer bisphosphonate to pamidronate in 280 patients with lytic bone metastases from either myeloma ($n = 108$) or breast cancer ($n = 172$).³⁸ Patients were randomized to 9 monthly infusions of 0.4 mg, 2.0 mg, or 4.0 mg of zoledronic acid in a 5-minute infusion, or to 90 mg of pamidronate as a 2-hour infusion. The primary end point was to determine a dose(s) of zoledronic acid that reduced the need for radiation to less than 30% of treated patients, although all SREs were also evaluated as in the previously reported pamidronate trials. Duration of follow-up was not reported. Radiation treatment was required in a similar proportion of patients receiving pamidronate and zoledronic acid at 2.0 mg or 4.0 mg (18% to 21%), whereas more patients receiving 0.4 mg of zoledronic acid underwent radiotherapy (24%). Similarly, the proportion of patients with any SRE was lower (30% to 35%) in the 2.0 mg and 4.0 mg zoledronic acid and the pamidronate groups compared with the 0.4-mg zoledronic acid group (46%).

This phase II trial was not powered to show superiority of zoledronic acid compared with pamidronate. In light of the above results as well as those from a large phase III trial showing the superiority of zoledronic acid at 4- or 8-mg doses over pamidronate for the treatment of hypercalcemia of malignancy,¹⁶ a larger phase III randomized trial compared 4- or 8-mg doses of zoledronic acid to 90 mg of pamidronate every 3 to 4 weeks in patients with multiple myeloma or breast cancer who had lytic disease.³² Because of increases in creatinine occurring more frequently among patients receiving zoledronic acid, the infusion time for zoledronic acid was increased from 5 minutes to 15 minutes during the trial. Despite this change in infusion time, renal problems continued to occur more often among patients randomized to 8 mg zoledronic acid, and their dose was subsequently reduced to 4 mg. The trial's sample size was based on showing the noninferiority, not superiority, of zoledronic acid to pamidronate. To show this noninferiority of either zoledronic acid dose to pamidronate, the trial's sample size was sufficient to have an 80% power (using a one-sided significance of 0.05) in the proportion of patients experiencing a SRE.

The trial included 1,648 eligible patients, of whom 510 had multiple myeloma (all stage III) and the remainder metastatic breast cancer. One thousand six hundred forty patients (eight exclusions) were evaluated in the intent-to-treat analysis approximately every 3 months for 13 months.

Table 4 compares the design and findings of this trial to previously discussed ones with pamidronate and clodronate. The proportion of patients with any SRE after 13 months did not differ among the three treatments and did not differ between the breast cancer and the multiple myeloma patients. A higher percentage of patients experienced an SRE in this trial (47% to 49%) than in the prior pamidronate versus placebo trial (28% to 38%). The median time to first SRE was similar between treatment groups (range, 12 to 13 months). The authors speculate that the difference in SRE rates was a result of the treatment of patients early in the course of their disease (a median of 3 months versus 15 months from diagnosis) when skeletal events are more likely to occur; and therefore, this study captured more events despite the initiation of therapy.

Secondary end points of pain and performance status showed similar effects to those in prior studies. Details related to pain were not reported other than to say that of patients whose pain score was greater than zero at the beginning of the study, 53% to 69% had a decrease in pain scores. The average decline in pain score was approximately 0.5 on a five-point scale. Analgesic scores and ECOG performance status over the 13 months was fairly stable.

In all treatment groups, approximately 50% of patients reported an adverse event, however, less than 5% of those events were thought to have been related to the study drug. Seven percent of patients discontinued therapy because of an adverse effect. The frequency of renal impairment was approximately 2% in the higher dose zoledronic acid group compared with those who received 4 mg of zoledronic acid (0.5%) or pamidronate (0.2%). After modifying the infusion schedule of zoledronic acid, the incidence of renal impairment declined but the numbers of patients was small.

Panel Deliberations

Several other groups or individuals have addressed the role of bisphosphonates in multiple myeloma. The Cochrane Myeloma Review Group has recently completed an extensive literature review of previously reported randomized trials evaluating bisphosphonates in multiple myeloma patients.³⁹ This review identified 11 trials (range, 13 to 536 patients) involving 2,183 assessable patients (Table 5).^{22,23,28,29,35-37,40-45} These trials included several with small numbers of patients and used widely divergent end points in their analysis of skeletal complications. The review concluded that clodronate and pamidronate compared with placebo were beneficial to myeloma patients in terms of reducing bone pain and vertebral fractures but were not beneficial in reducing nonvertebral fractures. In addition, etidronate, oral pamidronate, and ibandronate were found to be ineffective.

In an earlier evidence-based review, Bloomfield et al³⁰ concluded that the use of oral clodronate had level I evidence in reducing the progression of osteolytic lesions. However, only intravenous pamidronate was given level I evidence for reducing more clinically relevant end points including skeletal events and bone pain. Another recent review addressed the role of oral bisphosphonates in myeloma and breast cancer and concluded that oral bisphosphonates do not seem to be as effective as those administered intravenously.⁴⁶

Although the conclusions of the Cochrane review suggest that both clodronate and pamidronate are likely to be superior to placebo, the judgment of the Panel was that the recommendation be made only for the use of intravenous pamidronate and zoledronic acid. Reasons for this decision include the following: (1) that clodronate has not yet been approved for use in the United States; (2) the evidence for clodronate was clouded by the potential for an overestimation of its beneficial effect, based on the use of events per person per year; (3) the incomplete follow-up in the MRC study; and (4) the inability to aggregate all the relevant skeletal end points. There was a lack of consensus in the panel on the appropriateness of using meta-analysis methods to pool results from the small trials. A separate, universal limitation of all studies is their failure to separately analyze symptomatic versus asymptomatic events.

2. Monitoring

Guideline: In patients with pre-existing renal disease and a serum creatinine less than 265 $\mu\text{mol/L}$ or less than 3.0 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates in 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 intermittent evaluation (every 3 to 6 months) of all patients receiving chronic pamidronate or zoledronic acid therapy for the presence of albuminuria and azotemia. In patients experiencing unexplained albuminuria (defined as more than 500 mg/24 hours of urinary albumin) or azotemia (defined as an increase of ≥ 0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL among patients with normal baseline serum creatinine levels), discontinuation of the drug is warranted until the 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 reinstated over a longer infusion time (≥ 2 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline.

Level of Evidence: V

Grade of Recommendation: D

The dose and interval recommended for pamidronate (90 mg given intravenously for at least 2 hours every 3 to 4 weeks) is based on several recent reports on the use of this schedule in comparison to zoledronic acid.^{32,38} Current FDA approval recommends a 4-hour infusion time for pamidronate, however, these two recent reports show no adverse effects of a shorter infusion time. In a randomized trial, 280 patients with either multiple myeloma (n = 108) or breast cancer with lytic bony metastases (n = 172) were given either nine monthly infusions of pamidronate 90 mg as a 2-hour infusion, or zoledronic acid at one of three doses.³⁸ Myeloma patients receiving the 2-hour pamidronate experienced no unexpected toxicity or adverse effects. Thus, consensus of the Panel is that an infusion time of at least 2-hours is safe and well tolerated.

Although shorter infusion times may be tolerated on a short-term basis, infusion times less than 2 hours, especially those ≤ 1 hour given on a long-term basis (more than 1 year), have been occasionally associated with renal toxicity including albuminuria followed by azotemia. Similar effects are observed with long-term use of higher doses of pamidronate (≥ 180 mg) or more frequent dosing of the drug (weekly or biweekly schedules of 90-mg infusions).⁴⁷ The kidney pathology may show a collapsing focal segmental glomerulosclerosis.⁴⁷

Recently, several case reports have appeared related to adverse renal consequences with prolonged pamidronate use.⁴⁷ Importantly, the appearance of albuminuria in these patients should lead the treating physician to hold the dose of pamidronate until the albuminuria and/or azotemia reverses itself. Based on the algorithm used in the comparative pamidronate versus zoledronic acid trials, if detected early, this renal dysfunction has been reversible in most cases. Re-treatment of these patients with 90 mg monthly infused over ≥ 2 hours has been tolerated without the return of kidney problems. Therefore, the development of albuminuria and/or azotemia unrelated to either myeloma or another medical condition is cause for concern and warrants discontinuation of the drug until reversal of the renal abnormalities occurs.

The Panel's specific recommendation was that the presence of unexplained albuminuria and/or azotemia should warrant discontinuation of pamidronate or zoledronic acid until these renal problems are resolved. Unexplained albuminuria is defined as more than 500 mg/24 hours of urinary albumin; azotemia is defined as an increase of ≥ 0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL among patients with normal baseline serum creatinine levels. These patients should be reassessed every 3 to

4 weeks, with a 24-hour urine collection for a total protein and urine protein electrophoresis, and pamidronate reinstated over a longer infusion time (≥ 2 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline. Although no published studies exist to guide monitoring of patients for renal abnormalities on long-term intravenous pamidronate or zoledronic acid, the Panel recommends intermittent evaluation (every 3 to 6 months) of all patients receiving chronic pamidronate therapy for albuminuria and azotemia. However, in myeloma patients, part of their routine assessment for the status of their underlying cancer usually involves assessment of a 24-hour urine for total protein and protein electrophoresis, as well as renal function. It is essential that physicians infuse pamidronate 90 mg at a rate no faster than 2 hours every 3 to 4 weeks and not attempt to shorten the infusion time, increase the dose, or reduce the dose interval.

The safety and frequency of nonrenal adverse events with pamidronate were well characterized in the pamidronate versus placebo trial^{22,23} and the recent pamidronate versus zoledronic acid studies.^{32,38} The incidence of most adverse effects in patients treated with pamidronate was similar to that observed in the placebo group. Transient myalgias, arthralgias, and flu-like symptoms with fever tend to occur more often in patients treated with pamidronate than placebo.⁴⁸ These symptoms usually occur only after the first and/or second infusion of pamidronate and are not an indication to discontinue treatment with the drug. Mild infusion site reactions have also been infrequently reported. Patients have rarely discontinued pamidronate therapy because of adverse effects. In the long-term follow-up of multiple myeloma patients treated as part of the randomized controlled trial, new or worsening anemia occurred more often in the pamidronate-treated patients than in the placebo group (38% v 25%) during the last 12 cycles of treatment.²³ Long-term results of the breast cancer chemotherapy trial also reported that anemia and thrombocytopenia occurred slightly more often in the pamidronate group than in the placebo group.²⁵ However, the levels of anemia and thrombocytopenia were not sufficient to lead to differences in transfusions or erythropoietin use. In the recently completed phase III trial comparing zoledronic acid versus pamidronate, approximately 30% of patients in both groups developed anemia.³² In fact, because bisphosphonates are not myelosuppressive, these agents can be combined with cytotoxic chemotherapy or radiotherapy without increasing the bone marrow suppression that results from treatment with these modalities. Uveitis and other ocular manifestations, including iritis, are rare but well-described adverse manifestations of these drugs.⁴⁸

3. Duration of Therapy

Guideline: The Panel suggests that, once initiated, intravenous pamidronate or zoledronic acid be continued until there is evidence of a substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide at what point the potential palliative benefits of pamidronate or zoledronic acid are less than the inconvenience of receiving this intravenously administered drug. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.

Level of Evidence: None available (N/A).

Grade of Recommendation: Panel Consensus

The optimal duration of bisphosphonate use is unknown because this issue has never been the focus of a clinical trial. In the previously described trials of intravenous pamidronate in myeloma patients with osteolytic disease, pamidronate (or placebo) was given for 21 months or until patient refusal, physician- or patient-defined unacceptable toxicity, or death.²³ At this point, there were continued beneficial effects of pamidronate in both reducing the number of patients who developed any SRE as well as in the number of events experienced by each patient.

Discontinuation of pamidronate or zoledronic acid because of performance status changes should only be considered if the patients' likely palliative benefit is believed to be less than the inconvenience of receiving an intravenous infusion. There is supporting evidence for the continuation of intravenous pamidronate because of its benefit on performance status, even in relapsing patients.^{22,23} Patients in stratum 2 (relapsing patients) who received monthly pamidronate were significantly less likely to show a deterioration in ECOG performance status than those who received placebo. Although this study was not analyzed beyond 21 months, the rate of bone resorption returns to baseline (before initiation of intravenous pamidronate) within 1 to 2 months of discontinuation of the drug.^{22,23} In the osteoporosis studies, discontinuation of oral bisphosphonates after several years of therapy leads to renewed bone loss as determined by bone densitometry or bone turnover within months of discontinuation of treatment.⁴⁹ A trial evaluating oral alendronate for patients with postmenopausal osteoporosis demonstrated renewed bone loss with discontinuation of the drug after 2 years of administration; however, patients who continued the bisphosphonate for an additional 2 years showed continued increases in bone density.⁵⁰ Because the rate of bone loss is much greater in individuals with myeloma than in women with postmenopausal osteoporosis, the discontinuation of monthly intravenous pamidronate is

likely to be met by bone loss within a much shorter period with negative consequences for the patient.

The consensus of the Panel members is that bisphosphonates should be continued until the patients' likely benefit is believed to be less than the inconvenience of receiving an intravenous monthly infusion or that the patient develops significant side effects related to the drug.

4. Myeloma Patients With Osteopenia Based on Normal Plain Radiograph or Bone Mineral Density Measurements

Guideline: It is reasonable to start intravenous bisphosphonates in multiple myeloma 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 and never of sufficient number to be separately analyzed.

Level of Evidence: Insufficient data, N/A.

Grade of Recommendation: Panel Consensus

Given that the benefit of pamidronate was seen in all potential subgroups of patients with lytic bone disease and that 75% of patients with myeloma at presentation have bone disease, it is reasonable to consider whether all myeloma patients at diagnosis should begin pamidronate (or be enrolled in a clinical trial). Myeloma patients with less advanced disease (stage I and II) were not included in the randomized clinical trial that demonstrated the efficacy of monthly intravenous pamidronate.^{22,23} Despite this, it is the Panel's impression that this drug is likely to be effective for patients with earlier stages of myeloma as well as for those patients without lytic bone disease. However, no current or planned studies will evaluate the use of pamidronate for these groups of patients. Clinical judgment is also required as some clinical scenarios may dictate that bisphosphonates be withheld until the clinical course is clarified, as in the example of a patient with preterminal disease for whom the benefit of the drug may be outweighed by the inconvenience of the infusion.

Although there is no direct comparison of bisphosphonates versus a suitable control in this population, the Panel felt that the burden for using bisphosphonates in this clinical situation should be on those who would not generalize the results of randomized studies from closely related patient populations. This conclusion is based on our understanding of the mechanism of action of bisphosphonates and the efficacy of these drugs among myeloma patients with lytic disease as well as other types of patients without malignancy with associated enhanced bone loss. Additionally, the Panel took into account our knowledge of the mechanism of osteopenia in myeloma patients, our knowledge of the natural history of osteopenia among these patients and its clinical consequences. This was weighed against the risks

and side effects of bisphosphonates. Based on all these considerations, the Panel members felt it would be prudent to recommend the use of bisphosphonates for patients with osteopenia as the only manifestation of their bone disease. Despite the lack of direct level I evidence, the Panel feels quite strongly that this is an appropriate treatment strategy. However, because of the lack of direct evidence, Panel members also support placing such patients on placebo-controlled or other suitably controlled randomized trials if they become available.

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

Guideline: Starting bisphosphonates for patients with solitary plasmacytoma⁶ or smoldering or indolent myeloma^{7,8} is not suggested.

Level of Evidence: N/A

Grade of Recommendation: Panel Consensus

Patients with either solitary plasmacytoma or indolent or smoldering myeloma have not been evaluated in clinical trials evaluating bisphosphonates. In the context of the known natural history and clinical course of these conditions, the Panel was not prepared to generalize the favorable results of randomized trials with documented lytic disease to include patients with these early manifestations of plasma cell dyscrasias. There is a growing body of animal and in-vitro evidence that bisphosphonates reduce tumor burden in bone and possibly at extra-skeletal sites.^{20,51,52} It is unknown whether all bisphosphonates have the same anti-tumor effects, which drugs have the best effects, and if these effects are clinically meaningful. Although some laboratory data suggest that these drugs, especially the more potent bisphosphonates, may have direct and indirect antimyeloma effects, the clinical results supporting these effects have only been seen in patients with overt myeloma receiving chemotherapy. There is currently no evidence to show the efficacy of bisphosphonates for patients with either solitary plasmacytoma or indolent or smoldering myeloma. The conduct of future clinical trials with bisphosphonates in patients with these conditions will be important in the evaluation of their ability to prevent the progression of lytic bone disease as well as myeloma itself. A recently initiated German trial comparing zoledronic acid to placebo among patients with early-stage myeloma should provide important data on which to base use of these drugs in this group of patients.

6. Patients With Monoclonal Gammopathy of Undetermined Significance (MGUS)

Guideline: Starting bisphosphonates for patients with MGUS⁸ is not suggested.

Level of Evidence: N/A

Grade of Recommendation: Panel Consensus

Although data have shown the increased rate of bone resorption in patients with MGUS, this patient subgroup has not been specifically evaluated in any bisphosphonate trial. Because of the slow rate at which these individuals transform to myeloma or to a related B-cell malignancy, it is unlikely that trials will be conducted to determine whether these drugs prevent the development of B-cell malignancy. In the context of the known natural history and clinical course of this disorder, the Panel was not prepared to generalize the favorable results of randomized trials with documented lytic disease to include individuals with this monoclonal gammopathy without evidence of a malignant plasma cell disorder. However, studies to evaluate the role of bisphosphonates to prevent skeletal complications related to bone loss in this nonmalignant disorder would be important to undertake since several previous studies show enhanced bone loss in a significant proportion of MGUS patients.⁵³ Importantly, patients with other nonmalignant conditions demonstrating enhanced bone loss who receive bisphosphonates reduce their risk of fracture.⁵⁴ However, until these studies are conducted, there is no information on which to base treatment of patients with MGUS with bisphosphonates.

7. Biochemical Markers

Guideline: The use of the biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care.

Level of Evidence: III

Grade of Recommendation: C

With the increasing measurement of biochemical markers of bone resorption and formation in mostly postmenopausal women with osteoporosis and as part of clinical trials involving cancer patients with skeletal involvement, the Panel felt it was important to address the role of these markers in the routine evaluation of myeloma patients. Biochemical markers could have several important roles in the management of myeloma: identification of patients most at risk of bony complications; monitoring bisphosphonate therapy, especially to identify patients who are not benefiting from them; and to identify individuals with bone pain that will benefit from bisphosphonates compared with other treatments.⁵⁵ A variety of markers of bone resorption (pyridinoline, deoxypyridinoline, and *N*- or *C*- telopeptide) is undergoing investigation.⁵⁶ A recent Japanese study has suggested that elevated urinary *N*-telopeptide levels predicted the presence of bone metastases among patients with lung cancer.⁵⁷ Some have been correlated with prognosis or response but have not been shown to be statistically signif-

icant predictors. Although recent studies suggest the possible benefit of monitoring individual, postmenopausal osteoporosis patients treated with bone-enhancing therapy,⁵⁸ little data are available to show similar utility in the setting of myeloma or metastatic bone disease. In breast cancer patients receiving monthly intravenous pamidronate, the patients whose urinary *N*-telopeptide levels remained elevated were more likely to show bony disease progression ($P = .03$), and there was a trend toward more patients developing new fractures ($P = .07$).⁵⁶ However, biochemical marker data emerging from the ongoing large clinical trials evaluating newer bisphosphonates should help more clearly determine the place of these markers in the management of patients with metastatic bone disease. In multiple myeloma patients, a recent study suggests that levels of biochemical bone markers provide evidence that high-dose chemotherapy followed by autografting normalizes the high bone turnover rates present before transplantation.⁵⁹ In addition, serum markers of bone turnover have shown some prognostic significance in a Nordic Myeloma Study Group trial.⁶⁰ Although the results of these studies are interesting, at this time, the use of these markers should only be done within research protocols and have no role in routine care.

8. Role in Pain Control Secondary to Bony Involvement

Guideline: 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, or surgical intervention to stabilize fractures or impending fractures.

Level of Evidence: II

Grade of Recommendation: B

There is evidence to support a role for intravenous bisphosphonates as an adjunctive therapy to radiation therapy for patients with pain due to osteolytic bone disease. The role of bisphosphonates vis-à-vis radiation therapy as the sole therapy in this setting has not been determined. Among patients already treated with local radiotherapy that have persistent or recurrent pain, bisphosphonates are an attractive but little studied salvage therapy.

In parallel with the prior discussion of bisphosphonates' role in the primary or secondary prevention of skeletal complications, their role in pain management secondary to bony metastases must be separated into the consideration of helping a patient with current bone pain versus reducing future pain. In the previously discussed trial of intravenous pamidronate versus placebo concurrent with systemic therapies, pamidronate was associated with a pain control benefit.²² The vast majority of patients had some bone pain at study entry. The bone pain scores were calculated by multiplying the pain severity (0 to 3) by the pain frequency

(0 to 3). In this trial, the mean pain score improved between 1 and 1.5 units after each 3-month assessment up to 9 months. Just what a clinically relevant change in pain score is cannot be ascertained from the reports. In addition, global Spitzer quality-of-life scores and ECOG performance status did not deteriorate in the pamidronate-treated patients during the trial, whereas placebo-treated patients showed worsening on these indicators. During the first 9 months, patients receiving pamidronate were less likely to require radiotherapy for bone pain.²²

To date, there have been no studies conducted comparing the efficacy of intravenous bisphosphonates to radiotherapy in patients with current bone pain. Many studies of bisphosphonates as primary therapy for bony pain are nonrandomized, open-label design, involving a mixture of cancers and have not controlled for concurrent use of systemic therapy. Therefore, a placebo effect is possible. These studies generally focus on establishing dose, schedule, and time to analgesic effect. Body et al⁶¹ summarized the available phase II trials. Few myeloma patients were included in these studies. An analgesic effect was consistently observed, especially with the intravenously administered bisphosphonates. In general, the onset of benefit required 6 weeks (two treatments of at least 60 mg of pamidronate),⁶² and bisphosphonates had a greater effect in reducing a summary pain score than in reducing the concurrent need for narcotics.⁶³

INITIATION AND MANAGEMENT OF OTHER THERAPIES FOR OSTEOLYTIC BONE DISEASE

For patients with known lytic bone disease or previously treated cancer at high risk for bony metastases, symptoms in the spine, pelvis, or proximal femur require careful evaluation to monitor for spinal cord compression and pathologic fracture. Diagnostic assessment is recommended if symptoms are present despite current therapy or recur in a previously treated site. Symptoms in other bones important to functional integrity also warrant specific diagnostic evaluation and follow-up. A detailed discussion of the appropriateness criteria for imaging and of treatment decisions for the use of radiation oncology and surgery is beyond the scope of this bisphosphonate-focused guideline. Other sources are available for an expanded discussion of these issues.^{64,65}

Localized treatment of bone metastases with radiotherapy and/or surgery is used for sites of progressive disease that compromise function.^{64,66} Uncontrolled localized pain, reducing the risk for pathologic fracture, and spinal cord compression are the most common indications in treating bone metastases with radiotherapy. The goal of palliative radiation is to relieve symptoms, restore function, and prevent the sequelae of disease progression in the area

treated. Radiopharmaceuticals are an option in the treatment of diffuse symptomatic bone metastases or if symptoms recur in a previously irradiated site when preservation of bone marrow function is not an issue.⁶⁷ Combining external-beam irradiation and radiopharmaceuticals is an increasing focus of research. The role of combining bisphosphonates with these radiopharmaceuticals has not been evaluated. New attempts to combine a radiopharmaceutical (Holmium 166) with a bone-seeking tetrakisphosphonate as treatment for myeloma have moved into early clinical trials and seem promising as treatment for the underlying cancer itself.⁶⁸

Significant morbidity caused by pathologic fracture and spinal cord compression can result from untreated bone metastases. Spinal cord compression and pathologic fracture require emergent intervention regardless of other recent therapies. Surgical intervention for bone metastases is appropriate to prevent or relieve spinal cord compression or to prevent or treat a pathologic fracture.

The optimal combination or sequencing of radiotherapy or radiopharmaceuticals with bisphosphonates has not been studied. All of these therapies are associated with substantial costs. The relative rank order of their costs will depend mostly on the dose and schedule of radiation therapy and on the specific radiopharmaceutical. Based on the small number of studies discussed above and the lack of direct comparisons, the Panel recommends that current standards of care for cancer pain, analgesics, and local radiation therapy not be displaced by bisphosphonates. The optimal complementary role of bisphosphonates needs to be further defined.

COMMENTARY: PUBLIC POLICY AND COST-UTILITY IMPLICATIONS

The widespread use of bisphosphonates will have a major impact on drug budgets within capitated or nationalized health care systems. The cost consequences and patient expectation of benefit will vary depending on (1) the phase of myeloma when bisphosphonates are initiated, eg, solitary plasmacytoma, stage I, II, or III, asymptomatic lytic disease, symptomatic lytic disease, or osteopenia only; (2) the specific bisphosphonate used; and (3) how the bisphosphonate is delivered.

The time to initiate bisphosphonates is a critical issue with an incomplete database. The available clinical trials show a clear benefit from intravenous pamidronate or zoledronic acid administered intravenously every 3 to 4 weeks in myeloma patients with radiographic evidence of lytic bone disease.

Preventing feared complications such as fracture and bone pain should lead to measurable changes in quality of life indicators. In the pamidronate trial, if patients had bone

pain at entry, a consistent improvement in subsequent pain control was found. For many patients, this drug was associated with better maintenance of ECOG or World Health Organization performance status over time. Therefore, the costs and modest inconvenience of intravenous bisphosphonates are important concerns that must be balanced against these benefits.

Cost-benefit analyses could compare the various bisphosphonates to each other and/or no treatment. Two retrospective cost-effectiveness analyses using data from two of the clodronate-placebo trials found that reducing hospitalization costs associated with SREs was the critical variable. Although these studies were incomplete in many key elements, each projected an increase in overall treatments of 22% and 17% with clodronate.^{69,70} No cost-effectiveness studies of either pamidronate or zoledronic acid versus placebo or each other are available. Because these agents are each more effective than clodronate but substantially more expensive, it is unlikely that overall costs will be reduced.

With the recent approval of zoledronic acid, in the United States the decision facing most cancer providers will be whether to switch from pamidronate to zoledronic acid. In 2001, pamidronate became a generic drug with at least two different companies (Bedford Pharmaceuticals, Bedford, OH and American Pharmaceutical Partners, Los Angeles, CA) distributing a generic form that is typically hundreds of dollars lower in price. However, pamidronate's longer infusion time compared with zoledronic acid (2 hours versus 15 minutes) is associated with an opportunity cost to the patient (time), the cancer location (use of infusion chair), and extra staff time (reflected in common procedural terminology codes). A time and motion study at three outpatient chemotherapy infusion sites participating in the zoledronic acid versus pamidronate clinical trial found an average visit time for zoledronic acid patients was 1 hour, 6 minutes, compared with 2 hours, 52 minutes for pamidronate patients. From the infusion center perspective, the opportunity benefit for zoledronic acid was an average increase in 1.8 chairs per day available for other patients.⁷¹

OTHER BISPHOSPHONATES

Ibandronate

Ibandronate is another newer potent bisphosphonate. A phase III placebo-controlled trial of 214 stage II or III myeloma patients was recently completed.^{42,72} Entry criteria, design, and end points were similar to the previous discussed intravenous pamidronate study. Patients either received monthly bolus injections of 2 mg of ibandronate or placebo injections in addition to their antineoplastic ther-

apy. Ninety-nine patients in each group were assessable for efficacy. The median duration of follow-up was 17 months. The mean number of events per patient year on treatment was similar in both groups (ibandronate 2.13 versus placebo 2.05). However, in the subgroup of ibandronate-treated patients showing a sustained reduction in bone resorption markers, fewer SREs per year occurred. There was no difference in overall survival. Thus, this dose of ibandronate is inadequate to show significant effects on preventing skeletal complications in myeloma.

Commentary: Future Research Directions

Questions of the specific drug, when to initiate, duration of therapy, and the use of markers to select high-risk patients define the direction of current clinical trials with bisphosphonates. The third generation bisphosphonates, ibandronate and zoledronic acid, seem to be more powerful inhibitors of osteoclasts from *in vitro* and *in vivo* animal studies. However, only randomized clinical trials will provide information on relative clinical efficacy related to reduction in skeletal complications. The intriguing potential antitumor effects of bisphosphonates have been observed in laboratory studies. However, except for a subset of myeloma patients showing improved survival with monthly intravenous pamidronate, there are no other data showing a survival advantage with the use of bisphosphonates. With

these newer, more potent agents, the antitumor effect of these drugs may be realized clinically.

The Panel recognized the dilemma that future clinical trials of myeloma are likely to consider some form of bisphosphonate the standard of care, even in settings where it has not been addressed. Given the recent precedent of using pamidronate as the control or standard arm when evaluating zoledronic acid, it is likely to be difficult to enroll patients in comparative trials with a placebo arm even if the clinical setting differs. Economic studies evaluating the cost of bisphosphonates compared with surgical or radiation treatment procedures will be important to evaluate as part of future clinical trials, as will the positive impact of these drugs on quality of life.

Although it is not generating new data, many controversies in this guideline could have been addressed if individual-patient data meta-analysis were feasible. Such an analysis could potentially address the role of bisphosphonates on survival. Although ASCO itself cannot undertake such a project, it supports efforts by the Cochrane Collaboration or others to pursue such work

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APPENDIX

The appendix listing the ASCO Bisphosphonates Expert Panel is available online at www.jco.org.

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