Mayo Clinic Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma

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Bisphosphonates are effective in the prevention and treatment of bone disease in multiple myeloma (MM). Osteonecrosis of the jaw is increasingly recognized as a serious complication of long-term bisphosphonate therapy. Issues such as the choice of bisphosphonate and duration of therapy have become the subject of intense debate given patient safety concerns. We reviewed available data concerning the use of bisphosphonates in MM. Guidelines for the use of bisphosphonates in MM were developed by a multidisciplinary panel consisting of hematologists, dental specialists, and nurses specializing in the treatment of MM. We conclude that intravenous pamidronate and intravenous zoledronic acid are equally effective and superior to placebo in reducing skeletal complications. Pamidronate is favored over zoledronic acid until more data are available on the risk of complications (osteonecrosis of the jaw). We recommend discontinuing bisphosphonates after 2 years of therapy for patients who achieve complete response and/or plateau phase. For patients whose disease is active, who have not achieved a response, or who have threatening bone disease beyond 2 years, therapy can be decreased to every 3 months. These guidelines were developed in the interest of patient safety and will be reexamined as new data emerge regarding risks and benefits.

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ASCO = American Society of Clinical Oncology; MM = multiple myeloma; ONJ = osteonecrosis of the jaw; SRE = skeletal-related event

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for more than 15,000 new cases annually in the United States and more than 11,000 deaths per year.[1] The introduction of new pharmacological agents such as bortezomib,[2] thalidomide,[3-5] and other immunomodulatory drugs[6] has improved treatment options for patients with MM. However, MM is still thought to be incurable with current therapies. Therefore, emphasis must be placed on quality-of-life considerations when selecting treatment options.

Bone destruction is a significant cause of morbidity in patients with MM. Multiple myeloma cells and stromal cells of the bone marrow secrete cytokines that increase osteoclast activity, including interleukin 1,[7,8] interleukin 6,[8,9] and tumor necrosis factor,[10,11] resulting in osteoporosis, lytic bone disease, and skeletal fractures. The most frequent sites of bony involvement include the vertebrae, calvarium, sternum, ribs, pelvis, and proximal humeri and femurs. Pathologic fractures are a devastating cause of morbidity and pain.

Bisphosphonates are synthetic analogues of the naturally occurring pyrophosphate. They have an affinity for bone and are preferentially delivered to sites of increased bone formation or resorption.[12] Once deposited, bisphosphonates are internalized by osteoclasts that are engaged in bone resorption and modulate signaling from osteoblasts to osteoclasts. They are potent inhibitors of osteoclast-induced bone resorption and are effective in treating cancer-induced hypercalcemia malignancy and osteoporosis.[12] Bisphosphonates have been shown to reduce bony complications associated with MM[13-19] in a variety of studies. On the basis of this finding, in 2002 the American Society of Clinical Oncology (ASCO) issued clinical practice guidelines regarding the role of bisphosphonates in MM.[20]

Adverse effects associated with the use of bisphosphonates are usually mild and consist of fever, renal function impairment, myalgias and hypocalcemia.[12] Renal complications are rare but include renal insufficiency and proteinuria.[21-31] Recently, osteonecrosis of the jaw (ONJ) was described as a serious new complication associated with bisphosphonates.[17,32-42] Bisphosphonate-associated ONJ has been described in various malignancies, including MM, breast cancer, and prostate cancer, and can be a

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debilitating problem associated with significant morbidity (a photograph showing ONJ involving the mandible of a patient with MM can be found in the case report by Kademani et al[43] in this issue of *Mayo Clinic Proceedings*). The underlying pathophysiologic mechanisms have not yet been clarified.[38] However, the clinical similarity of ONJ to osteoradionecrosis encountered in patients after receiving head and neck irradiation is striking. Studies suggest that the incidence of ONJ is related to duration of exposure and the type of bisphosphonate used.[33,39,40] Treatment strategies used in osteoradionecrosis are often unsatisfactory when applied to ONJ because patients are left with severe morbidity, pain, and permanent disability.[39] As a result, there is increasing concern about the indefinite use of bisphosphonates in patients with MM and remarkable interest in determining the optimal way to administer these agents that would maximize the risk-benefit ratio. In view of this, the Mayo Clinic Myeloma Group reexamined practice guidelines regarding bisphosphonate use for MM. Since pamidronate and zoledronic acid are the only bisphosphonates approved for use in MM in the United States, we chose to restrict our comments and recommendations to these 2 agents.

EVIDENCE SUPPORTING BISPHOSPHONATE USE IN MM

The evidence supporting the use of bisphosphonates to prevent bony disease in MM comes from 4 randomized phase 3 clinical trials, 2 of which used oral clodronate, which is not available in the United States.

The first trial evaluated the use of intravenous pamidronate in patients with MM.[14] In this randomized, placebo-controlled trial, 392 patients with stage III MM and at least 1 lytic lesion were randomized to placebo or pamidronate, 90 mg, given as a 4-hour infusion every 4 weeks for 21 cycles. All patients' chemotherapy regimens had to have been unchanged for at least 2 months before entry into the study. The primary preplanned end points were the reduction of skeletal-related events (SREs) after 9 cycles of therapy and evaluation of safety and survival after 21 cycles of randomized treatment. Patients were stratified before randomization on the basis of having received either their first anti-MM regimen (stratum 1) or their second or further anti-MM regimen (stratum 2). A total of 377 patients were assessable for the primary end point (SREs), 179 in the placebo group and 198 in the pamidronate group. Of these patients, 247 were in stratum 1. At 9 months, the number of SREs per year was 2.1 in the placebo group and 1.1 in the pamidronate group (P=.0006). At 21 months of follow-up, the number of SREs changed minimally, 2.2 per year in the placebo group and 1.3 per year in the pamidronate group (P=.008). The median time to the first SRE 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 vs 44% in the placebo group had an SRE (P=.001). Other benefits in the pamidronate group included a lower percentage of patients developing pathologic fracture or requiring radiation to bone, significant decreases in pain, and no increase in analgesic drug use. The placebo group had no improvement in pain and required escalating analgesic drug use during the trial. Quality-of-life studies also favored the use of pamidronate. This prospective study subsequently led to the Food and Drug Administration approving the use of this drug for MM.

In February 2002, the Food and Drug Administration approved an expanded indication for zoledronic acid for the treatment of patients with bone metastases that included its use in MM. Two randomized trials showed that zoledronic acid had similar efficacy and safety compared to 90 mg of pamidronate. The first, a randomized phase 2 study,[13] compared zoledronic acid to pamidronate in 280 patients with lytic bone metastases from either MM (n=108) or breast cancer (n=172). Patients were randomized to 9 monthly infusions of 0.4 mg, 2 mg, or 4 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 the dose of zoledronic acid required to reduce the need for radiation to less than 30% of treated patients. Duration of follow-up was not reported. Radiation treatment was required in a similar proportion of patients receiving pamidronate and zoledronic acid at 2 mg or 4 mg (18% to 21%). A slightly higher number of patients receiving zoledronic acid at 0.4 mg required radiation therapy (24%).

A larger phase 3 randomized trial compared 4- or 8-mg doses of zoledronic acid to 90 mg of pamidronate every 3 to 4 weeks in patients with MM or breast cancer who had lytic disease.[16] The infusion time for zoledronic acid was increased from 5 minutes to 15 minutes during the trial because of an increase in creatinine that occurred more frequently among patients receiving the rapid infusion. Renal problems continued to occur more often among patients randomized to 8 mg of zoledronic acid, and their dose was subsequently reduced to 4 mg. The sample size was based on showing non-inferiority of zoledronic acid to pamidronate. The study enrolled 1648 patients in an intent-to-treat analysis; 510 had MM, and the remainder had metastatic breast cancer. The portion of patients with any SRE after 13 months did not differ among the 3 treatments and did not differ between patients with breast cancer and those with MM. Notably, none of these trials included formal quality-of-life measures or adverse event measures

of oral-related conditions and pathology. Since the trials were conducted before ONJ was a known complication of bisphosphonate therapy, they did not report this long-term adverse event.

These trials led the ASCO panel to advocate the use of either pamidronate or zoledronic acid monthly for patients with MM and lytic bone disease.[20] These guidelines recommended the use of pamidronate at 90 mg delivered intravenously for at least 2 hours or zoledronic acid at 4 mg intravenously for 15 minutes every 3 to 4 weeks for patients with MM and lytic bone disease. The panel also extrapolated these data and recommended use of bisphosphonates for patients with MM and osteopenia. The panel suggested that once initiated,

> intravenous pamidronate or zoledronic acid be continued until there was evidence of substantial decline in a patients general performance status….Discontinuation of pamidronate or zoledronic acid, because of performance status changes, should only be considered if patients' likely palliative benefit is believed to be less than the inconvenience of receiving an intravenous infusion.[20]

Of note, currently no data are available from randomized trials regarding the long-term adverse event rate associated with monthly bisphosphonates beyond 2 years of therapy.

OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw is not a new phenomenon. Descriptions of "phossy jaw" date back to the 19th century among workers in the matchstick making industry.[44,45] High levels of phosphorus-containing products held in the oral cavity of workers often led to spontaneous jaw exposure and pain.[46] Since the initiation of routine use of radiotherapy for solid tumors of the head and neck, it has been well recognized that jaw "osteoradionecrosis" is frequently observed and can occur either spontaneously or secondary to dental infection or oral surgical manipulation. The use of irradiation creates hard and soft tissue hypoxia-hypocellularity and hypovascularity, and it significantly decreases the healing ability of the soft tissue and bone in the oral-facial region.[47] Osteoradionecrosis is not the same entity as ONJ but is similar pathophysiologically.

In 2003, ONJ was first recognized as a complication of bisphosphonate therapy.[32] It has been seen with a higher frequency in the mandible (63%) than in the maxilla (38%).[17] The etiology of ONJ remains unclear but is likely to be multifactorial in origin. Although most patients who develop ONJ have had recent dental or oral surgical procedures (70%), a large subset (30%) develops spontaneous ONJ without a history of recent oral therapy.[17] In one series of 22 patients, 91% of the ONJ occurred posterior to canine teeth, and 45% of the lesions were spontaneous. The authors described the spontaneous ONJ as occurring on the lingual surface of the mandible, a region easily traumatized during normal mastication.[39] Interestingly, this location mimics that of osteoradionecrosis in oncology patients who have received irradiation. Proposed induction mechanisms are that inhibition of osteoclast activity reduces bone turnover and remodeling and that bisphosphonates prevent release of bone-specific factors that promote bone formation.[38] In addition, bisphosphonates, particularly zoledronic acid, may have antiangiogenic effects,[48,49] and impaired blood supply has been implicated in the development of ONJ. Finally, after dental extractions, healing of an open osseous oral wound is challenged by bacterial insult from oral microflora, especially if the protective fibrin clot does not form or is dissolved. This may explain the strong association of ONJ with dental or oral surgical procedures.[38]

Numerous reports have discussed ONJ in patients using bisphosphonates,[17,33,35-37,39-41,50-56] indicating that this is a serious problem that can affect how bisphosphonates are currently used in the treatment of MM. Estimating the true incidence of this complication is difficult. Durie et al[33] performed a Web-based survey of 1203 patients with MM and breast cancer and found an incidence of 6.8% in patients with MM and of 4.4% in patients with breast cancer. These authors suggested that the incidence is higher in patients treated with zoledronic acid than in those treated with pamidronate. A criticism of the study by Durie et al is that, because it was Web based and ONJ was self-reported by patients, the prevalence of ONJ may have been overestimated.

Bamias et al[40] prospectively studied 17 patients with ONJ among 252 patients who had been treated with bisphosphonates between January 1997 and February 2005. The overall incidence was 6.7%, with 9.9% among patients with MM and 2.9% among patients with breast cancer. All occurrences of ONJ were among patients who were treated with zoledronic acid alone (6.7%) or pamidronate followed by zoledronic acid (13%). The authors found no cases among patients treated with pamidronate alone. The time of exposure was strongly associated with development of ONJ. Patients who developed ONJ received a median number of 35 infusions (range, 13-68) compared to 15 infusions (range, 6-74) for patients without ONJ. The median time of exposure to bisphosphonates was 39.3 months for patients with ONJ (range, 11-86 months) compared with 19 months (range, 4-84.7 months) for patients with no osteonecrosis. Finally, the cumulative hazard rates of developing ONJ between patients who received zoledronic acid alone vs those who received pamidronate alone or with subsequent zoledronic acid were significantly higher in the zoledronic acid group ($P<0.001$). The hazard rate was 1% the first year of treat-

TABLE 1. **Mayo Clinic Practice Guidelines for the Use of Bisphosphonates in Patients With Multiple Myeloma (MM)**

Clinical scenario	Guideline
MM and lytic disease evident on plain radiographs	Intravenous bisphosphonates should be administered monthly for patients with MM and lytic disease evident on plain radiographs
Osteopenia or osteoporosis but no lytic disease evident on plain radiographs or bone mineral density studies	It is reasonable to start intravenous bisphosphonates in these patients with MM who do not have lytic bone disease if osteopenia or osteoporosis is evident on bone mineral density studies but not in patients with normal results on bone density studies
Smoldering MM	Bisphosphonates are not recommended for patients with smoldering MM; bisphosphonate therapy should be used only in the setting of a clinical trial
Duration of bisphosphonate therapy	Patients should receive infusions of bisphosphonates monthly for 2 y After 2 y If the patient has achieved remission and is in stable plateau phase off treatment, the bisphosphonates can be discontinued If the MM still requires active treatment, the frequency of bisphosphonate infusions can be decreased to every 3 mo
Choice of bisphosphonate	In patients with newly diagnosed MM, we favor use of pamidronate over zoledronic acid
Dental evaluation and follow-up of patients taking bisphosphonates	Encourage patients to Have comprehensive dental evaluation before receiving any bisphosphonate treatment Undergo invasive dental procedures before starting bisphosphonate treatment See a dentist at least annually and maximize preventive care; report oral/dental symptoms promptly Manage new dental problems conservatively and avoid dental extractions unless absolutely necessary See an oral and maxillofacial surgeon if surgery is required Practice good dental hygiene Encourage physicians to Withhold bisphosphonate treatment for at least 1 mo before the procedure and do not resume until the patient has fully recovered and healing of the surgery is complete

ment and increased to 21% at 3 years of treatment for zoledronic acid, whereas the hazard rate among those who received pamidronate alone or with subsequent zoledronic acid was 0% the first 2 years and increased to only 7% after 4 years of treatment. Additionally, 15 of the 17 patients with ONJ had a history of either dental procedures or use of a denture within the past year, potentially contributing to ONJ development.[40]

RECOMMENDATIONS FOR THE USE OF BISPHOSPHONATES IN MM

In the context of the aforementioned data, our group met and reviewed practice guidelines for bisphosphonate use in patients with MM (Table 1). We used methodology that has been described in prior ASCO practice guidelines.[20]

Patients With MM and Lytic Disease Evident on Plain Radiographs

Guideline: Intravenous bisphosphonates should be administered monthly for patients with MM and lytic disease evident on plain radiographs. In this respect, we concur with published ASCO recommendations.

***Level of Evidence*:** II

***Grade of Recommendation*:** A

Patients With Osteopenia or Osteoporosis but With No Lytic Disease Evident on Plain Radiographs or Bone Mineral Density Studies

Guideline: It is reasonable to start intravenous bisphosphonates in patients with MM who do not have lytic bone disease if there is evidence of osteopenia or osteoporosis on bone mineral density studies.

***Level of Evidence*:** Not available

***Grade of Recommendation*:** Mayo Myeloma Group Consensus Opinion

Although no randomized clinical trials have been performed in this particular population, our group took into account knowledge of the mechanism of bone loss in patients with MM as well as the published ASCO recommendations. Because osteoporosis is often the first manifestation of bone disease in MM, we believe that bisphos-

phonate treatment in this group is warranted. We do not recommend routine use of intravenous bisphosphonates for patients without evidence of skeletal involvement on plain radiographs or bone mineral density studies.

Patients With Smoldering MM

Guideline: No randomized clinical trials support the use of bisphosphonates in patients with smoldering MM. We believe that bisphosphonates should be used only in the setting of a clinical trial.

***Level of Evidence*:** Not available

***Grade of Recommendation*:** Mayo Myeloma Group Consensus Opinion

Duration of Bisphosphonate Therapy

Guideline: We recommend infusion of bisphosphonates monthly for 2 years. After 2 years, if the patient has achieved response and is in a stable plateau phase off treatment, the bisphosphonates can be discontinued. If the MM still requires active treatment, the frequency of bisphosphonate infusions can be decreased to every 3 months.

***Level of Evidence*:** II, for the recommended duration of 2 years; not available, no randomized data to support use of bisphosphonates beyond 2 years

***Grade of Recommendation*:** A, for the recommended duration of 2 years; Mayo Myeloma Group Consensus Opinion for recommendations beyond 2 years of therapy

None of the published randomized trials have reported use of bisphosphonates beyond 2 years except the Intergroupe Francophone du Myelome 9902 trial,[57] which has a median follow-up of 3 years but has been reported only in a preliminary fashion. Detailed toxicity data are not yet available from that trial. The rationale for monthly administration is based on the randomized trial of pamidronate by the Myeloma Aredia Study Group. Subsequent trials comparing pamidronate to zoledronic acid used the same schedule. Evidence shows that bisphosphonates have long half-lives and that once deposited, they remain in bones for prolonged and perhaps indefinite periods.[58] Animal studies suggest that the terminal phase of elimination half-life in bone is approximately 300 days.[58] In this recommendation, we differ from the published ASCO guidelines. We believe this is justified because use of bisphosphonates in patients with MM is intended to reduce morbidity and improve quality of life. With mounting evidence that ONJ may be related to duration of use and total cumulative bisphosphonate exposure, we believe we must balance these 2 competing sources of morbidity. In the absence of randomized clinical trials justifying long-term use in this population, we cannot advocate indefinite monthly use of bisphosphonates. We realize there are no clinical trials to guide our recommendation to use bisphosphonates every 3 months for patients still requiring active antimyeloma therapy beyond 2 years. This recommendation is our group's consensus and is based on the knowledge that most treatment regimens for MM incorporate corticosteroids, which have potential to worsen osteoporosis. We also recognize that patients with active MM may have bone loss mediated by cytokines, and bisphosphonates have been associated with reduced levels of interleukin 6.[59,60] It is reasonable to check results of bone mineral density studies and use clinical judgment to guide whether the patient should be taking any ongoing bisphosphonate treatment. Furthermore, resumption of bisphosphonates can be considered if the patient experiences relapse.

Choice of Bisphosphonate

Guideline: In patients with newly diagnosed MM, we favor use of pamidronate over zoledronic acid. We do not necessarily advocate switching patients already using zoledronic acid to pamidronate and stress that clinical judgment must guide physicians in making this decision.

***Level of Evidence*:** III and IV

***Grade of Recommendation*:** C

In this recommendation, we again differ from the published ASCO guidelines. Our recommendation is based on data that have emerged since the publication of the ASCO guidelines and suggest a higher risk of ONJ with zoledronic acid than with pamidronate. Since there are no data that zoledronic acid is more efficacious, with the only advantage being a shorter infusion time, we believe it is prudent to err on the side of safety when data suggest that the risk of ONJ is likely higher with zoledronic acid. No published data suggest that switching patients from zoledronic acid to pamidronate will be of benefit in preventing ONJ; thus, we do not recommend routinely switching patients who are already taking zoledronic acid but suggest that this decision be made based on the preferences of individual patients after the risks and benefits have been explained.

Dental Evaluation and Follow-up of Patients Taking Bisphosphonates

Guideline: We strongly advise patients to undergo a comprehensive dental evaluation before taking any bisphosphonate treatment. The goal of such an evaluation is to identify and treat teeth that may eventually require surgical intervention (dental extraction, pulpectomy, incision and drainage, or periodontal surgery) or other invasive dental procedures and to complete care before starting bisphosphonate treatment. After bisphosphonate therapy has been initiated, patients should see a dentist at least annually, and elective procedures should be attempted only after careful consideration of the potential ONJ risk. New dental prob-

lems should be managed conservatively, with care to avoid dental extractions or other surgical procedures unless absolutely necessary. When required, dental extractions should be performed by an experienced oral and maxillofacial surgeon. Although there are no data on which to base a firm guideline, for patients who must undergo a major oral surgical procedure, we recommend that physicians withhold bisphosphonate treatment for at least 1 month before the procedure and not resume treatment until the patient has fully recovered and the wound has fully healed.

Patients should be encouraged to practice good dental hygiene and see a dentist promptly if oral or dental symptoms appear. The physician treating the MM should be proactive with the general dental practitioner to create a viable oncologic and dental treatment plan that addresses the patient's dental needs with the least morbidity and potential for devolving ONJ. This "proactive communication" may differ depending on the patient's dental history. Patients who regularly see a dentist will likely require less intervention before starting bisphosphonate therapy, and the communication will be less involved. In contrast, if the physician recognizes that her or his patient has not regularly seen a dentist in the past, the potential dental needs might be substantial, and the time required before initiating bisphosphonate therapy may be longer.

Of note, dental restorative or periodontal procedures on long-standing chronic unattended conditions (caries or periodontitis) may lead quickly to an acute or subacute condition that requires oral surgical intervention (dental extraction, pulpectomy, or incision and drainage) and predisposes the patient to ONJ. Conversely, if left untreated, these chronic dental conditions will eventually become infected in a high percentage of patients, and oral surgical treatment will be necessary. This situation presents a clear dilemma to the dental practitioner who is asked to manage oral symptoms in this group of patients after they have received bisphosphonate therapy.

Patients with ONJ are best managed by an experienced oral and maxillofacial surgeon. Treatment measures should be instituted to limit progression and to maintain the highest level of function. These include the use of local saline irrigation and antibiotic therapy in situations of obvious infection.

***Level of Evidence*:** V

***Grade of Recommendation*:** Mayo Myeloma Group Consensus Opinion

The Mayo Myeloma Group recommends this approach after reviewing the evidence that ONJ may be precipitated by dental procedures and after discussions with dental specialists. These recommendations are the result of joint interdepartmental consensus.

CONCLUSION

Bisphosphonates have played an important palliative role in the care of patients with MM. Use of these agents has a demonstrated benefit in reducing painful bone complications. However, there may be negative long-term adverse effects, and physicians engaged in the care of patients with MM need to periodically reevaluate the role of these agents. As more data become available, the guidelines may need to be amended.

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