Clinical Trials of Bisphosphonates in Multiple Myeloma

Anuj Mahindra, MD, Samantha Pozzi, MD, and Noopur Raje, MD

Dr. Mahindra is an Instructor and Dr. Raje is an Associate Professor at Massachusetts General Hospital Cancer Center, Harvard Medical School, in Boston, Massachusetts. Dr. Pozzi is an Assistant Professor at the University of Modena and Reggio Emilia, in Modena, Italy.

Address correspondence to:
Anuj Mahindra, MD
POB 236, Center for Multiple Myeloma
MGH Cancer Center
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114
Phone: 617-724-4000
Fax: 617-724-6801
E-mail: amahindra@partners.org

Abstract: More than 80% of patients with multiple myeloma (MM) have osteolytic bone disease, which increases the risk of skeletal-related events (SREs) such as pathologic fracture, spinal cord compression, and the need for radiotherapy or surgery. Bone disease is primarily due to increased osteoclastic activity and impaired osteoblast activity. Bisphosphonates are pyrophosphate analogues with high bone affinity that can inhibit osteoclastic activity. Pamidronate and zoledronic acid are the most commonly used bisphosphonates in multiple myeloma. Other agents include ibandronate and clodronate. Bisphosphonates are associated with several adverse events, such as renal toxicity and osteonecrosis of the jaw. The optimal duration of bisphosphonate therapy has yet to be determined. Clinical trials are investigating tailored approaches to management based on treatment-related changes in levels of bone resorption markers.

Keywords
Zoledronic acid, pamidronate, bisphosphonates, myeloma

Introduction

Multiple myeloma (MM) is a plasma cell disorder characterized by plasma cell infiltration of the bone marrow (>10%). In most patients, it is associated with a monoclonal gammopathy in serum and/or urine.[1] More than 80–90% of MM patients will develop bone involvement.[2] Other signs of MM include anemia, impaired renal function, and hypercalcemia.[2]

Bone disease in MM patients occurs when plasma cells interact with the bone microenvironment, which results in increased rates of osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation. This imbalance is caused by the dysregulation of several cytokines, including upregulation of RANK ligand (RANKL), downregulation of osteoprotegerin (OPG), the production of macrophage inflammatory protein (MIP)-1α by MM cells, and the increased concentration of IL-6 and IL-3 within the bone marrow.[2] Suppression of osteoblastogenesis also occurs due to increased expression of Dickkopf-1 protein (DKK1) and secreted frizzled-related protein 2, which leads to inhibition of the wingless (wnt) pathway.[3]

Bisphosphonates (BPs) are pyrophosphate analogues. They have a high bone affinity that can inhibit the function of osteoclasts.[1,2] Pamidronate and zoledronic acid (ZA) are the most commonly used BPs for the treatment of myeloma-related bone disease.

Structure and Properties

BPs are characterized by 2 phosphonate groups linked to a P-C-P core.[4] They have a high affinity for calcium, which allows them to bind to bone hydroxyapatite, particularly in areas that have a high bone turnover. There are 2 groups of BPs, one that contains nitrogen (N-BP) and one that does not. Ibandronate, pamidronate, and ZA contain nitrogen; etidronate and clodronate do not. The N-BPs are second- and third-generation BPs with potencies that are 100 to 10,000 times higher than the BPs without nitrogen, and their properties differ slightly. Pamidronate, ZA, and ibandronate are administered intravenously. Clodronate can be administered orally. About half of the administered BP accumulates in the bone, and the remaining half is excreted unaltered by the kidneys.[5,6] Factors influencing the retention of BPs in the skeleton include their chemical structure, mineral affinity, and the grade of bone turnover. BPs can remain in the bone for several years but are mostly inactive. Skeletal distribution varies based on BP chemical properties, which partly explains the differences in preventing bone fractures in different skeletal sites (vertebral vs non-vertebral).[7]

BPs affect the recruitment and differentiation of osteoclasts[7] and can be toxic to osteoblasts at high doses.[8,9] Antiangiogenic activity has been suggested by studies of pamidronate and clodronate.[10] In vitro and in vivo studies have suggested that BPs may have anticancer properties. Pamidronate and ZA have induced cytotoxicity in MM cell lines and patient-derived samples.[11-13]

Clinical Trials of BPs in Plasma Cell Disorders

Symptomatic MM

In a pivotal randomized trial and subsequent extension study, the effect of 90 mg of pamidronate was evaluated in 392 patients with symptomatic MM.[14-16] Monthly infusions of pamidronate were associated with reduced bone pain and SREs, as well as improved quality of life, when compared with placebo. Subsequently, in a non-inferiority randomized trial, escalating doses of ZA were compared with 90 mg of pamidronate.[16] Equivalent results were observed with pamidronate 90 mg and ZA 4 mg administered monthly. Pamidronate and ZA are now considered the standard of care as supportive treatment in patients with symptomatic MM. Recently, pamidronate 30 mg has been shown to be equivalent to pamidronate 90 mg in patients with MM.[17]

The Medical Research Council (MRC) Myeloma IX study compared ZA versus clodronate in patients with newly diagnosed MM. After a median follow-up of 3.7 years, improvement in overall survival by 5.5 months and progression-free survival by 2.2 months was noted in the ZA arm when compared with clodronate.[18] The improvement in overall survival in the arm treated with ZA was independent of the reduction of SREs, possibly due to the anti-MM activity of N-BPs or synergism between ZA and anti-MM treatment (Table 1).

Guidelines for the administration of BPs in MM patients have been drafted by expert panels. Pamidronate and ZA are the BPs of choice for symptomatic MM patients.[19-21] The 2007 American Society of Clinical Oncology (ASCO) guidelines recommend treatment in patients with bone disease, including osteopenia. In the 2009 guidelines from the European Myeloma Network (EMN), treatment is recommended for patients with pathologic fractures and/or radiologic evidence of osteolytic lesions (grade A recommendation). Treatment, starting with BPs, is also recommended in patients who require chemotherapy, even if no visible lesions are evident on plain radiography (grade B recommendation). Guidelines from the National Comprehensive Cancer Network (NCCN) recommend that MM patients with documented bone disease receive BP treatment.[21]

The optimal duration of BP therapy is unknown. Guidelines from ASCO recommend monthly infusions for 2 years.[19] Treatment can be discontinued in responsive or stable patients or restarted if the patient relapses or bone disease progresses.[19] For patients with ongoing bone disease, treatment may be extended for more than 2 years.

MGUS

Monoclonal gammopathy of undetermined significance (MGUS) is a preneoplastic condition. The chance that MGUS will evolve to MM is 1% per year.[22] This condition has been associated with altered bone turnover leading to increased bone resorption markers and an altered RANKL/OPG ratio.[23-26] Patients with MGUS are at particular risk of axial fractures.[27] In the setting of MGUS, BPs are not recommended unless the patient has osteopenia or osteoporosis.[19] In a phase II, open-label, single-arm study of 54 MGUS patients with bone loss, ZA (in a regimen of 3 doses of 4 mg every 6 months) increased bone mineral density (BMD).[28] A study of 19 patients with MGUS and smoldering MM showed improvement of bone turnover after treatment with ZA.[29]

Smoldering MM

Patients with smoldering myeloma (SMM) lack organ damage but have an M-component greater than 3 g/dL and/or more than 10% plasma cells in the bone marrow.[30] The chance that a patient with SMM will develop symptomatic MM is approximately 10% per year during the first 5 years after diagnosis.[31] In a prospective, multicenter, open-label

Table 1. Antiresorptive Agents in Patients With MM

Bisphosphonate	Dose and Duration	Outcomes
Pamidronate vs placebo[14,15]	90 mg IV every 4 weeks for 21 cycles	Pamidronate was associated with lower rates of SREs (24% vs 41% after 9 cycles, *P*<.001; 38% vs 51% after 21 cycles, *P*=.015)
Ibandronate vs placebo[56]	2 mg IV every 4 weeks	No benefit: 2.13 SREs/pt-yr vs 2.05 SREs/pt-yr for placebo
Zoledronic acid vs pamidronate[57]	4 mg or 8 mg vs 90 mg IV once a month for up to 2 years	Non-inferior
Zoledronic acid vs clodronate[62]	4 mg every 21–28 days vs 1,600 mg/day	ZA was associated with lower rates of SREs (35% vs 43% in patients with bone lesions at baseline and 10% vs 17% in patients without bone lesions at baseline)
Pamidronate[17]	30 mg or 90 mg IV once a month for at least 3 years	Median time to first SRE was 9.2 months (range, 8.1–10.7) in the 90 mg arm vs 10.2 months (range, 7.3–14.0) in the 30 mg arm (*P*=.63)
Denosumab vs zoledronic acid[72]	120 mg SQ once a month vs 4 mg IV once a month	Non-inferior (complete trial population). Increased risk of death with denosumab vs ZA in subgroup of pts with MM (HR, 2.26; 95% CI, 1.13–4.50); trial in MM-specific population is ongoing

CI=confidence interval; HR=hazard ratio; IV=intravenously; MM=multiple myeloma; pt-yr=patient-year; SQ=subcutaneously; SRE=skeletal-related event; ZA=zoledronic acid.

phase III trial, 163 patients with SMM were randomized to receive ZA (4 mg monthly for 1 year) or no treatment. ZA reduced the rate of skeletal-related events (SREs) after a median follow-up of 64.7 person-months. There was no effect on the evolution from asymptomatic to symptomatic MM.[32] Pamidronate was also shown to increase bone density and reduce bone turnover in 12 SMM patients, but without a significant antitumor effect.[33] In another study of 16 SMM patients, ZA increased serum osteoprotegerin and BMD at the lumbar spine, but it did not affect disease progression.[34]

Side Effects and Toxicity

Patients with MM generally tolerate BP treatment well when it is administered at the approved dose and frequency, and with adherence to monitoring guidelines. Daily oral calcium and vitamin D supplements are recommended to minimize the risk of hypocalcemia during treatment with BPs and the newer antiresorptive agents.

In approximately 40% of patients, the first administration of intravenous N-BPs is associated with a flu-like syndrome caused by the release of cytokines by γδT cells and macrophages, particularly IL-1, IL-6, TNF-α, and CRP.[35] Symptoms include fever, fatigue, malaise, myalgia, arthralgia, and bone pain. They are benign and self-limited.

Kidneys are especially sensitive to BPs. About half of an administered BP is excreted through glomerular filtration and active tubular excretion.[36] When BPs are used at recommended doses and infusion rates, severe renal toxicity is unusual,[37] as indicated by long-term follow-up data from clinical trials.[38] Nephrotoxicity is related to the dose, infusion time, and maximum plasma concentration (C_{max}) that affects the intracellular concentration of BPs.[36] There is the potential for BPs with prolonged renal tissue half-life, such as ZA, to accumulate in renal tissue and cause damage. Pamidronate has been associated with collapsing focal segmented glomerulosclerosis.[39,40] Acute tubular necrosis with tubular cell degeneration, loss of brush border, and apoptosis has been observed in biopsies of patients who received ZA.[41]

Between 2001 and 2003, 72 cases of renal failure associated with the administration of ZA were reported to the US Food and Drug Administration (FDA). Among the 42 patients with MM, 8 received dialysis, and 7 died.[42] Multiple mechanisms contribute to nephrotoxicity in patients with MM, including hypercalcemia and concomitant treatment with other potentially nephrotoxic drugs.[42,43] To minimize toxicity, the 2007 ASCO guidelines[44] suggest dose adjustments of ZA in patients with creatinine clearance ranging from 30–60 mL/min. ZA is not recommended for patients with severe renal impairment. For patients with severe renal insufficiency (creatinine clearance <30 mL/min), an alternative is pamidronate 90 mg; it is recommended that the administration of this dose be increased to 4–6 hours. Monitoring of serum creatinine is recommended before each BP infusion.

Osteonecrosis of the jaw (ONJ), a dreaded complication of BP treatment, has been defined by the American Society for Bone and Mineral Research (ASBMR) and the American Association of Oral and Maxillofacial Surgeons (AAOMS) as a lesion of exposed bone in the maxilla or mandible that persists for 8 weeks in patients treated with BPs who are not receiving radiotherapy to the craniofacial area.[44] This definition excludes stage 0, which is defined as clinical suspicion of ONJ in the absence of clinical

evidence of necrotic bone or specific clinical findings and symptoms.[45] Presentations of ONJ include pain, swelling of the mucosa, ulcer, and loose teeth or a nonhealing socket after tooth extraction. The severity of the complication can vary, from asymptomatic forms, to exposed necrotic bone associated with infection, to very severe lesions complicated by the appearance of fistula or fracture.[46]

Several hypotheses have been proposed for the pathogenesis of ONJ.[47] Inhibition of bone remodelling, resulting in microdamage in an area prone to microtrauma caused by mastication, is one such hypothesis. It is supported by the observation that gene expression profiling of MM patients treated with BPs with and without ONJ showed downregulation of genes involved in both osteoclastogenesis and osteoblastogenesis.[48] ONJ has been noted in patients receiving antiangiogenic compounds, raising the possibility that the antiangiogenic properties of BPs[49-51] contribute to the problem. ONJ has also been noted with the use of other antiresorptives, such as denosumab,[52] raising the possibility that ONJ is likely a consequence of altered bone remodelling due to antiresorptive agents in general.[53] The oral microflora is believed to play an important role in the development of ONJ, and is responsible for the evolution of osteonecrosis to osteomyelitis, hence the consideration of antibiotic prophylaxis for the prevention of this condition.[54,55] ONJ is estimated to occur in approximately 0.8–12% of patients with cancer.[46] The incidence in patients with MM is higher (8.5%) than in patients with breast (3.1%) and prostate cancer (4.9%).[56] Ibandronate and pamidronate appear to have a better safety profile when compared with ZA.[56] Resolution with complete healing has been noted in 23–62% of cases, with 20% of patients having persistent symptoms. After an initial improvement or resolution, 12–23% of patients manifest a recurrence of the lesion, sometimes secondary to the reintroduction of BPs. However, good control of pain and symptoms has been achieved with conservative treatment in over 90% of the cases.[57,58] When a lesion develops, conservative treatment appears to be useful. For advanced disease, more aggressive approaches may be necessary.[46]

With the recognition of risk factors, measures to prevent ONJ are now recommended. In 1 study, preventive strategies, such as dental evaluation and dental procedures prior to BP use, reduced the development of ONJ from 26.3% to 6.7%.[59] The addition of antibiotic prophylaxis (amoxicillin-clavulanate 1 g bid orally or levofloxacin 500 mg/day orally, starting 1 day before the dental procedure and continuing until 3 days after), is noted to be effective, particularly in patients undergoing high-risk dental procedures.[60] However, in a sequential, observational, multicenter, non-randomized study, there was no risk reduction associated with the introduction of dental screening before starting BP treatment, the limitation of BP administration for 2 years, and the avoidance of invasive dental procedures.[61] In the MRC IX trial, patients treated with ZA had a higher risk of developing ONJ compared to patients treated with clodronate (4% vs 1%, respectively). Among the 10 patients with ONJ (9 patients in the ZA arm and 1 patient in the clodronate arm), 3 achieved complete healing, 2 improved, and 5 patients were stable.[62]

Another complication noted in patients with osteoporosis who were treated with alendronate is the presence of low-energy fractures.[63-65] These fractures have been noted with minor trauma, with the subtrochanteric region as a common site. They have usually been associated with a BP treatment duration of 4–10 years.[64-66] One possible explanation is that long-term administration of alendronate induces an oversuppression of bone turnover, with possible accumulation of microdamage and hypermineralization that leads to increased bone brittleness and impaired bone resistance.[64] However, 2 extension studies failed to confirm the association between low-energy fractures and BPs.[67,68] In MM patients treated with intravenous BPs, cases of atypical fractures resembling the features described with alendronate have been reported.[69-71]

Future Directions

Bone disease is a significant cause of morbidity in a majority of patients with MM, and BPs remain the standard of care for this population. However, the optimal duration of BP therapy has yet to be determined; ongoing trials are investigating tailored treatment approaches based on treatment-related changes in levels of bone resorption markers. The phase IV Z-MARK (Bone Marker Directed Dosing of Zoledronic Acid for the Prevention of Skeletal Complications in Patients With Advanced Multiple Myeloma) study evaluated the efficacy and safety of 4 mg of ZA every 4 or 12 weeks in MM patients, based on urinary N-telopeptide levels. An interim analysis of 60 patients indicated that the use of bone markers is safe for the prevention of SREs in MM patients previously treated with BPs for 1–2 years.[72] Similarly, a comparison of 30 mg of pamidronate versus 90 mg every month in newly diagnosed patients with MM did not show any difference in SREs between the 2 doses tested.[17]

Denosumab, a monoclonal antibody against RANKL, has received regulatory approval in the United States for preventing SREs in patients with bone metastases from solid tumors, but it is not approved for use in patients with myeloma. In a randomized comparison to ZA that included 180 patients with MM, denosumab was noninferior to ZA for the prevention of SREs.[73]

Several novel targets are currently under investigation for bone-directed therapy. For example, myeloma

cells secrete the soluble Wnt inhibitor DKK1, which downregulates osteoblast function. In preclinical murine xenograft models of human MM, the anti-DKK1 mAb BHQ880 not only triggered new bone formation, but also inhibited myeloma-cell growth, and a clinical trial of BHQ880 is ongoing.[74]

Patients with MM also seem to have increased levels of activin A, which is involved in bone remodeling by promoting osteoclastogenesis.[75] Myeloma-induced expression of activin A from stromal bone-marrow cells downregulates gene expression of the transcription factor DLX 5 via activation of SMAD2. The physiologic action of activin A can be effectively blocked by the administration of a soluble activin-A receptor. ACE 011 is a human fusion protein derived from the activin-receptor type IIA that binds to, and prevents signaling of, certain members of the TGF-β super-family through the activin receptor. A clinical trial of ACE 011 in patients with MM is ongoing.[76]

Targeting of the tyrosine protein kinase BTK has been shown to block osteoclast formation and growth, as well as myeloma-cell growth, in preclinical models,[77] and a clinical trial is planned.[78] Outcomes from these and other ongoing studies evaluating the potential of new agents to manage myeloma-induced bone disease are eagerly awaited, and may expand the therapeutic repertoire in advanced MM. Although these are exciting targets, BPs remain the standard of care for myeloma-induced bone disease.

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