Optimal use of bisphosphonates in patients with multiple myeloma

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Case presentation

A 71-year-old woman presented with extreme low back pain. Her lumbar spine radiographs revealed a pathological fracture of L4. The hematology profile was normal (hemoglobin: 12.6 g/dL). The serum electrophoresis revealed an "M"-protein of 39 g/L and the immunofixation showed an immunoglobulin (Ig) G-λ paraprotein. The bone marrow trephine biopsy demonstrated a clonal plasma-cell infiltration of 35%. The diagnosis of IgG-λ multiple myeloma was made. The skeletal survey using conventional radiography showed an L4 fracture but no lytic lesions in the skeleton. The magnetic resonance imaging (MRI) of the lumbar spine and the pelvis revealed a diffuse pattern of marrow infiltration. The patient had normal creatinine (1.1 mg/dL; estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration formula was 51 mL/min/1.73 m^2) and normal serum calcium (9.9 mg/dL) levels. How should we manage bone disease in this myeloma patient?

Introduction

Osteolytic disease is the most common complication of multiple myeloma (MM) leading to devastating skeletal-related events (SREs), such as pathological fractures, need for radiation or surgery and spinal cord compression.[1] A challenge for the physicians is the definition of myeloma-related bone disease in the absence of lytic lesions on the conventional radiography or the definition of a myeloma-related fracture in a postmenopausal woman, as in our case. The International Myeloma Working Group has suggested that patients with normal skeletal survey using conventional radiographs be evaluated with whole-body MRI for the presence of focal lesions.[2] MRI can also differentiate the myeloma-related fracture from a benign osteoporotic-type fracture in the vast majority of cases.[3] In our case, the diffuse pattern of infiltration in the fractured vertebra is highly suggestive of a myeloma-related fracture that needs antimyeloma treatment and bone-targeted agents. Bisphosphonates are the cornerstone for management of myeloma-related bone disease.[1,3] Intravenous pamidronate and zoledronic acid and oral clodronate are the only drugs that have been licensed in different countries for the treatment of myeloma bone disease.[1,3] The aim of this review is to provide practical recommendations for the use of bisphosphonates in MM based on the published current evidence.

Methodology

We reviewed all published randomized clinical studies, clinical guidelines and systematic reviews, meta-analyses, observational studies, and case reports on the use of bisphosphonates in MM. Our research was performed through PubMed and ISI, until the 30 September 2012. We used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for the development of grades of recommendations (Table 1).

When should treatment with bisphosphonates be started?

During the past 2 decades, several randomized, placebo-controlled trials have shown that oral clodronate, intravenous pamidronate, and intravenous zoledronic acid effectively reduce bone pain, the incidence of SREs, and time to first and subsequent SREs in patients with myeloma-related bone disease assessed by conventional radiography.[4-6] There are only 3 large randomized studies comparing 2 different bisphosphonates or 2 different dosages of the same bisphosphonate. In the first, which was performed in the conventional chemotherapy era, zoledronic acid was found to be as effective as pamidronate in reducing pain, incidence of SREs, and delaying the time to first SRE.[7] In the second study, the Nordic group compared 2 doses of intravenous pamidronate (30 mg vs 90 mg, every month) that were administered to 504 patients for more than 3 years. The authors showed that 30 mg of pamidronate produced comparable time to SRE and similar SRE-free survival time as 90 mg.[8] However, the study was powered to show quality of life differences only and not differences on SREs. Finally, the third study, which was conducted by the Medical Research Council (MRC-IX Myeloma study), compared intravenous zoledronic acid (4 mg, every 3 to 4 weeks) with oral clodronate (1600 mg/daily) in approximately 2000 patients who received as an antimyeloma therapy either conventional chemotherapy or thalidomide-based regimens.[9] The study included symptomatic myeloma patients who had bone disease by conventional skeletal radiography but also patients without bone lesions on the skeletal survey. The authors found that zoledronic acid reduced the SRE risk by 26% compared with clodronate, regardless of the antimyeloma treatment given to the patients. Interestingly, this SRE reduction by zoledronic acid was evident in both patients with and without bone disease at diagnosis.[10] However, a recent meta-analysis by the Cochrane

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Table 1. GRADE recommendations for grading levels of evidence

Grade			
1	Evidence strongly suggests that the benefit of the procedure outweighs potential risk or risks of the procedure outweighs potential benefits	A	Consistent evidence from systemic reviews or high-quality randomized studies or high-quality observational studies
2	Evidence suggests the benefit and risk of a procedure is finely balanced or uncertain	B	Evidence from randomized and observational studies with important methodological flaws
		C	Evidence from randomized and observational studies with major methodological flaws or other sources of evidence (eg, case series)

database was not able to confirm superiority of any 1 bisphosphonate over another (zoledronic acid vs pamidronate or clodronate).[11] According to this latter analysis, bisphosphonates have to be administered in 6 to 15 myeloma patients in order to prevent a SRE in 1 of them.[11]

In patients with asymptomatic myeloma, no bisphosphonate has shown prolongation of time to progression to symptomatic disease.[12,13]

Based on the available data, we suggest that all patients with myeloma-related bone disease at diagnosis should to be treated with either zoledronic acid or pamidronate, intravenously, in addition to antimyeloma therapy (GRADE 1A). The suggested dose of zoledronic acid is 4 mg, in a 15-minute infusion, every 3 to 4 weeks and the dose of pamidronate is 90 mg, in a 2-hour infusion, every 3 to 4 weeks, in patients with normal renal function (GRADE 1A). For symptomatic patients without bone disease by conventional radiography, zoledronic acid should be given (GRADE 1B), but its advantage is debatable for patients with no bone disease on MRI or positron emission tomography/computed tomography (PET/CT). In asymptomatic (smoldering) myeloma, bisphosphonates are not recommended (GRADE 1A). If an asymptomatic patient has age-related osteoporosis, bisphosphonates can be given at the dose used for benign osteoporosis (GRADE 2C). When it is not possible to differentiate a myeloma-related from age-related bone loss in patients with asymptomatic disease, we suggest that patients with an abnormal MRI or PET/CT should be treated with bisphosphonates at the dose for symptomatic patients (GRADE 2C).

Is there any anti-myeloma effect of bisphosphonates?

Placebo-controlled, phase 3 randomized studies in the conventional chemotherapy era showed that subsets of myeloma patients receiving bisphosphonates had a survival advantage. Patients with vertebral fractures had a superior survival with clodronate over placebo,[4] whereas patients who received second-line antimyeloma therapy and pamidronate had a borderline survival advantage against placebo.[5] The recent MRC-IX study showed that zoledronic acid prolonged the median overall survival of the patients by 5.5 months over clodronate.[9] This was mainly the result of the beneficial effect of zoledronic acid in patients who had bone disease at baseline. Patients presenting with bone disease who received zoledronic acid had a survival advantage of 10 months, whereas all other patients had similar survival with those who received clodronate.[14] This result was independent of the antimyeloma treatment that was administered to the patients. A recent Cochrane meta-analysis confirmed that zoledronic acid was the only bisphosphonate that produced superior overall survival compared with placebo (hazard ratio 0.61, 95% confidence interval 0.28-0.98), but the authors found no differences compared with other bisphosphonates regarding all studied end-points, including survival.[11]

We suggest that zoledronic acid has to be preferred over clodronate because of its possible antimyeloma effect and survival advantage (GRADE 1A). Zoledronic acid is the only bisphosphonate that has increased patients' survival in a randomized study. The largest meta-analysis to date has not demonstrated an overall survival advantage of zoledronic acid over other bisphosphonates used in myeloma, including pamidronate, but confirmed its survival advantage over placebo (GRADE 2A).

What is the appropriate duration of bisphosphonate therapy?

In all randomized, placebo-controlled trials, the bisphosphonates were given for a maximum period of 2 years. Therefore, the recommended period of bisphosphonate administration was 2 years by all major associations and organizations, including American Society of Clinical Oncology and European Myeloma Network. In the recent MRC-IX trial, the bisphosphonates were given until disease progression. The subset of patients who received zoledronic acid for more than 2 years continued to experience a reduction in SREs and an improvement of overall survival compared with clodronate.[14] However, there is no information whether the reduction of SREs and the survival advantage of zoledronic acid was independent of the response status of the patients to their antimyeloma therapy, ie, if patients who have achieved complete response (CR) continue to have these advantages with continuous use of zoledronic acid.

We suggest that zoledronic acid should be given beyond 2 years only in patients with active myeloma (GRADE 1B). It is unclear if patients who achieve a CR will continue to have benefits from zoledronic acid administration. Because there are no data supporting the continuous use of pamidronate, pamidronate should be given initially for 2 years and then at the physician's discretion for patients with active disease (GRADE 2C).

How can bisphosphonates be used in patients with renal impairment?

Renal impairment is another common complication of MM.[15] Both zoledronic acid and pamidronate can cause acute tubular damage and deterioration in renal function. In the MRC-IX study, 5% of patients in the autologous transplantation arm and 7% in the nonautologous transplantation arm who received zoledronic acid developed acute renal failure.[9] According to the summary of product characteristics of the drug, zoledronic acid should be given at lower doses when there is renal impairment (Table 2). In the study comparing zoledronic acid with pamidronate, 10.7% of patients in the zoledronic acid group and 9.3% of patients in the pamidronate group had increased serum creatinine, whereas after 2 years of administration grade 3-4 serum creatinine increases occurred in 0.4% of patients in the zoledronic acid group and in 1.9% of patients in the pamidronate group.[7] Pamidronate's

Table 2. Bisphosphonate dosing according to renal function

CrCl rate (mL/min)	CLO recommended dosage (1600 mg)	ZOL recommended dosage (mg)	Recommended infusion time for PAM (90 mg/500 mL NS IV)
>80	100%		
50-80	75%		
12-50	50-75%		
<12	50% or discontinue		
>60		4.0	
50-60		3.5	
40-49		3.3	
30-39		3.0	
<30		Not recommended	Not recommended
>30			2-4 h

CLO, clodronate; IV, intravenous; NS, ; PAM, pamidronate; ZOL, zoledronic acid; NS, normal saline.

pharmacokinetics is characterized by a 2- to 3-hour distribution phase followed by rapid elimination of the drug in the urine. The elimination of pamidronate is slower in patients with a creatinine clearance (CrCl) <30 mL/min compared with patients with CrCl > 90 mL/min.[16] A pharmacokinetic study with oral clodronate in patients with renal impairment but not with MM showed that clodronate can be given even in patients with ClCr < 12 mL/min at 50% of the normal dose.[17]

We suggest that all myeloma patients receiving bisphosphonates be closely monitored for their renal function by measuring urinary albumin, serum electrolytes, and CrCl before administration of each intravenous infusion (GRADE 1A). Patients with mild to moderate renal impairment (CrCl 30 to 60 mL/min) should receive reduced doses of zoledronic acid and clodronate (Table 2). No change to zoledronic acid infusion time is recommended (GRADE 1A). Pamidronate should be administered via 4-hour infusion in patients with mild to moderate renal impairment (GRADE 1C). Pamidronate and zoledronic acid are not recommended for patients with CrCl < 30 mL/min (GRADE 1A), whereas clodronate can be safely given in patients with a CrCl > 12 mL/min (GRADE 2C). Bisphosphonate therapy should be discontinued in patients experiencing renal problems until CrCl returns to within 10% of baseline values (GRADE 1B).

Optimal management of bisphosphonates side effects

Side effects of bisphosphonates mainly include acute phase reactions, hypocalcemia, hypophosphatemia, gastrointestinal events after oral administration, and inflammatory reactions at the injection site.[4-9] Osteonecrosis of the jaw (ONJ) is an important but rare complication of bisphosphonates, more often observed with zoledronic acid and prolonged administration of bisphosphonates.[18] The use of preventive dental measures has reduced the incidence of ONJ.[19] Regarding precautions before dental extraction in patients who received bisphosphonates, the most recent American Dental Association recommendations do not suggest suspension of bisphosphonates in these cases because there are no data that it helps, and bisphosphonates persist for years in bone.[20]

For the management of these side effects, we suggest that calcium and vitamin D3 supplementation should be used in all patients to maintain calcium homeostasis (GRADE 1A). Caution is required for patients with renal insufficiency. Patients should receive a thorough dental examination, and all dental problems treated before the initiation of bisphosphonates (GRADE 2C). If ONJ develops, the bisphosphonates should be stopped; they can be readministered according to physician opinion (GRADE 2C).

Conclusion

Bisphosphonates should be considered in all patients with myeloma-related bone disease. Intravenous zoledronic acid or pamidronate are the recommended bisphosphonates. Zoledronic acid should be given continuously in patients with active disease, whereas pamidronate should be given for 2 years and then at the physician's discretion. The advantages of bisphosphonates in patients who have achieved a CR are unclear. Zoledronic acid is the only bisphosphonate to show survival advantage in a randomized study. Bisphosphonates are well tolerated, but preventive strategies must be instituted to avoid renal toxicity or ONJ.

Authorship

Contribution: E.T. designed research, performed the search, data extraction and wrote the manuscript; G.D.R. and M.A.D. performed the search, data extraction, and critically revised the manuscript.

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