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 X-rays 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 IgG-lambda paraprotein. The bone marrow trephine biopsy demonstrated a clonal plasma-cell infiltration of 35%. The diagnosis of IgG-lambda multiple myeloma was made. The skeletal survey using conventional radiography showed an L4 fracture but no lytic lesions in the skeleton. The MRI of the lumbar spine and the pelvis revealed a diffuse pattern of marrow infiltration. The patient had normal creatinine (1.1 mg/dl; eGFR by CKD-EPI formula was 51 mL/min/1.73 m²) 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 post-menopausal woman, as in our case. The IMWG has suggested that patients with normal skeletal survey using conventional X-rays 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 anti-myeloma treatment and bone targeted agents. Bisphosphonates are the cornerstone for the
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 30th of 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 last two 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 two different bisphosphonates or two different dosages of the same bisphosphonate. In the first, which was performed in the conventional chemotherapy era, zoledronic acid was found 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 two doses of intravenous pamidronate (30 mg versus 90 mg,
every month) that were administered to 504 patients for more than three 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 MRC (MRC-IX myeloma study), compared
intravenous zoledronic acid (4 mg, every 3-4 weeks) with oral clodronate (1600
mg/daily) in approximately 2000 patients who received as an anti-myeloma 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 to
clodronate, regardless of the anti-myeloma 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 database was not able to confirm superiority of any one bisphosphonate
over another (zoledronic acid versus 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 one 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 anti-myeloma therapy (GRADE 1A).
The suggested dose of zoledronic acid is 4 mg, in a 15-min infusion, every 3-4
weeks and the dose of pamidronate is 90 mg, in a 2-hour infusion, every 3-4
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 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 III, 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], while patients who received second line anti-myeloma 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 due to 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, while all other patients had similar survival with those who received clodronate [14]. This result was independent of the anti-myeloma treatment that was administered to the patients. The recent Cochrane meta-analysis confirmed
that zoledronic acid was the only bisphosphonate which produced superior overall survival compared to placebo (HR 0.61, 95% CI 0.28 to 0.98), but the authors found no differences compared to other bisphosphonates regarding all studied end-points, including survival [11].

**We suggest that zoledronic acid has to be preferred over clodronate due to its possible anti-myeloma 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 two years. Therefore, the recommended period of bisphosphonate administration was two years by all major associations and organizations, including ASCO and EMN. 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 anti-myeloma therapy, i.e. 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 two 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. Since there are no data supporting the continuous use of pamidronate, pamidronate should be given initially for two 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 non-autologous transplantation arm who received zoledronic acid developed acute renal failure [9]. According to the SPC 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, while 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 pharmacokinetics is characterized by a 2-3 hours 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 to 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/minute at 50% of the normal dose [17].
We suggest that all myeloma patients receiving bisphosphonates should be closely monitored for their renal function by measuring urinary albumin, serum electrolytes and CrCl before administration of each IV infusion (GRADE 1A). Patients with mild to moderate renal impairment (CrCl: 30-60 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 hours 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), while 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 ADA recommendations do not suggest suspension of bisphosphonates in these cases, since there is not 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 re-administered 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, while pamidronate should be given for two 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.

Conflict-of-interest disclosure: E.T. and M.A.D. have received honoraria by NOVARTIS; G.D.R. is a consultant for Amgen.
References


### Table 1. GRADE recommendations for grading levels of evidence

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<th>Grade</th>
<th>Evidence</th>
<th>Grade</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>1</td>
<td>Evidence strongly suggests that the benefit of the procedure outweighs potential risk or risks of the procedure outweighs potential benefits</td>
<td>A</td>
<td>Consistent evidence from systemic reviews or high quality randomized studies or high quality observational studies</td>
</tr>
<tr>
<td>2</td>
<td>Evidence suggests the benefit and risk of a procedure is finely balanced or uncertain</td>
<td>B</td>
<td>Evidence from randomized and observational studies with important methodological flaws</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>Evidence from randomized and observational studies with major methodological flaws or other sources of evidence e.g. case series</td>
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</table>

### Table 2: Bisphosphonate dosing according to renal function

<table>
<thead>
<tr>
<th>Creatinine Clearance rate (mL/min)</th>
<th>Recommended dosage of CLO (1600 mg)</th>
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<tbody>
<tr>
<td>&gt;80</td>
<td>100%</td>
</tr>
<tr>
<td>50-80</td>
<td>75%</td>
</tr>
<tr>
<td>12-50</td>
<td>50-75%</td>
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<tr>
<td>&lt;12</td>
<td>50% or discontinue</td>
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<table>
<thead>
<tr>
<th>Creatinine Clearance rate (mL/min)</th>
<th>Recommended dosage of ZOL (mg)</th>
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<tbody>
<tr>
<td>&gt;60</td>
<td>4.0</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0</td>
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<tr>
<td>&lt;30</td>
<td>Not recommended</td>
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<table>
<thead>
<tr>
<th>Creatinine Clearance rate (mL/min)</th>
<th>Recommended infusion time for PAM (90mg/500mL NS IV)</th>
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<tbody>
<tr>
<td>&gt;30</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Not recommended</td>
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