Dear Colleague:

It is with great pleasure that I present the final issue of our third annual “Considerations in Multiple Myeloma” newsletter series. The goal of this case-based curriculum is to help clinicians integrate the latest advances in the treatment of multiple myeloma (MM) into the clinical setting. Each issue features 2 case studies, with faculty perspectives by an oncologist, a pharmacist, and a nurse from a leading cancer institution.

In this issue, faculty from the Institute for Myeloma & Bone Cancer Research discuss a multidisciplinary approach to the prevention and management of skeletal-related events in 2 patients with myeloma. Past issues in this series have focused on first-line treatment options, maintenance therapy, retreatment for relapsed/refractory disease, stem cell transplantation, the management of MM in the transplant setting, the evolving role of cytogenetic testing, and side-effect management.

It is my sincere hope that the information presented in this newsletter series will be of value to you in your care of patients with MM.

Sincerely,

Sagar Lonial, MD
Associate Professor of Hematology and Oncology
Emory University School of Medicine
At the completion of this educational activity, participants should be able to:

- Review the role of bisphosphonate therapy as effective maintenance treatment for multiple myeloma (MM)
- Assess the potential of newer strategies, including the use of novel antimielyoma agents, to optimize bone health in patients with MM
- Develop effective management strategies for myeloma-induced bone complications, based on key clinical evidence, appropriate practice guidelines, and individual patient factors

This activity is supported by an educational grant from Millennium Pharmaceuticals, Inc.

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Articles/Commentaries: 45 minutes
Evaluation/Posttest: 15 minutes

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Case Study: Treatment of a Patient with Hypercalcemia and Renal Dysfunction

Introduction

Multiple myeloma (MM) is the most frequent malignancy to involve the skeleton. As a result, patients often experience serious and debilitating skeletal-related events (SREs), including pathologic vertebral and nonvertebral fractures, severe bone pain, and spinal cord compression. The intravenous (IV) bisphosphonates zoledronic acid and pamidronate are considered the mainstay of treatment for myeloma-related bone disease and hypercalcemia, common complications of the disease. Although highly effective, these agents may cause side effects that require careful monitoring throughout the course of treatment. Consideration of patient comorbidities, such as renal dysfunction, prior to initiation of bisphosphonate therapy is necessary, as this will determine the choice of agent as well as the dose and schedule of administration, as illustrated in the following case study.

Case Presentation

LN is a 68-year-old retired dentist in his usual state of health until 2 weeks prior to his initial visit, when he began experiencing mental confusion and memory loss. While undergoing initial assessment, the patient had a syncopal episode and was admitted to the hospital. Work-up showed a calcium level of 14.2 mg/dL, a creatinine of 3.3 mg/dL, and a total protein of 10.2 g/dL with an albumin of 3.1 g/dL. His hemoglobin was 9.1 g/dL and white blood cell count was $9.1 \times 10^9$ cells/L with normal differential and platelet count of $238 \times 10^9$ cells/L.

Bone survey revealed multiple lytic lesions in the skull, pelvis, and long bones.

Further studies showed a monoclonal gammopathy of IgG kappa type, with an IgG of 3280 mg/dL, a monoclonal protein of 2.4 g/dL, and a 24-hour urine protein of 1200 mg, of which 850 mg was monoclonal kappa protein. Beta-2-microglobulin was 5.9 mg/L. Vitamin $D_3$ was also low at 16 ng/mL. Bone marrow showed 60% kappa-restricted plasma cells. Bone survey revealed multiple lytic lesions in the skull, pelvis, and long bones. Karnofsky performance status was 50% and Eastern Cooperative Oncology Group performance status was 3. The patient was diagnosed with Durie-Salmon stage IIIB/international Staging System stage III MM. He also had a long history of several chronic conditions: hypertension (treated with atenolol), degenerative joint and disc disease (treated with diclofenac), hyperlipidemia (treated with simvastatin), and peripheral neuropathy (PN) (treated with amitriptyline).

LN was admitted to the hospital and received 2 units of packed red blood cells. He was started on IV zoledronic acid 4 mg, which was infused over 2 hours along with IV normal saline (200 mL/h) and oral allopurinol. He also began an antmyeloma regimen consisting of IV bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 of a 21-day cycle and oral dexamethasone 40 mg weekly, as well as oral acyclovir 400 mg twice daily for prophylaxis of herpes zoster.

The patient’s calcium normalized over the next week and creatinine decreased to 1.3 mg/dL. He received 4 cycles of bor-
tezomib plus dexamethasone therapy and monthly zoledronic acid, which was infused over 15 minutes since his renal function had now improved. His IgG, monoclonal protein, and 24-hour urine paraprotein decreased to 2200 mg/dL, 1.4 g/dL, and 300 mg, respectively, and his hemoglobin improved to 11.0 g/dL. He was then started on oral vitamin D 50,000 IU weekly and oral elemental calcium 1 g daily. He continued on monthly bisphosphonate therapy, as well as the bortezomib-based regimen, with an ongoing response.

It was important to recognize the hypercalcemia as an oncologic emergency that needed immediate attention.

After 3 months, the patient developed a sudden onset of pain in his left ribs. Radiographs showed a new fracture in the left seventh rib. His IgG and monoclonal protein increased to 4924 mg/dL and 3.7 g/dL, respectively. A 24-hour urine protein collection showed an increase in his urinary monoclonal protein to 900 mg. His creatinine increased to 1.7 mg/dL.

Oncologist Perspective
James R. Berenson, MD

Hypercalcemia is a common metabolic complication of myeloma, resulting from excessive osteolysis.1 In the above case, the patient presented with significant central nervous system effects due to an elevation in serum calcium and its associated dehydration.2 In addition, he developed azotemia, which was caused by dehydration and the deleterious effects of excess calcium on renal function. This is a common occurrence among patients with hypercalcemia, and may contribute to changes in mental function.3

It was important to recognize the hypercalcemia as an oncologic emergency that needed immediate attention. Hypercalcemic patients require vigorous hydration with normal saline,2 as sodium facilitates the loss of calcium through the kidney. It is essential that rehydration be completed prior to initiation of treatment with loop diuretics (eg, furosemide). Loop diuretics will prevent overhydration and fluid overload, which may occur without proper monitoring of a patient’s fluid status; diuretics will also help facilitate loss of calcium in the urine. Thiazide diuretics should be avoided in situations such as this, since they can exacerbate hypercalcemia. It is also important to monitor serum levels of potassium, bicarbonate, magnesium, calcium, phosphorous, and creatinine frequently, and to check urine electrolytes during the first few days of treatment.

Bisphosphonates for hypercalcemia

Due to the degree of hypercalcemia observed in LN, it was decided that he should receive zoledronic acid infused at a 4-mg dose. According to a pooled analysis of 2 randomized clinical trials, this bisphosphonate was shown to be superior to pamidronate for normalizing calcium in cancer patients with hypercalcemia.3 It is essential to normalize calcium as quickly as possible in MM patients with renal dysfunction and hypercalcemia, and an elevated serum creatinine should not prevent the use of zoledronic acid in this population of patients. In the case of LN, high serum calcium was likely contributing to his renal dysfunction, although another component of this dysfunction may have been attributed to effects of urine monoclonal protein. An increased infusion time of 4 mg over 2 hours (instead of 15 minutes) was used to reduce the risk of potential negative effects that the zoledronic acid might have on his renal impairment, which is our practice with patients who present with a high serum creatinine. Negative renal impact of IV bisphosphonates is related to C_{max} and not AUC, and so is determined by the rate of infusion rather than the dose of the drugs.4 Conversely, their efficacy is related to the total dose infused and not to the rate of infusion. As is reported in the majority of patients with hypercalcemia,3 LN’s calcium level normalized within 1 week of zoledronic acid administration.

Vitamin D and calcium supplementation

Since the patient presented with a high calcium level, it was important for him to temporarily avoid vitamin D and limit calcium-containing foods. However, once his calcium level normalized, he was given 1 g of elemental calcium daily along with vitamin D supplements. His vitamin D levels were low, which is a common occurrence in cancer patients,7 including those with myeloma.6 Patients such as this often require additional vitamin D supplements7 (eg, 50,000 IU weekly for 6 weeks) in order to normalize their levels. Once this occurs, they can be supplemented with daily doses as maintenance, and levels of vitamin D should be checked periodically to ensure that they are being maintained in the normal range. In order to promote optimal bone health in patients with myeloma-associated bone loss, vitamin D and calcium need to be supplemented beyond a normal dietary intake.

LN began treatment with bortezomib plus dexamethasone, a highly active regimen in MM.

Front-line therapy

LN began treatment with bortezomib plus dexamethasone, a highly active regimen in MM.8 Corticosteroids such as dexamethasone, in addition to being effective for the treatment of the disease itself, have also been shown to reverse hypercalcemia.9,10 The rapid reduction in tumor burden that occurred after 4 cycles of this therapy led to a decreased urinary secretion of potentially nephrotoxic paraproteins, which may also have contributed to the improvement in LN’s renal function.

Preclinical data have also suggested that bortezomib induces formation of bone-building cells—the osteoblasts—and boosts the survival of these cells.11 Some
clinical trials of bortezomib have shown an increase in alkaline phosphatase, a marker of bone formation, among patients responding to therapy with this agent.12

Managing SREs with bisphosphonate therapy

Bisphosphonates support bone health by suppressing the activity of osteoclasts, thereby slowing bone resorption. In the Medical Research Council (MRC) Myeloma IX trial, IV zoledronic acid was shown to be more effective than oral clodronate for reducing the relative number of SREs (including fractures).13 However, zoledronic acid cannot prevent bone complications from occurring altogether. Similarly, pamidronate has demonstrated efficacy in reducing SREs compared with placebo in myeloma patients with osteolytic bone disease.14,15 A large clinical trial comparing pamidronate with zoledronic acid showed equivalent effects in the prevention of SREs (Figure 1),16 although zoledronic acid can be safely administered over a much shorter period of time than pamidronate (15 minutes vs 2 hours, respectively). Furthermore, a recently completed trial comparing monthly administration of 4 mg of zoledronic acid over 15 minutes versus 30 minutes showed no significant difference in the occurrence of renal events between the 2 administration times.17

The complications LN experienced within the first several months of treatment were likely due to irreversible bone damage that developed prior to the initiation of bisphosphonate therapy; their occurrence should not be interpreted as meaning that the zoledronic acid was ineffective. Therefore, he should continue ongoing monthly IV bisphosphonates despite progression of his myeloma and the occurrence of a new pathologic rib fracture.

A large clinical trial comparing pamidronate with zoledronic acid showed equivalent effects in the prevention of SREs.

Pharmacist Perspective

Russell Mapes, BS Pharm, RPh

Zoledronic acid and pamidronate are important components in the treatment plan for patients with MM. These agents, in combination with chemotherapy, have been shown to be especially effective in reducing the occurrence of SREs and decreasing the need for surgery and radiation therapy to treat bone-related complications.13-16 Patients receiving bisphosphonate therapy also tend to experience less bone pain, and often need less analgesic medications.13 Recommended standard dosing is IV zoledronic acid 4 mg over 15 minutes18 or IV pamidronate 90 mg over at least 2 hours19 both monthly (every 3–4 weeks). However, dosing adjustments may be necessary, based on individual patient factors, as was the case with LN.

IV bisphosphonates: mechanisms of action

Bisphosphonates are potent inhibitors of osteoclastic activity (Figure 2).20,21

Bone resorption is diminished through several actions: inhibition of several critical intracellular enzymes; binding to and stabilizing calcium phosphate within the bone matrix; disrupting intracellular effects within the osteoclast; and interrupting metabolic pathways to cause apoptosis of osteoclasts and their precursor cells, the monocytes. Interestingly, nitrogen-containing bisphosphonates (eg, zoledronic acid and pamidronate) have been shown to block the mevalonic-acid biosynthesis pathway, which is the same pathway affected by cholesterol-lowering statins.21 This results in a lack of production of fat derivatives, especially geranylated moieties.21 Many critical intracellular proteins, especially GTPases, require the presence of these fats to function properly,20,22,23 so that in their absence these proteins are unable to work, resulting in the induction of osteoclast apoptosis. Recent prestudies have shown that zoledronic acid also blocks the induction of osteoblast-induced osteoclastogenesis.20 This occurs through the drug’s ability to reduce the levels of the pro-osteoclast protein receptor activator for NF-κB ligand (RANKL) and to increase the levels of the decoy receptor osteoprotegerin that binds to RANKL; these mechanisms prevent RANKL’s function in stimulating osteoclastogenesis.20,20

IV bisphosphonates: dosing and renal issues

Because bisphosphonates are cleared renally,4,18,19,24 IV administration requires
monitoring of kidney function on an ongoing basis. Although long-term use of zoledronic acid is not recommended if a patient’s calculated or actual creatinine clearance (CrCl) is less than 30 mL/min, this limitation in the setting of hypercalcemia may not always apply.3

In the absence of hypercalcemia, initial treatment with zoledronic acid should be administered over at least 15 minutes, with the dose adjusted based on results of the calculated CrCl for levels between 30 and 60 mL/min, according to the drug’s package insert (Table 1).18 The basis for these dose adjustments is not derived from any specific clinical trial data; the risk of bisphosphonate use in the presence of renal dysfunction is primarily related to Cmax. Thus, in our practice, we have found that increasing the infusion time has made it feasible to give 4 mg to patients with CrCl <60 mL/min, although this is not the FDA label recommendation. Moreover, among patients with irreversible dialysis-dependent renal failure, zoledronic acid can be administered long-term at the 4-mg dose over 15 minutes on a monthly basis without untoward effects, since kidney function will not recover in this population of patients. Although the drug molecule is small and potentially dialyzable, the serum half-life is only approximately 30 minutes.18 Therefore, as long as the patient does not undergo immediate dialysis, anti–bone-resorptive benefits of taking this drug on a regular basis may still be attainable.

It is important to assess serum creatinine before each monthly bisphosphonate treatment.

Figure 2. Mechanism of action of bisphosphonates.

After binding to calcium phosphate in bone matrix, bisphosphonates interrupt key metabolic pathways within osteoclasts, causing them to undergo apoptosis. They also reduce the level of RANKL and increase the level of osteoprotegerin (OPG) in osteoblasts, thus inhibiting osteoclast maturation and activation.

Table 1. Suggested Initial Dose of Zoledronic Acid Based on Creatinine Clearance18

<table>
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<th>CrCl (mL/min)</th>
<th>Zoledronic Acid Dose (mg)</th>
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<tr>
<td>&gt;60</td>
<td>4</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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*aCalculated using the Cockcroft-Gault formula.  
*bDoses calculated assuming target AUC of 0.66 (mg•h/L) (CrCl = 75 mL/min).  
AUC indicates area under the curve; CrCl, creatinine clearance.

It is important to assess serum creatinine before each monthly bisphosphonate treatment to ensure that renal function has not deteriorated. Treatment should be withheld in the following instances: (1) if serum creatinine increases by ≥0.5 mg/dL in patients who demonstrated normal renal function (<1.4 mg/dL) at the time of their first administration of zoledronic acid; or (2) if serum creatinine increases by ≥1.0 mg/dL from baseline in patients who demonstrated elevated serum creatinine (≥1.4 mg/dL) at baseline. Once creatinine returns to within 10% of baseline, the drug can be restarted at the same dose as initially used, although it should be infused over a longer period of time.

Frequently, changes in renal function observed in myeloma patients are not due to bisphosphonate treatment, but are a result of disease progression, comorbid conditions such as diabetes mellitus or hypertension, or use of other nephrotoxic medications. Results of the randomized MRC Myeloma IX trial support this concept, since the risk of renal failure was similar in patients who received monthly IV zoledronic acid and those who received daily therapy with oral clodronate, which has not been shown to cause significant kidney problems.13 Thus, discontinuation of bisphosphonate therapy when the rise in creatinine is due to other causes may place a patient at unnecessary risk for additional SREs. Clinicians should emphasize to all patients treated with bisphosphonates—and indeed all myeloma patients—that they need to maintain adequate hydration on an ongoing basis to minimize the risk of renal problems.
HYPERCALCEMIA AND RENAL DYSFUNCTION

Table 2. CRAB Features of Multiple Myeloma25

<table>
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<tr>
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<tr>
<td>Calcium elevation</td>
<td>Serum calcium &gt;11.5 mg/dL or ULN</td>
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<tr>
<td>Renal insufficiency</td>
<td>Serum creatinine &gt;2 mg/dL</td>
</tr>
<tr>
<td>Anemia</td>
<td>Hemoglobin &gt;2 g/dL below lower limit or value &lt;10 g/dL</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>Lytic lesions, severe osteopenia, or pathologic fractures</td>
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ULN indicates upper limit of normal.

IV bisphosphonates: additional side effects

Patients need to be counseled regarding the possibility of other adverse events related to bisphosphonate therapy, including infusion reactions and osteonecrosis of the jaw,18 which will be discussed in more detail in the next case study. Infusion-related effects may include flu-like symptoms (eg, fever, chills, bone pain, arthralgias, and myalgias)18, and less frequently, local reactions at the infusion site (eg, redness or swelling). In most cases, no specific treatment is required and symptoms subside after 24 to 48 hours.18

Nurse Perspective

Regina Swift, RN, BSN

Initial presentation of the patient in this case included mental confusion, memory loss, and weakness—classic symptoms of hypercalcemia. Based on the confirmation of at least 1 CRAB feature of end-organ damage (Table 2)25 he was considered symptomatic and required immediate treatment. Bisphosphonate therapy with zoledronic acid was administered to reverse the hypercalcemia. This drug was initially infused over 2 hours to minimize the chance of worsening his renal dysfunction. As noted above, the resolution of hypercalcemia improved LN’s renal function within the first week of treatment. This is significant, since it would suggest that his initial renal dysfunction was related more to the hypercalcemia than to the effect of myeloma paraprotein on his kidney. When formulating treatment plans for our patients, decisions regarding the use of specific drugs always take into account dose adjustments for renal insufficiency, as well as each drug’s potential effect on the kidney.

Supportive pharmacotherapy

Bortezomib plus dexamethasone was selected as front-line therapy for LN. Given his history of neuropathy, and the fact that PN is a common side effect of bortezomib-based therapy,26 it was imperative to closely monitor for neuropathic symptoms. In addition to the amitriptyline that the patient was already taking, he was started on alpha lipoic acid (ALA) 600 mg/day orally. Although this agent is commonly used to prevent and manage PN, he was advised not to take it on bortezomib treatment days, since preliminary data has suggested that ALA may interfere with this drug’s antitumor effects.27 Acyclovir prophylaxis was also initiated to reduce the risk of herpes zoster. In the VISTA trial, 13% of patients who received front-line therapy with bortezomib/melphalan/prednisone experienced varicella zoster virus, although the incidence of this side effect was reduced to 3% in patients who received antiviral prophylaxis.28

Supportive measures initially provided to LN included blood products to treat his anemia. As his disease responded to therapy, however, these interventions were no longer necessary. Allopurinol was administered to control uric acid levels, an important form of support in the event that he developed tumor lysis syndrome (TLS) during therapy. Without management of uric acid, there could have been additional stress on his already compromised renal function noted at the time of initial presentation, due to uric-acid nephropathy that can arise from TLS.

LN’s preexisting hypertension also required careful monitoring throughout treatment. In some cases, antihypertensive medications may need to be adjusted, as agents such as bortezomib may occasionally cause hypotension.26 We instructed the patient to move slowly and purposefully when changing positions from lying to sitting or sitting to standing, to allow time for his body to equilibrate to the change. This was done to reduce the chance of sudden dizziness, which could lead to a fall and cause further fractures in this patient with compromised bone density. We also recommended a home safety assessment for tripping hazards (such as throw rugs) and safety features like railings in the bathtub or rubber bathtub mats to reduce the risk of slipping.

Unfortunately, 3 months after diagnosis, LN experienced a relapse, which was initially suspected when he complained of sudden onset of pain in his left ribs. This complication occurred despite monthly bisphosphonate therapy, supplemental vitamin D therapy, and 1 g of elemental calcium per day. Pain management was initiated until healing began and new therapy could be started.

Patient education

Oncology nurses play an important role in providing patient education and emotional support to patients and their families. Since LN had become ill very suddenly, he felt overwhelmed and needed guidance through the various stages of care. Ongoing communication between nurses, caregivers, and patients is crucial.
to ensure timely reporting of events that can affect outcomes. This strategy facilitates nursing care and allows prompt interventions for complications, thereby minimizing the impact of these problems. This is especially important for patients such as LN, whose risk of complications was high due to his comorbid conditions.

Conclusion

The patient in this case presented with symptomatic MM, hypercalcemia, and several comorbidities, including renal insufficiency. He was effectively treated with IV zoledronic acid, which not only rapidly normalized his calcium, but his creatinine level as well. He continued treatment with this bisphosphonate on an ongoing monthly basis to prevent further bone loss and associated complications. A bortezomib-based regimen was chosen as front-line therapy; as this agent has shown good efficacy and safety in clinical trials that include renally impaired patients.

References

Case Study: Management of a Patient with Osteonecrosis of the Jaw

Introduction

Intravenous (IV) monthly bisphosphonate therapy has been shown to prevent, reduce, and delay skeletal-related events (SREs), and has become an essential component of multiple myeloma (MM) treatment. One of the complications associated with treatment with these agents, however, is damage and death of the jaw, known as osteonecrosis of the jaw (ONJ). This relatively uncommon but sometimes difficult to manage condition may lead to infectious complications and reduced intake of calories and nutrients in a patient population that can ill-afford these risks. Therefore, every effort should be made to educate patients and caregivers regarding the potential for this adverse event and the necessary steps to reduce the risk of its occurrence and its severity if it does occur. In the following case, a patient who was treated with first-line myeloma therapy and IV bisphosphonates for bone complications developed ONJ due to a tooth extraction. This case further illustrates the importance of effective communication among all healthcare providers associated with the care of patients with MM.

Case Presentation

PK is a 69-year-old man who was in good health until 6 months prior to an evaluation with his internist, at which time he complained of low back pain that had intensified during the past week. The physician ordered vertebral compression fractures (VCFs) at T11, L1, and L2. Spinal magnetic resonance imaging revealed an infiltrative process in the spine and within the VCFs. The patient was hospitalized and underwent T11 kyphoplasty, plus a biopsy that showed a lambda-restricted plasma cell tumor.

PK was referred to an oncologist, who ordered a skeletal survey. The survey revealed multiple lytic lesions in the spine and large lesions in the right proximal humerus and left proximal femur. Since the lesion in the femur was felt to be at high fracture risk, the patient underwent internal fixation and placement of a rod. A femoral biopsy showed another plasma cell tumor, and he underwent radiotherapy to the lower thoracic and lumbar spine and to the right humerus and left femur. Further laboratory tests showed the following: an IgG lambda monoclonal gammopathy, a monoclonal protein of 1.7 g/dL, an IgG of 2130 mg/dL, no urinary paraprotein, a hemoglobin of 11.2 g/dL, a white blood cell count of 6.3 × 10^9 cells/L, a platelet count of 196 × 10^9 cells/L, creatinine 0.8 mg/dL, albumin 3.9 g/dL, and calcium 8.3 mg/dL. Vitamin D₃ was 39 ng/mL and beta-2-microglobulin was 4.62 mg/L. The patient was diagnosed with International Staging System stage II MM.

PK’s back pain improved and he received bisphosphonate therapy with IV zoledronic acid 4 mg infused over 15 minutes. Approximately 24 hours later, he experienced flu-like symptoms with myalgia, arthralgia, and a fever of 38.4°C. He was given oral acetaminophen and these symptoms resolved within 8 hours.

It was discovered that the patient had exposed bone in the left anterior maxilla at the site of the dental extraction.

Physical therapy was initiated, resulting in further improvement in the patient’s back disability. He was started on the DVD regimen, consisting of pegylated liposomal doxorubicin 5 mg/m², bortezomib 1.0 mg/m², and IV dexamethasone 40 mg, administered on days 1, 4, 8, and 11 of a 28-day cycle. He also received oral acyclovir 400 mg twice daily for prophylaxis of herpes zoster and oral alpha lipoic acid 600 mg daily (except on the days he received bortezomib) to help prevent peripheral neuropathy. He continued on zoledronic acid every 28 days and took vitamin D 1200 IU and elemental calcium 1 g daily.

After 4 cycles of DVD, the patient’s IgG and monoclonal protein decreased to 676 mg/dL and 0.56 g/dL, respectively. His hemoglobin improved to 13.5 g/dL. Para-protein remained stable after 2 more cycles, and he was started on maintenance therapy with IV dexamethasone 40 mg and bortezomib 1.3 mg/m² every other week, with oral methylprednisolone 20 mg every other day between the dexamethasone infusions. He continued monthly zoledronic acid at a dose of 4 mg.

Four months later, PK visited a dentist and underwent a root canal on a left anterior upper tooth. He had a long history of poor dental care. The area became infected and he required ongoing antibiotics. At the next visit, he informed the dentist that he was on monthly zoledronic acid, had recently received an infusion, and had been told not to have teeth extracted while he was being treated with the drug. Despite this warning, the dentist removed the problematic tooth. Two months later, the area in the left upper jaw became increasingly symptomatic. Upon evaluation by the oncology team, it was discovered that the patient had exposed bone in the left anterior maxilla at the site of the dental extraction. He was referred to a peri-
odontist, who diagnosed ONJ, an uncommon adverse event associated with bisphosphonate therapy.

Zoledronic acid was held, but the other therapies used to treat the myeloma were continued. He was started on oral antibiotics, cyclohexidine washes, lysine tablets, vitamin B–complex pills, and irrigation of the involved area with povidone-iodine. The patient was reminded to maintain excellent dental hygiene. He was able to eat only soft foods because of pain on mastication. A bridge was placed at the involved site and the area slowly improved. His antibiotics were discontinued and he was able to resume a normal diet that included solid foods after 3 months. However, the area of exposed bone remained present in the maxilla. Zoledronic acid was restarted on a monthly basis, and PK remained in remission on maintenance therapy without further change in ONJ.

Oncologist Perspective

James R. Berenson, MD

This case illustrates several important aspects regarding the management of myeloma-associated bone disease. Patients with MM frequently develop symptomatic VCFs, as was the case with this patient. In the past, these fractures were managed with cumbersome operative procedures that were poorly tolerated in this patient population. The development of vertebroplasty, followed more recently by kyphoplasty, has allowed patients to undergo minimally invasive procedures to help reduce their symptoms. A recent large, randomized study comparing immediate kyphoplasty with nonsurgical management among cancer patients with symptomatic VCFs showed a marked advantage in terms of back disability, reduced pain, and improved overall quality of life with this surgical procedure (Table 1). Although external beam radiation may also reduce pain in most patients, this treatment can have potentially deleterious effects on bone marrow function and possibly other adjacent organs. In addition, it may preclude administration of other effective antmyeloma therapies, such as anthracyclines and bortezomib, which have been shown to be radiosensitizing (ie, they may increase the side effects from external beam radiotherapy). It is important to recognize that MM affects the bone marrow throughout the body; as a result, treatment with local radiation does not address the remainder of the myeloma-involved bone marrow outside the radiation-treated site.

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Use of IV bisphosphonates to prevent SREs

Studies have shown that the administration of monthly IV nitrogen-containing bisphosphonates reduces the occurrence of further SREs (including fractures) in myeloma patients with lytic bone disease. The Medical Research Council Myeloma IX trial also showed that treatment with IV zoledronic acid given at a dose of 4 mg monthly not only reduced skeletal morbidity but improved overall survival compared with oral clodronate (a weaker non–nitrogen-containing bisphosphonate) given at a dose of 1600 mg daily. All patients in this trial also received antmyeloma therapy. Preclinical studies have shown antmyeloma effects of zoledronic acid through multiple mechanisms, including direct cytotoxic effects on MM cells and monocytes, antiangiogenic effects, suppression of production of myeloma growth and antiapoptotic proteins, prevention of tumor cell adherence to stroma, and immunostimulatory effects.

IV bisphosphonate therapy: acute-phase reactions and ONJ

PK experienced an acute-phase reaction following the first dose of zoledronic acid. These adverse events occur in approximately 10% to 15% of patients receiving IV bisphosphonate therapy, typically 24 to 48 hours after the first infusion. Patients should be warned of these potential reactions, and reassured that they are unlikely to occur with continued dosing of the drug. Since these are caused by a release of inflammatory cytokines, steroids may reduce the severity. Therefore, if steroids are planned as part of the patient’s regimen, it is reasonable to administer them on the same day as the zoledronic acid. In addition, in preclinical studies, steroids have been shown to have synergistic antmyeloma effects when administered with zoledronic acid.

While on bisphosphonate therapy, the patient developed ONJ following removal of a tooth. Over the past several years, it has become evident that patients receiving IV treatment of zoledronic acid or pamidronate may develop this complication. The severity of ONJ varies greatly: some patients only show asymptomatic

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Table 1. Balloon Kyphoplasty vs Nonsurgical Management for Vertebral Compression Fractures Among Cancer Patients at 1 Month of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>BKP (n=68)</th>
<th>NSM (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean improvement in RMDQ</td>
<td>-8.3 points</td>
<td>+0.1 points</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean improvement in back pain score</td>
<td>-3.9 points</td>
<td>-0.6 points</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*RMDQ is a 0- (no disability) to 24-point (maximum disability) instrument validated for assessing back-specific physical functioning. Negative change indicates improvement.

BKP indicates balloon kyphoplasty; NSM, nonsurgical management; RMDQ, Roland-Morris Disability Questionnaire.
areas of exposed bone in the mandible or maxilla; others (a minority of cases) have areas of infected jawbone that may develop secondary infections, leading in some cases to fractures that require surgical intervention. Notably, one of the risk factors for ONJ beyond exposure to IV bisphosphonates includes dental extraction, as was performed in our patient.

Dentists need to be aware of patients’ prior exposure to IV bisphosphonates, so that extractions can be avoided if at all possible. It is considered prudent to allow patients 3 months off IV bisphosphonate therapy before and after the procedure if extraction of the tooth is required. Although this approach has been recommended as a way to reduce the risk of ONJ for patients who have been previously treated with an IV bisphosphonate, there are actually no studies showing that this course of action will prevent or reduce the development of this event.

It is also important to conduct a complete dental exam prior to initiation of bisphosphonates so that tooth extractions can be performed before starting treatment with these drugs. There is no proven treatment for ONJ once it occurs, but it is important to reduce the risk of secondary infection through optimizing dental hygiene with excellent self-care and regular dental exams. Patients may occasionally require antibiotics, antiviral medications, and antifungal drugs. There is no evidence that discontinuation of the IV bisphosphonate will improve outcome for MM patients diagnosed with ONJ. The key is to adopt preventive measures that can reduce the occurrence of ONJ altogether. A recently published study suggests that implementation of specific dental preventive measures may, in fact, greatly reduce the risk of ONJ.

Pharmacist Perspective
Russell Mapes, BS Pharm, RPh

Optimizing bone health

Calcium and vitamin D supplementation has become an integral part of the treatment of patients with MM. Calcium is an integral part of any new bone mineralization, and vitamin D aids in the absorption of calcium. It is important to remember that IV bisphosphonates, given their ability to correct hypercalcemia, can also induce hypocalcemia. Therefore, the use of supplemental calcium and vitamin D can reduce this complication.

Most MM patients cannot achieve adequate vitamin D levels simply from their diet and sun exposure. For the patient in this case study, our recommendation was daily amounts of elemental calcium 1 g and vitamin D 1200 IU (ergocalciferol or cholecalciferol). It is important to remember that calcium supplements contain additional elements; therefore, patients need to consult with a pharmacist to determine the proper amount of calcium supplementation to take in order to achieve the desired 1 g daily of elemental calcium. The pharmacokinetic absorption of calcium is dependent upon the strength and availability of gastric acid. The maximum dose of elemental calcium that can be absorbed at any one time is 0.5 g. Therefore, our recommendation is to give the elemental calcium 1 g in divided doses. Patients on protein pump inhibitors (PPIs) or antacid therapy have a limited availability of gastric acid, and so should avoid calcium carbonate products, which need adequate gastric acid for absorption. Patients on PPIs or antacids should use calcium citrate as an alternative source of calcium supplementation.

Osteonecrosis of the jaw

ONJ has been associated with bisphosphonates, especially when these agents are administered intravenously. The course of ONJ is variable, and in some cases may spontaneously resolve even during ongoing IV bisphosphonate therapy. In rare cases, patients with ONJ may develop fractures and require extensive surgical intervention. Although no specific therapy has been shown to effectively treat ONJ, antibiotics, oral rinses, and a variety of other practices have been tried, as discussed earlier. The pharmacist should place great emphasis on counseling affected patients to promote good oral hygiene and prevent dental and periodontal infections that can greatly worsen ONJ. It is essential to advise patients of the need to have frequent dental examinations before and during IV bisphosphonate therapy, and to report any symptoms immediately.

Nurse Perspective
Regina Swift, RN, BSN

PK had significant myeloma-related bone involvement that resulted in multiple fractures, even in the absence of hypercalcemia. This bone involvement caused pain and significantly limited mobility. Nurses play an important role in the stabilization of bone health in patients with MM. Supportive care to optimize bone health and the prevention of VCFs and other fractures contribute markedly to improved quality of life for these patients.

The patient in this case received surgical intervention with kyphoplasty to stabilize the vertebral column and minimize pain caused by friction of moving bone on bone. This alone was not deemed sufficient after discovery of a plasma cell tumor; therefore, he underwent radiation treatments to several anatomic areas, including the involved parts of the spine. Significant improvement in pain and
mobility did occur with the combination of surgery and radiation therapy. Although such interventions can be highly effective, nurses must be alert for long- and short-term effects following these procedures. Physical therapy can be very helpful in getting patients back to their baseline activity status. It is important to regularly question patients and conduct periodic pain and functional assessments to elicit subjective responses to these and other strategies.

In addition to the above-mentioned interventions, IV bisphosphonate therapy (specifically, zoledronic acid) was initiated and maintained on a monthly basis. Two recent studies have demonstrated that the occurrence of SREs prior to or following treatment with bisphosphonates predicts for a shorter survival among patients with MM.\textsuperscript{29,35} Zoledronic acid has been shown to reduce the occurrence of these events.\textsuperscript{8,9}

Bisphosphonate therapy is certainly warranted among patients with MM, but must be approached cautiously due to adverse events associated with this class of drugs. The decision to initiate this therapy should be made collaboratively with the input of the patient and the treating physician, weighing both the potential benefits and risks of this type of treatment.

In the case of our patient, a nutritionist assisted him in finding soft foods and liquids that would maintain his caloric and nutritional needs.

\textbf{Nursing considerations for ONJ}

At the time of his first bisphosphonate infusion, PK was educated on both the short-term flu-like symptoms as well as the long-term adverse events that can occur with this therapy; specifically, renal dysfunction and ONJ. In addition, he was seen by his dentist to determine if there were any major dental problems that required attention prior to starting treatment. At that point in time, there were none that needed attention. The patient had been told that in the future if any dental work was required, he should inform the oncology team prior to having the work done and have his dentist contact the center. Unfortunately, patients may forget to tell the oncology team about dental work they are planning to undergo. An even more troubling scenario, as occurred in this case, is the suboptimal communication among dental care professionals. Despite the education of the patient and his instructions to the dentist, a tooth extraction was performed, resulting in osteonecrosis of the left frontal maxilla several months later at the site of extraction. Notably, only dental extractions and implants pose risks for patients receiving IV bisphosphonates; dental cleaning, cavity repairs, crowns, or root canals are without significant risk for the development of ONJ.

To help reduce the occurrence of ONJ, nurses must reiterate instructions about dental care and the avoidance of dental extractions or implants before each dose of IV bisphosphonate therapy. At the same time, it is important to ask patients about dental issues; they should be advised not to have any invasive dental procedures without first checking with the oncology team. In the case of PK, his visits to the oncology center were less frequent once he was placed on maintenance therapy. Unfortunately, it was during this time that he needed dental work.

The development of ONJ requires the involvement of an experienced dental professional. There is no proven effective treatment for this condition, but infection control, good dental hygiene, and regular dental follow-up are essential aspects of care. There may be nutritional issues to address, since a patient’s ability to chew may be compromised. This can result in significant weight loss and poor nutrition. In the case of our patient, a nutritionist assisted him in finding soft foods and liquids that would maintain his caloric and nutritional needs.

When infections occur among patients with ONJ, taste for certain foods may be negatively impacted, leading to even poorer nutrition. In the case of PK, infection risk was minimized with the involvement of a periodontist, who had him establish a specific mouth regimen including cyclohexidine rinses and local povidone-iodine application. Optimization of personal dental hygiene was reinforced by both the oncology and dental teams.

\textbf{One question that often arises is whether a patient who develops ONJ should be continued on IV bisphosphonate therapy.}

Some patients with ONJ may require antibiotics to control infection; however, this may lead to other microbial infections. For example, oral candidiasis may occur, so attention must be paid to examining the tongue closely. Many patients develop gastrointestinal complications (eg, diarrhea, abdominal cramping, bloating) from the chronic use of antibiotics, which can also diminish caloric and nutritional intake. In our patient, we managed these problems with over-the-counter treatments such as loperamide.

One question that often arises is whether a patient who develops ONJ should be continued on IV bisphosphonate therapy. There are no definite answers to this question. The course of ONJ has not been shown to be affected by the continuation or discontinuation of IV bisphosphonates.\textsuperscript{29,31} Therefore, it is necessary to weigh the potential benefits of ongoing treatment (ie, improvement in bone health, prolonged overall survival) against the potential for ONJ to be worsened. In some cases, patients have stopped bisphosphonate therapy ≥3 months prior to a planned dental extraction and resumed therapy ≥3 months following the procedure, resulting in the prevention of ONJ. However, this approach is not successful in all cases.
I. Effectively treated with a minimally invasive kyphoplasty procedure, he also received radiotherapy, which had the potential to compromise bone marrow function with no guarantee of adding benefit. He then received antimyeloma therapy and was started on monthly IV zoledronic acid at the standard dose of 4 mg monthly. Although he developed another rib fracture and progressive myeloma 3 months later, he was appropriately continued on this therapy. Unfortunately, the patient’s course was complicated by ONJ, an uncommon but potentially serious complication of IV bisphosphonates. In this case, a tooth extraction during therapy most likely led to this occurrence. Through proper management, this patient’s ONJ has now been stabilized and he is able to maintain his dietary needs while continuing to use IV zoledronic acid to prevent further SREs.

References

OSTEONECROSIS OF THE JAW

Table 2. ASCO Recommendations for Bisphosphonate-related ONJ

- ONJ is an uncommon but potentially serious complication of IV bisphosphonates.
- Recommendations described in product labeling for zoledronic acid and pamidronate should be followed.
- All cancer patients should receive:
  - Comprehensive dental exam and any needed preventive dentistry before starting bisphosphonate therapy
  - Treatment of active oral infections and elimination of sites at high risk for infection
- While on bisphosphonate therapy, patients should:
  - Maintain excellent oral hygiene
  - Avoid invasive dental procedures (eg, extractions)

ASCO indicates American Society of Clinical Oncology; ONJ, osteonecrosis of the jaw.

Recent guidelines for the use of bisphosphonates
Several guidelines have been established regarding the use of bisphosphonates for the treatment of myeloma-associated bone disease. The most recent include the 2006 consensus statement issued by the Mayo Clinic and the 2007 guidelines published by the American Society of Clinical Oncology (ASCO). ASCO’s recommendations for the prevention and management of ONJ are summarized in Table 2.

Although both sets of guidelines suggest discontinuation of bisphosphonate therapy after 2 years for patients who no longer demonstrate active disease, these recommendations are not based on data indicating these drugs lose their efficacy after that time. Unfortunately, the large, randomized clinical trials of IV bisphosphonate therapy that were conducted in MM typically assessed treatment for only 2 years, because at the time of the design of these trials, the average survival of patients was approximately that long.

Conclusion
The patient in this case presented with myeloma-related bone disease, resulting in bone pain and VCFs, which significantly affected quality of life. Although he was effectively treated with a minimally invasive kyphoplasty procedure, he also received radiotherapy, which had the potential to compromise bone marrow function with no guarantee of adding benefit. He then received antimyeloma therapy and was started on monthly IV zoledronic acid at the standard dose of 4 mg monthly. Although he developed another rib fracture and progressive myeloma 3 months later, he was appropriately continued on this therapy. Unfortunately, the patient’s course was complicated by ONJ, an uncommon but potentially serious adverse effect associated with the administration of IV bisphosphonates. In this case, a tooth extraction during therapy most likely led to this occurrence. Through proper management, this patient’s ONJ has now been stabilized and he is able to maintain his dietary needs while continuing to use IV zoledronic acid to prevent further SREs.
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