Treatment for Myeloma Bone Disease

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Abstract   Multiple myeloma (MM) is a B cell malignancy characterized by enhanced bone loss commonly associated with diffuse osteopenia, focal lytic lesions, pathologic fractures, hypercalcemia, and bony pain. Bone destruction in MM results from asynchronous bone turnover wherein increased osteoclastic bone resorption is not accompanied by a comparable increase in bone formation. Consequently, patients with MM frequently require radiation therapy, surgery, and analgesic medications. The recent development of minimally invasive surgical procedures such as kyphoplasty allows patients with myeloma with vertebral compression fractures to have immediate improvement in their quality of life with shorter hospital stays. Bisphosphonates are specific inhibitors of osteoclastic activity, and these agents have been evaluated in patients with MM with bone disease during the past 15 years. Monthly i.v. infusions of either pamidronate or zoledronic acid have reduced the skeletal complications among patients with MM and are now a mainstay of myeloma therapy. Orally administered bisphosphonates, in contrast, have shown little ability to slow the development of skeletal complications in these patients. Although preclinical studies suggest that nitrogen-containing bisphosphonates have potent antitumor effects, clinical trials will be necessary, probably at higher doses given more slowly, to establish their possible antitumor effects clinically. Moreover, recent advances in the use of bone-seeking radiopharmaceuticals make these attractive therapeutic candidates to combine with bisphosphonates or radiosensitizing drugs (e.g., bortezomib) to achieve a synergistic effect. As our understanding of the pathophysiology of myeloma bone disease continues to grow, new target therapies will continue to emerge, offering new and more advanced options for the management of myeloma bone disease.

Patients with multiple myeloma (MM) commonly experience skeletal-related complications that result from a shift in the normal balance between bone formation and bone resorption toward enhanced bone loss (1). As a result, diffuse osteopenia, focal lytic lesions, pathologic fractures, hypercalcemia, and bony pain are common clinical manifestations in patients with MM. These complications are major causes of morbidity and mortality (2). The lytic process observed in MM is different from other cancers that metastasize to the bone in which bone destruction is followed by new bone formation. Even when patients with MM respond to anti-MM therapies, they may still have progression of skeletal events (3, 4) without repair of osteolytic lesions. These patients frequently require radiation therapy, surgery, and use of analgesics to overcome pain and improve their quality of life.

Bone destruction in MM results from asynchronous bone turnover wherein increased osteoclastic bone resorption is not accompanied by a comparable increase in bone formation.

Recent characterization of osteoclast-activating factors (5–14), macrophage inflammatory protein-1α, receptor activator of nuclear factor-κB (RANK) ligand (RANKL)/osteoprotegerin/ RANK system (15–22), and inhibitors of Wnt signaling (23, 24) has provided a better understanding of myeloma bone disease on the molecular level. As our understanding of the pathophysiology of myeloma bone disease continues to grow, therapies will continue to evolve, offering new and more advanced options for the management of myeloma bone disease.

Markers of Bone Resorption and Bone Formation

A variety of markers of bone resorption and formation have been used to assess bone disease in patients with myeloma (Table 1).

Patients with MM have increases in bone resorption markers such as COOH-terminal telopeptide of type I collagen, NH_2-terminal telopeptide of collagen I, pyridinoline, and deoxy-pyridinoline, and decreases in bone formation markers such as osteocalcin (25–28). In recent clinical trials (27, 29, 30), changes in these markers were shown to predict the development of new skeletal complications and were associated with survival.

Treatment of Myeloma Bone Disease

Radiation therapy. Radiation therapy has been a major component of antimyeloma therapy and palliative care in patients with MM. Early studies have shown a curative effect for

Table 1. Bone markers in the evaluation of myeloma bone disease

(A) Bone resorption markers
    Urinary pyridinoline
    Urinary deoxypyridinoline
    Urinary NH_2-terminal telopeptide of collagen I
    COOH-terminal telopeptide of type I collagen
(B) Bone formation markers
    Osteocalcin
    Bone alkaline phosphatase

some patients with solitary plasmacytoma of bone. However, the most common indication for radiotherapy is a painful lesion (31, 32). Most patients significantly achieve pain relief with local radiotherapy at a dose of ~ 3,000 cGy given in 10 to 15 fractions (32). Occasional patients with more extensive bone pain may benefit from more extensive hemibody irradiation (33, 34). Other indicators include the treatment of impending or actual pathologic fractures, spinal cord compression, tumor causing local neurologic problems, and large soft tissue plasma cell tumors (34).

Radiotherapy has also been shown to prevent the development of new vertebral fractures in patients with myeloma (35). However, caution must be used in the application of radiotherapy because this will result in permanent bone marrow damage in the treated areas. The importance of this point cannot be overemphasized in a patient whose overall clinical status depends on chemotherapy and other agents that cause loss of bone marrow function (36).

Bone-seeking radionuclides. Bone-seeking radionuclides, although used more widely in the palliation of bone pain for patients with osteoblastic tumors from prostate or breast cancer, are beginning to be evaluated in patients with myeloma in a bone marrow transplant setting (37, 38). The clinical impact and quality of life of samarium-153 ethylenediaminetetramethylenephosphonate (^{153}Sm-EDTMP) and zoledronic acid for patients with symptomatic refractory MM were also studied in elderly patients (39). ^{153}Sm-EDTMP (2 GBq) was administered every 12 weeks and zoledronic acid (4 mg) was administered every 28 days. The combination of zoledronic acid and ^{153}Sm-EDTMP resulted in a reduction in bone pain and analgesic use. This study suggested that ^{153}Sm-EDTMP and zoledronic acid might be safe and synergistic in reducing skeletal-related complications for elderly patients with myeloma.

In a recent preclinical study, Goel et al. (40) showed that ionizing radiation in combination with bortezomib showed a synergistic inhibition of proliferation of myeloma cells by modulating apoptotic sensitivity. These studies support the notion that bortezomib is a radiosensitizer, and combining this drug with targeted radionuclide therapy can be a new therapeutic strategy. The combination of the bone-seeking phosphonate-containing radiopharmaceuticals, ^{153}Sm-EDTMP, with the radiosensitizer, bortezomib, is currently being assessed for its safety and efficacy in patients with myeloma with progressive disease.

Surgery. Surgical intervention may be required in patients with an impending or actual fracture or a destabilized spine (41, 42). In some patients, the presence of myeloma not evident radiographically in areas adjacent to the surgical site may impede the success of the procedure. Most patients also require radiotherapy in conjunction with surgical procedures. Importantly, consideration must be given to the patient's overall clinical status in decisions regarding the timing of surgery.

Kyphoplasty and vertebroplasty. Although previous attempts to reduce the morbidity of vertebral compression fractures (VCF) through techniques such as vertebroplasty were met with limited success and a significant risk of extravasation of cement (43, 44), the recent development of a new minimally invasive surgical procedure known as kyphoplasty (45) has made a major change in the quality of lives of patients with myeloma with VCFs. A recent report from the Cleveland Clinic on 18 patients with myeloma with VCFs undergoing 55 kyphoplasty procedures confirms the safety and efficacy of this procedure for patients with myeloma with VCFs (46). A follow-up report confirmed the benefit of this surgical intervention in a larger series that involved 52 patients with myeloma (47). Because of these early promising results, a large, national, randomized study is now evaluating kyphoplasty for cancer patients with VCFs.

Bisphosphonate therapy. Bisphosphonates are specific inhibitors of osteoclastic activity and are effective in the treatment of hypercalcemia associated with malignancy (10, 48).

Etidronate. The effect of daily etidronate versus placebo on the osteolysis of MM was studied by the Cross Cancer Institute in Canada (3). This randomized double-blind study of patients with newly diagnosed MM showed that etidronate therapy did not have a clinically significant effect in MM.

Clodronate. Three large randomized trials have been published comparing oral clodronate and placebo in patients with myeloma (49–51). The results of these three clinical trials showed variable clinical results. The Medical Research Council reported a significant reduction in nonvertebral fractures (6.8% versus 13.2%; $P = 0.04$) and vertebral fractures rate (38% versus 55%; $P = 0.01$) compared with the placebo arm, whereas a Finnish trial reported no differences in the reduction of overall pathologic fractures, as well as vertebral and nonvertebral fractures.

Ibandronate. A phase III double-blind trial comparing monthly injections of 2 mg of ibandronate versus placebo in addition to their antineoplastic therapy of patients with stage II or stage III MM with osteolytic bone was conducted by a German group (52). This monthly dose of i.v. ibandronate did not show significant benefits in reducing skeletal complications in patients with myeloma with lytic bone disease.

Oral pamidronate. Daily oral pamidronate (300 mg/d) was evaluated in a double-blind randomized trial by a Danish-Swedish cooperative group compared with placebo in 300 patients with newly diagnosed myeloma (53). After a median duration of 18 months, no significant reduction was apparent in the primary end point defined as skeletal-related morbidity, hypercalcemic episodes, or survival between treatment arms.

I.v. pamidronate. The results of small open-label trials that lasted up to 24 months suggested that pamidronate disodium might be effective in reducing skeletal complications for patients with MM (54, 55). Thus, a large, randomized, double-blind study was conducted to determine the effect of monthly 90-mg infusions of pamidronate in patients with MM (56). At the preplanned primary end point after nine cycles of therapy (57), the proportion of patients with myeloma having any skeletal event was 41% in patients receiving placebo, but

only 24% in pamidronate-treated patients. The patients who received pamidronate also had a significant decrease in bone pain, no increase in analgesic use, and no deterioration in performance status and quality of life at the end of 9 months. The proportion of patients developing any skeletal event and the skeletal morbidity rate continued to remain significantly lower in the pamidronate group than the placebo group during the additional 12 cycles of treatment (56). However, overall survival for all patients was not significantly different between the two treatment groups; in stratum 2, the median survival time was 21 months for pamidronate patients compared with 14 months for placebo patients.

Zoledronic acid. Zoledronic acid is an imidazole-containing bisphosphonate that shows more potency in preclinical studies than any other bisphosphonate currently available (58). A phase III trial evaluated two doses of zoledronic acid (4 and 8 mg) compared with pamidronate (90 mg) infused every 3 to 4 weeks for the treatment of patients with myeloma or breast cancer with metastatic bone disease (59). The doses and infusion times (5 minutes) of zoledronic acid were selected based on the safety and superiority of these doses in reversing hypercalcemia of malignancy compared with pamidronate (90 mg; ref. 48). The results of the study showed that the proportion of patients with any skeletal event did not differ among the three treatment arms. In addition, the time to first skeletal event and analgesic use was similar in the three groups (12-13 months). Moreover, after 25 months of follow-up, the overall proportions of patients developing skeletal events remained similar between the zoledronic acid (4 mg) and pamidronate-treated patients (60). However, in an additional preplanned analysis, the multiple-events analysis, zoledronic acid–treated patients showed a 16% reduction in the risk of developing skeletal complications compared with those patients who received pamidronate. These long-term results show the efficacy and convenience of this more potent bisphosphonate for treating patients with myeloma with skeletal involvement (see ref. 61 for American Society of Clinical Oncology Clinical Practice Guidelines).

Importantly, during the clinical trial, increases in creatinine level were more frequently observed in the zoledronic acid treatment arms. Because of the renal toxicity, the infusion time of zoledronic acid was increased to 15 minutes, and patients in the 8 mg zoledronic acid group subsequently had their dosage reduced to 4 mg. Long-term follow-up data are now available that show no difference in the renal profile between patients receiving 4 mg of zoledronic acid infused during 15 minutes and 90 mg of pamidronate infused during 120 minutes (60).

Recent concerns by the Food and Drug Administration regarding the potential risk of increases in creatinine level from long-term administration of zoledronic acid (64) has prompted a risk-adapted approach to dosing this bisphosphonate based on the patient's calculated creatinine clearance. Whether this is either necessary or will reduce the low risk of renal toxicity from this bisphosphonate is unknown.

Osteonecrosis of the jaw. Another complication that may result from bisphosphonate therapy is osteonecrosis of the jaw (ONJ). Over the past 2 to 3 years, a number of case reports in the medical and dental literature suggest that this potential complication develops among cancer patients receiving either long-term zoledronic acid or pamidronate treatment (65). ONJ has also been observed in patients treated with oral alendronate and risedronate for postmenopausal osteoporosis (65). The frequency with which this complication occurs in cancer patients receiving bisphosphonate therapy is unknown. However, it seems that there is a higher risk of this complication among patients receiving these drugs with an incident rate of 1% to 10% (66–68). The mean time to onset of ONJ among patients receiving zoledronic acid was 18 months and 3 to 6 years for patients receiving pamidronate (69). Most cases are associated with exposed mandibular bone with minimal symptoms, but infrequently, patients may require more extensive intervention, including surgical procedures to treat this problem. Necrotic bone is sometimes associated with Actinomyces colonization. Risk factors for ONJ may be multifactorial. To date, no reliable, predictive pattern has been clearly identified to allow for calculations of risk for ONJ in a particular patient. It is now recommended that patients receiving bisphosphonates, including most patients with myeloma, should be evaluated early in their treatment for dental problems and encouraged to maintain excellent dental hygiene. No evidence exists that discontinuation use of the bisphosphonate or replacement with other bisphosphonates would change the course of this complication. Therefore, it is critical that clinicians weigh the risks and benefits of the continued use of bisphosphonates among patients with this complication.

Antimyeloma effects of bisphosphonates. The role of bisphosphonates for patients with myeloma may go beyond simply inhibiting bone resorption and the resulting skeletal complications. Radl et al. (70) suggest that pamidronate might reduce myeloma tumor burden in treated mice. *In vitro* studies also suggest that pamidronate may possess antimyeloma properties as shown by its ability to induce the apoptosis of myeloma cells (71) and the suppression of IL-6 production (72) and antiangiogenesis (73, 74). Interestingly, the antitumor effects of bisphosphonates are not only observed alone but seem to be synergistic with glucocorticoids, farnesyl transferase inhibitor, and thalidomide (62, 63, 75–77). The potent antitumor effects of bisphosphonates bring the notion that higher doses of bisphosphonates given at a slower rate may establish possible antitumor effects clinically in patients with MM.

Emerging therapies. An analogue of the natural inhibitor of the RANK signaling known as osteoprotegerin has recently completed a phase I trial, with promising results in terms of suppression of bone resorption markers (78). Notably, osteoprotegerin binds tumor necrosis factor–related apoptosis-inducing ligand/Apo2 ligand (TRAIL), and, as a result, osteoprotegerin can inhibit the induction of apoptosis of myeloma cells generated by TRAIL (79). Moreover, it is possible that the development of antibodies to osteoprotegerin may occur in patients treated with the analogue, resulting in the prevention of its normal anti–bone resorptive function.

To avoid potential problems with the use of osteoprotegerin analogues, a recombinant form of RANK ligand (RANKL), RANK-Fc, which is an antagonist of RANKL-RANK signaling, was recently developed and consequently inhibits both bone disease and myeloma growth in a murine severe combined immunodeficiency-hu model of human myeloma (80). This recombinant protein is now being evaluated in clinical trials among patients with metastatic bone disease.

Moreover, inhibitors of Src activity (81) have recently shown marked antiresorptive capability and may be entering clinical trials soon. The statin drugs have shown the potential to increase bone density by their stimulatory effects on specific bone morphogenetic proteins and their inhibitory effects on mevalonic acid biosynthesis in both bone and myeloma growth (82).

Summary

The major clinical problems that arise in patients with myeloma relate to the enhanced bone loss that commonly occurs in these patients. Recent development of minimally invasive surgical procedures such as kyphoplasty allows patients with myeloma with VCFs to have immediate improvement in quality of life and shorter hospital stays. The use of i.v. administered monthly bisphosphonates (zoledronic acid or pamidronate) in two large phase III clinical trials has shown safety and efficacy in reducing bone complications in patients with myeloma. Bisphosphonate treatment, therefore, should now be considered for all patients with myeloma with evidence of bone loss. Although preclinical studies suggest that nitrogen-containing bisphosphonates have potent antitumor effects, clinical trials will be necessary, probably at higher doses given more slowly, to establish their possible antitumor effects clinically. As the use of bisphosphonates expands for both malignant and nonmalignant conditions, ONJ could potentially become more prevalent. New therapies targeting bone (e.g., monoclonal antibody to RANKL and inhibitors of cathepsin) are in early development, and may eventually offer patients with myeloma additional effective and safe therapeutic options. Recent advances in the use of bone-seeking radiopharmaceuticals make these attractive therapeutic candidates to combine with bisphosphonates or radiosensitizing drugs (e.g., bortezomib). As our understanding of the biology of myeloma bone disease continues to develop, increasing numbers of new potential target therapies are emerging.

Open Discussion

Dr. Guise: In my bone clinic, I see a lot of referrals for osteoporosis patients who get fractures while taking bisphosphonates. I work them all up for myeloma, and I have discovered a significant number of patients with MGUS. When I measure their bone absorption markers and they are suppressed, I wonder what options I have to treat their osteoporosis. I have a couple patients taking teraperatide who are doing quite well. What is your opinion?

Dr. Berenson: Certainly, we don't have a lot of options at this point beyond the bisphosphonates.

Dr. Pearse: The problem with most of our patients with myeloma is that we are afraid that their bone resorption will flare with parathyroid hormone (PTH) therapy, and studies in the osteoporotic population suggest that the combination of bisphosphonates and PTH is worse than either by itself. It will be interesting to see the efficacy of PTH in combination with AMG 162.

Dr. Guise: Is switching them to intravenous bisphosphonates better?

Dr. Berenson: There is not much difference in terms of potency.

Dr. Roodman: I think the data from the Mayo Clinic showing that these patients had an increased incidence of fractures compared with a control group were surprising at first (83). Yet, to my knowledge, there was no correlation with the level of their monoclonal protein and the risk of fracture.

Dr. Berenson: I wasn't surprised by that.

Dr. Roodman: If you think it's related to their plasma cell activity, you would hope there would be some correlation with how much myeloma they have.

Dr. Suva: In a lot of cases, the MGUS appears to have resolved following PTH. But certainly, in MGUS patients who have low PTH, giving them a bisphosphonate is not going to stop their fractures.

Dr. Clohisy: What about disease progression? Does the risk of fracture go up?

Dr. Berenson: One of the criteria we've used for progression is bone related.

Dr. Roodman: I'm not sure that fracture per se goes with progression.

Dr. Berenson: It has not been well studied.

Dr. Roodman: All of us have seen patients whose myeloma is perfectly stable and they continue to have fractures because the bone density has gotten below the fracture threshold. They are going to fracture no matter what you do, which is why we should look at antibiotics.

Dr. Berenson: The other part of the equation is that when patients tend to have more events, you follow them up more closely; therefore, you find more.

Dr. Roodman: According to the M.D. Anderson data that were presented at the bone meeting just last month, of about 2,000 patients (American Society for Bone and Mineral Research meeting, September 2005, Nashville, TN), of which a subgroup had myeloma and most had breast cancer, a lower incidence of ONJ was found in patients who received pamidronate versus those who received zoledronic acid.

Dr. Berenson: Those were observational data. How many patients did you ask about their jaw 4, 5, or 6 years ago? Probably not a lot. We need prospective data.

Dr. Coleman: What's the time frame?

Dr. Berenson: The claim has been it's quicker with zoledronic acid than pamidronate but it's time at risk. You have to be very careful interpreting the data.

Dr. Coleman: I was surprised that you suggested that we just push on with the bisphosphonates in the presence of ONJ. I would have thought that was dangerous.

Dr. Berenson: No, there's no evidence either way.

Dr. Coleman: When you give an intravenous bisphosphonate to somebody who's got dental sepsis or dental trauma, you get a very high local concentration. I don't believe that there is a definite link between bisphosphonates and ONJ.

Dr. Berenson: I think there is a link.

Dr. Lipton: Do the new drugs for myeloma alter the rate of skeletal events?

Dr. Berenson: We don't know.

Dr. Roodman: Some recent data have shown that the IMIDSs have selected effects on osteoclast precursors and that they affect other hematopoietic precursors, so the newer agents may be having both antibone and antimyeloma effects. These data are from an *in vitro* study, and we will eventually have to look *in vivo* to sort that out.

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