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Myeloma bone disease and treatment options

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ABSTRACT

Multiple myeloma (MM) is a B-cell malignancy characterized by enhanced bone loss commonly associated with a 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. Recent characterization of osteoclast-activating factors (OAFs), receptor activator of nuclear factor-κB (RANK) ligand (RANKL)–osteoprotegerin–RANK system, and inhibitors of Wnt signaling have provided a better understanding of myeloma bone disease in molecular level. The development of minimally invasive surgical procedures such as kyphoplasty and vertebroplasty allows myeloma patients with vertebral compression fractures to have immediate improvement in quality of life and shorter hospital stays. Monthly intravenous infusion of either pamidronate or zoledronic acid have reduced the skeletal complications among MM patients 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 pre-clinical studies suggest nitrogen-containing bisphosphonates have potent anti-tumor effects, clinical trials will be necessary, probably at higher doses given more slowly, to establish their possible anti-tumor effects clinically. As our understanding of the pathophysiology of myeloma bone disease continues to increase, new target therapies will continue to emerge offering new and more advanced options for the management of myeloma bone disease.

1. Introduction

Multiple myeloma (MM) is a B-cell malignancy that substantially causes skeletal dysfunction during the course of their disease. MM induces osteolysis and shifts the normal balance of bone formation toward bone resorption.[1] As a result, diffuse osteopenia, focal lytic lesions, pathologic fractures, hypercalcemia, and bony pain are common clinical manifestations in MM patients. These prominent clinical features are major causes of morbidity and mortality.[2] The lytic process observed in MM is very different from other cancers that metastasize to bone in which bone destruction is followed by new bone formation. Even when MM patients 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 as well as improve their quality of life.

2. Biology of myeloma bone disease

Bone destruction in MM results from asynchronous bone turnover wherein increased osteoclastic bone resorption is not accompanied by a comparable increase in bone 1formation. Recent characterization of osteoclast-activating factors (OAFs) and receptor activator of nuclear factor-κB

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(RANK) ligand (RANKL)–osteoprotegerin–RANK system have provided a better understanding of myeloma bone disease in molecular level. The adhesive activity of myeloma cells with the bone marrow microenvironment cause release of OAFs by stromal cells. Together with hepatocyte growth factor (HGF) and parathyroid hormone-related peptide (PTHrP) released by MM cells, OAFs increase expression of RANKL on the marrow stromal cell surface. RANKL binds to the receptor activator of NF-κB (RANK) receptor on osteoclast precursors and triggers osteoclast differentiation and activation.[5,6] This interplay among the activated osteoclasts, stromal cells and OAFs in the bone marrow microenvironment, in turn, stimulates MM cell growth and perpetuates a cycle of bone destruction.[1,7–9]

The potent stimulatory effects of RANKL on osteoclastogenesis are usually counteracted by secreted osteoprotegerin (OPG), which acts as a safeguard mechanism for bone destruction. But in MM, OPG mRNA expression is markedly decreased. Pearse *et al.*[10] and Giuliani *et al.*[11] demonstrated that cell-to-cell contact of myeloma cells with bone marrow stromal cells and osteoblasts inhibit OPG mRNA levels and protein secretion by stromal cells. Moreover, Standal *et al.*[12] demonstrated that OPG binds to syndecan-1 (CD138) on myeloma cells and leads to internalization and degradation of OPG within the lysosomal compartment of myeloma cells. This imbalance between the RANKL and OPG ratio shifts the normal balance of bone formation in favor of bone resorption.

Bone resorption is typically reversed when osteoblasts fill lytic spaces with new bone matrix. This process in MM, however, is inhibited even when treated with bisphosphonates. Tian *et al.*,[13] recently showed that dickkopf1 (DKK1), an inhibitor of Wnt signaling secreted by MM cells, may be a cause for hindering of osteoblast differentiation and activity. Secreted Frizzled-related protein (sFRP)-2 is another soluble Wnt inhibitor expressed by MM.[14] Together with elevation of RANKL, DKK1 and sFRP-2 in patients with MM selectively block the normal remodeling process by diminishing bone formation. Other investigators, however, argue that the permanent change in bone formation may involve more then just the inability of osteoblast precursors to differentiate.[15,16] The basis of suppressed bone formation in MM remains to be completely determined.

In addition to the RANKL–osteoprotegerin–RANK system, several chemokines and cytokines known as OAFs, have been implicated in the pathogenesis of myeloma bone disease. These OAFs include interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), IL-11, macrophage inflammatory protein-1α (MIP-1α), hepatocyte growth factor (HGF), parathyroid hormone-related peptide (PTHrP), and others.[17–25] Investigators found that some of these OAFs may be RANKL-dependent and others are RANKL-independent, indicating that there is a high degree of redundancy of MM cells to induce osteoclastic bone destruction. As our understanding of the pathophysiology of myeloma bone disease increases, therapies will continue to evolve offering new and more effective options for the management of myeloma bone disease.

3. Fracture risk in MM

Although older studies suggested that a minority of myeloma patients presented with at least one fracture,[26] more recent studies with the addition of MRI assessment show a much higher proportion of patients actually have fractures at presentation.[27] Notably, the use of MRI increases the proportion of patients found to develop fractures during the course of their disease as shown in two recent studies.[28,29] In one of the placebo-controlled bisphosphonate trials, approximately one-third of myeloma patients with lytic bone disease not receiving bisphosphonate treatment (placebo arm) developed new fractures as assessed by plain x-rays after just nine months of follow-up.[30] These fractures may result from direct myelomatous involvement of the bone that shows the fracture but also may simply result from the generalized bone loss that is a hallmark of myeloma.[27] The most common site of fracture is in the spine (55%–70% of patients) especially in the lower thoracic or lumbar vertebral bodies.[31] Other common sites of fracture include the femur, pelvis, ribs, and humerus.

Recently, Melton *et al.* recently reported an increased fracture risk among patients with monoclonal gammopathy of undetermined significance (MGUS) in a retrospective cohort study.[32] There was nearly a three-fold increase in risk of vertebral compression fractures compared to a control group from Olmsted County, Minnesota. Furthermore, Melton *et al.* revealed fracture risk in MM significantly increases around the time of diagnosis of myeloma.[33] The majority of these fractures were pathologic. This is consistent with the notion that these patients have a higher prevalence of osteopenia and osteoporosis than the normal population and generally have higher risk of fracture particularly in the weight-bearing areas of the spine.[34]

4. Treatment of myeloma bone disease

4.1. *Radiation therapy*

Radiation therapy has been a major component of anti-myeloma therapy and palliative care in MM patients. Early studies have demonstrated a curative effect for some patients with solitary plasmacytoma of bone. However, the most common indication for radiotherapy is a painful lesion.[35,36] The vast majority of patients significantly achieve pain relief with local radiotherapy at a dose of approximately 3000cGy given in 10 to 15 fractions.[36] Occasional patients with more extensive bone pain may benefit from more extensive hemibody irradiation.[37,38] Other indications for radiotherapy include treatment of impending or actual pathologic fractures, spinal cord compression, tumor causing local neurologic problems, and large soft tissue plasma cell tumors.[36,37] Radiotherapy has also been shown to prevent the development of new vertebral fractures in myeloma patients.[39] In this small nonrandomized study, there was a suggestion that less vertebral fractures occurred in irradiated vertebrae than in nonirradiated ones as assessed by MRI.

However, caution must be used in the application of radiotherapy since 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 upon the use of agents that cause loss of bone marrow function such as chemotherapy. Therefore, it is advisable to radiate the minimal portion of the shaft of a long bone affected by MM to preserve as much functional marrow as possible.[40]

4.2. *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, is beginning to be evaluated in patients with myeloma in the stem cell transplant setting.[41,42] A phase II study using high dose samarium-153 ethylendiaminetetramethylenephosphonate (^{153}Sm-EDTMP) was conducted at the Mayo Clinic. Forty-six patients with MM and a median age of 58 years (range, 38–74 years) were treated with melphalan 200 mg/m2 and a targeted dose of 40 Gy ^{153}Sm-EDTMP to the red marrow. Engraftment was comparable to that seen among other patients undergoing transplantation during the same time period. No dose related toxicity or cases of thrombotic thrombocytopenic purpura, radiation nephritis, or bladder toxicity were observed at a median follow-up of 14.2 months.

The clinical impact and quality of life (QOL) of ^{153}Sm-EDTMP and zoledronic acid for symptomatic refractory MM patients were also studied in elderly patients.[43] Two GBq of ^{153}Sm-EDTMP was administered every 12 weeks and 4 mg of zoledronic acid every 28 days. A single course of ^{153}Sm-EDTMP plus zoledronic acid resulted in a prolongation of a decrease in MM-related symptoms. No significant hematological or non-hematological side effects were observed. This study suggested that this combination is safe and may be useful in the setting of refractory bone pain among myeloma patients with bony disease.

Recent studies also show that many of the newer agents (including bortezomib,[44] thalidomide,[45] and arsenic trioxide[46]) being used to treat myeloma also show radiosensitizing effects. Therefore, the use of these newer agents in combination with the bone-seeking phosphonate-containing radiopharmaceuticals which concentrate especially at sites of tumor in the bone may provide an ideal approach to treat myeloma. In a preclinical study, Goel and Dispenzieri *et al.* demonstrated that ionizing radiation in combination with bortezomib showed a synergistic inhibition of proliferation of myeloma cells by modulating the apoptotic sensitivity.[44] 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 in a clinical trial for its safety and efficacy for myeloma patients with progressive disease.

4.3. *Surgery*

Surgical intervention may be required in patients with an impending or actual fracture or a destabilized spine.[47,48] Several recent reports suggest that this modality is underutilized in myeloma patients with either long bone or vertebral fractures. 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.

4.4. *Kyphoplasty and vertebroplasty*

Although previous attempts to reduce the morbidity of vertebral compression fractures through techniques such as vertebroplasty were met with limited success and significant risk of extravasation of cement,[49,50]the recent development of a new minimally invasive surgical procedure known as kyphoplasty[51] has made a major change in the quality of lives of myeloma patients with vertebral compression fractures (VCFs). Specifically, a small surgical needle is implanted into the collapsed vertebral body and a balloon contained within the needle is inflated in order to reverse the compression. The balloon is withdrawn and within the cavity is placed methylmethacrylate cement. Because of the soft vascular nature of myeloma patients' bones, they are ideal candidates for expansion of the collapsed body followed by cement placement without significant morbidity. The risk of complications including cement extravasation appears to be much lower than with the vertebroplasty procedure.[52] In addition, the minimally invasive nature of the procedure allows this to be done without interruptions in the patient's ongoing anti-myeloma therapy. A report from the Cleveland Clinic on 18 myeloma patients with VCFs undergoing 55 kyphoplasty procedures confirms the safety and efficacy of this procedure for myeloma patients with VCFs.[53] A follow up report confirmed the benefit of this surgical intervention in a larger series involving 52 myeloma patients.[52] Because of these early promising results, a large national randomized study is now evaluating kyphoplasty for cancer patients with vertebral compression fractures.

5. Bisphosphonate therapy

Bisphosphonates are specific inhibitors of osteoclastic activity and are effective in the treatment of hypercalcemia associated with malignancy (see Table 1). They are non-hydrolyzable analogues of inorganic pyrophosphate that bind avidly to hydroxyapatite crystals and are subsequently released during the process of bone resorption. The released bisphosphonate is taken up by osteoclasts leading to the inhibition of that cell's activity and survival. Once internalized, bisphosphonates are cytotoxic to osteoclasts and the more potent bisphosphonates interfere with intracellular signaling pathways required for osteoclast activity and survival. Newer nitrogen-containing bisphosphonates, such as zoledronic acid, pamidronate and ibandronate, have a unique mechanism of action and greater clinical activity than first-generation bisphosphonates that lack nitrogen such as etidronate and clodronate (see Table 2).[54] Thus far, nine large randomized trials of long-term bisphosphonate use have now been published. The following are the summaries of the impact of bisphosphonates on skeletal disease as well as its clinical manifestations in MM patients.

Table 1 – Types of bisphosphonates

	Relative potency[a]	Dose (mg)	Mode of administration	Adverse effects
Non-nitrogen				
Clodronate	1	1600	oral	Hypersensitivity, renal insufficiency, hypocalcemia, hyperkalemia, hyperparathyroidism, hypocalcemia, abdominal pain, arthralgia
Single nitrogen				
Pamidronate	20	90	2 hours i.v.	Fever in 20% hypophosphatemia, hypocalcemia, hypomagnesemia, loss of appetite, nausea, vomiting
Ibandronate	857	6	1 hour i.v.	Rash, abdominal pain, constipation, diarrhea, dyspepsia, nausea, arthralgia, back pain, dizziness, headache
		50	oral	
Two nitrogens				
Zoledronic acid	16,700	4	15 minutes i.v.	Minor; fever, rarely hypocalcemia, hypophosphatemia, loss of appetite, nausea, vomiting

a Data from *Green et al.* [93].

5.1. *Etidronate*

In the Canadian study involving etidronate,[3] 173 newly diagnosed patients all received intermittent oral melphalan and prednisone as primary chemotherapy, and 166 were then randomized to receive either daily oral etidronate (5 mg/kg) or placebo until death or stopping the treatment due to side effects. The primary objective of this study was to evaluate whether etidronate would retard skeletal progression of multiple myeloma, based on patient's height, vertebral height and deformity, hypercalcemia, development of pathologic fractures, and bone pain. Although significant height loss occurred in both placebo- and etidronate-treated patients, no difference was found between the two arms. Similarly, the other outcome measures (new fractures, hypercalcemic episodes, and bone pain) showed no differences between the two arms. Lack of improvement with etidronate may be resulted from low absorption and potency and incorrect selection of regular daily therapy.

5.2. *Clodronate*

Three large randomized trials have been published using oral clodronate in myeloma patients and the clinical results are variable. In the Finnish trial,[55] 350 previously untreated patients were entered and 336 randomized to receive either clodronate (2.4 g) or placebo daily for 2 years. All patients were also treated with intermittent oral melphalan and prednisolone. The proportion of patients with progression of lytic lesions was less in the clodronate treated group (12%) than in the placebo group (24%). However, the progression of overall pathological fractures, as well as both vertebral and non-vertebral fractures, was not different between the arms. In addition, the number of patients developing hypercalcemia was similar in the two arms. Changes in pain index and use of analgesics were similar in both arms.

Clodronate has also been evaluated in an open-label randomized German trial.[56] In this study, 170 previously untreated patients were randomized to receive either no bisphosphonate or oral clodronate (1.6 g) daily for one year. All patients were also treated with intermittent intravenous melphalan and oral prednisone. Unfortunately, premature termination occurred in more than half of the patients despite the short length of the study (one-year). The results showed no difference in progression of bone disease as assessed by plain radiographs in the two arms.

Finally, a clinical trial conducted by the Medical Research Council has evaluated 536 recently diagnosed myeloma patients randomized to receive either oral clodronate 1.6 g or placebo daily in addition to alkylator-based chemotherapy.[57] After combining the proportion of patients developing either non-vertebral fractures or severe hypercalcemia including those leaving the trial due to severe hypercalcemia, there were less clodronate-treated patients experiencing these combined events than placebo patients. The number of patients experiencing non-vertebral fractures was lower in the clodronate group. Back pain and poor performance status were not significantly different between the two groups except at one timepoint (24 months). There was no difference in the time to the first skeletal event, the proportion of patients requiring radiotherapy or overall survival between the arms.

5.3. *Oral pamidronate*

Daily oral pamidronate (300 mg/day) was evaluated in a double blind randomized trial by a Danish-Swedish cooperative group compared to placebo in 300 newly diagnosed myeloma patients.[58] After a median duration of 18 months, there was no significant reduction in the primary endpoint defined as skeletal-related morbidity (bone fracture, surgery for impending fracture, vertebral collapse, or increase in number and/or size of lytic lesions), hypercalcemic episodes,

or survival between the arms. Fewer episodes of severe pain and less height loss were observed in the oral pamidronate-treated patients, however. Poor bioavailability of oral pamidronate may be the reason for the lack of efficacy shown in this trial.

5.4. *Intravenous pamidronate*

Results of small open-label trials lasting up to 24 months suggested that pamidronate disodium might be effective in reducing skeletal complications for MM patients.[59,60] Thus, a large randomized, double-blind study was conducted to determine whether monthly 90 mg infusions of pamidronate compared to placebo for 21 months reduced skeletal events in patients with multiple myeloma who were receiving chemotherapy.[61] This study included patients with Durie-Salmon Stage III multiple myeloma and at least one osteolytic lesion. Unlike the etidronate and clodronate trials, which involved untreated patients, patients were required to receive an unchanged chemotherapy regimen for at least two months prior to enrollment. The patients were stratified according to whether they were receiving first-line (stratum 1) or second-line (stratum 2) antimyeloma chemotherapy at entry into the study.

At the pre-planned primary endpoint after nine cycles of therapy,[62] the proportions of myeloma patients having any skeletal event was 41% in patients receiving placebo but only 24% in pamidronate-treated patients. The proportion of pamidronate-treated patients with skeletal events was lower in both stratum 1 (first line therapy) and stratum 2 ($\geqslant$ second line therapy). Unlike the placebo group, the patients who received pamidronate also had significant decreases in bone pain, no increase in analgesic usage and showed no deterioration in performance status and quality of life at the end of nine 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 twelve cycles of treatment.[62] Those myeloma patients who failed front-line therapy lived significantly longer when treated with pamidronate (stratum II patients with adjusted survival based on the levels of beta2-microglobulin and Eastern Cooperative Oncology Group performance scores), whereas myeloma patients responding to front-line therapy (stratum I) had no significant survival benefit from the pamidronate treatment. The lack of a difference in survival may have been due to the heterogeneity of the chemotherapeutic regimens the patients were receiving, the short period of follow-up (median, 17 months), or the fact that pamidronate does not have direct anti-MM effects.

5.5. *Ibandronate*

Ibandronate is a nitrogen-containing bisphosphonate that, in pre-clinical models, shows more anti-bone resorptive potency than pamidronate and the other non-nitrogen-containing bisphosphonates. The results of a Phase III placebo-controlled trial of 214 stage II or III myeloma patients with osteolytic bone disease were recently published.[63] Patients either received monthly injections of 2 mg of ibandronate or placebo in addition to their antineoplastic therapy. Ninety-nine patients were evaluable in each arm for efficacy. The mean number of events per patient year on treatment was similar in both groups (ibandronate 2.13 versus placebo 2.05). In addition, there was no difference in pain, analgesic usage or quality of life between the arms. However, among patients treated with ibandronate who showed a sustained and marked reduction in bone resorption markers, fewer skeletal complications occurred. There was no difference in overall survival. Thus, this monthly dose of intravenous ibandronate did not show significant benefits in reducing skeletal complications in myeloma patients with lytic bone disease. These disappointing data in myeloma patients may be attributed to an insufficiently low ibandronate dose, as a study of breast cancer patients showed that a higher dose of ibandronate at 6 mg IV once every 4 weeks was effective in reducing the incidence of skeletal-related events.[64] Moreover, the study outcome may have been biased favorably to placebo because of an unbalanced dropout behavior after the first skeletal-related event.

5.6. *Zoledronic acid*

Zoledronic acid is an imidazole-containing bisphosphonate that shows more potency in pre-clinical studies than any other bisphosphonate currently available.[65] Two small Phase I trials established the safety and marked sustained reduction in bone resorption markers for patients with myeloma and other cancers associated with metastatic bone disease with monthly infusions of small doses given over several minutes.[66,67] A large randomized Phase II study compared this newer bisphosphonate to pamidronate in 280 patients with lytic bone metastases from either multiple myeloma (n = 108) or breast cancer (n = 172).[68] Patients were randomized to nine monthly infusions of 0.4 mg, 2.0 mg, or 4.0 mg of zoledronic acid, or to 90 mg of pamidronate as a 2-hour infusion. The primary endpoint was to determine a dose of zoledronic acid that reduced the need for radiation therapy to less than 30% of treated patients, although all skeletal events were also analyzed similar to those determined in the previously reported Phase III pamidronate trials. Radiation therapy was required in a similar proportion of patients receiving pamidronate and zoledronic acid at 2.0 and 4.0 mg (18% to 21%), whereas more patients receiving the lowest dose of zoledronic acid underwent radiotherapy (24%). Similarly, the proportion of patients with any skeletal event was lower in these same groups compared to patients receiving 0.4 mg of zoledronic acid. Interestingly, significant increases in bone density (>6% in the lumbar spine) and inhibition of bone resorption markers were observed in this latter cohort but this failed to translate to any clinical benefit. Although the results of this study suggested that 0.4 mg was an inadequate monthly dose of zoledronic acid to be of clinical use in the prevention of skeletal complications for patients with myeloma or breast cancer metastatic to bone, the small size of this Phase II trial did not allow for a complete assessment of the efficacy of higher doses of zoledronic acid compared to pamidronate.

5.7. *Zoledronic acid vs. pamidronate*

A large Phase III trial evaluated two doses of zoledronic acid (4 and 8 mg) compared to pamidronate (90 mg) infused every 3-4

weeks for treatment of myeloma or breast cancer patients with metastatic bone disease was conducted.[69] The doses and infusion time (5 minutes) of zoledronic acid were selected based on the safety and superiority of these doses in reversing hypercalcemia of malignancy compared to pamidronate (90 mg).[70] Importantly, the primary efficacy endpoint of this trial was to show the non-inferiority of zoledronic acid compared to pamidronate in reducing skeletal complications for patients with myeloma or breast cancer metastatic to bone. The trial involved 1643 patients who were stratified among individuals with myeloma (n = 513) or breast cancer on either hormonal therapy or chemotherapy (n = 1130). 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 to 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.[70] However, using an additional pre-planned analysis, the multiple events analysis, zoledronic acid-treated patients showed a 16% reduced risk of developing skeletal complications compared to those patients who received pamidronate. These long term results show the efficacy and convenience of this more potent bisphosphonate for treating myeloma patients with skeletal involvement (see Table 2 for ASCO guideline).

Importantly, during the clinical trial, rises in creatinine were more frequently observed in the zoledronic acid arms. Because of the renal toxicity, infusion time of zoledronic acid was increased to 15 minute and patients in the 8 mg zoledronic acid group subsequently had their dosage reduced to 4 mg. Long-term follow-up data is now available and shows no difference in the renal profile between patients receiving 4 mg zoledronic acid infused over 15 minutes compared to 90 mg pamidronate infused over 120 minutes.[71]

Recent concern by the FDA regarding the potential risk of rises in creatinine from chronic administration of zoledronic acid[72] 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.

5.8. *Osteonecrosis of the jaw*

Another complication that may result from bisphosphonate therapy is osteonecrosis of the jaw (ONJ). A recent report suggests this potential complication develops among cancer patients receiving either chronic zoledronic acid or pamidronate treatment.[73] The frequency with which this complication occurs in cancer patients receiving bisphosphonate therapy is unknown. However, it appears that there is a higher risk of this complication among patients particularly among those with myeloma who receive these drugs. 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. It is now recommended that patients receiving bisphosphonates, including the vast majority of myeloma patients, should be evaluated early on in their treatment for dental problems and encouraged to maintain excellent dental hygiene. It should be noted that there is no evidence that discontinuation of the bisphosphonate or replacement with other bisphosphonates changes the course of this complication.

5.9. *Newly developed bisphosphonate*

Incadronate (YM175) and YM529 are new bisphosphonates that are currently under investigation for treatment of myeloma.[74,75]

5.10. *Anti-myeloma effects of bisphosphonates*

The role of bisphosphonates for myeloma patients may go beyond simply inhibiting bone resorption and the resulting skeletal complications. Radl *et al.* suggested that pamidronate might reduce myeloma tumor burden in treated mice.[76] Treating bone marrow mononucleated cells of patients with MM patients with increasing concentration of zoledronic acid *in vitro*, investigators found modified patterns of expression of adhesion molecules in plasma cell binding and increase apoptosis of myeloma bone marrow stromal cells.[77] *In vitro* studies also suggest pamidronate may possess antimyeloma properties as demonstrated by its ability to induce apoptosis of myeloma cells[78] and suppression of IL-6 production.[79] Several studies indicate that bisphosphonates may be markedly anti-angiogenic.[80,81] Interestingly, the antitumor effects of bisphosphonates appear to be synergistic with glucocorticoids, an investigational farnesyl transferase inhibitor, and thalidomide in preclinical and early clinical studies.[82–84] The potent anti-tumor effects of bisphosphonates observed in the laboratory suggest that higher doses of bisphosphonates given at slower rate may establish possible anti-tumor effects clinically in MM patients.

6. Emerging therapeutic approaches

An analog of the natural inhibitor of the receptor activator of nuclear factor κB (RANK) signaling known as osteoprotegerin (OPG) has recently completed a Phase I trial with promising results in terms of suppression of bone resorption markers.[85] Notably, OPG binds tumor necrosis factor-related apoptosis-inducing ligand/Apo2 ligand (TRAIL); and, as a result, OPG can inhibit the induction of apoptosis of myeloma cells generated by TRAIL.[86] Moreover, it is possible that the development of antibodies to OPG may occur in patients treated with the analog resulting in the prevention of its normal anti-bone resorptive function.

To avoid potential problems with the use of OPG analogs, a recombinant form of RANK ligand (RANKL), RANK-Fc, which is an antagonist of RANKL-RANK signaling, has been recently developed and consequently inhibits both bone disease and myeloma growth in a murine SCID-hu model of human myeloma.[87] This recombinant protein is now being evaluated in clinical trials among patients with metastatic bone disease.

Recent studies have shown that macrophage inflammatory protein-1alpha (MIP-1α) may play an important role in MM-associated osteolysis. It was not been clearly determined whether MIP-1α is RANKL-dependent or independent. It is

Table 2 – ASCO clinical practice guidelines on the role of bisphosphonates in multiple myeloma[94]

The panel recommended that, for multiple myeloma patients who have, on plain radiographs, evidence of lytic bone disease, receive either intravenous zoledronic acid 4 mg infused over 15 minutes or pamidronate 90 mg delivered over 120 minutes every 3 to 4 weeks. The panel also believes it is reasonable to start these agents for patients with osteopenia but without evidence of lytic bone disease. Once initiated, the Panel recommended that the intravenous bisphosphonate be continued until there was a substantial decline in the patient's performance status.
The Panel also recommended intermittent monitoring of renal function as well as urinary protein evaluation to assess possible renal dysfunction that may occur from these agents. It is important to recognize that when renal dysfunction occurs with pamidronate it is more often associated with a glomerular lesion so that albuminuria is often found whereas zoledronic acid usually causes tubular dysfunction so that albumin in the urine is uncommon in patients with renal problems from the newer bisphosphonate.
For patients with either solitary plasmacytoma or indolent myeloma, no data exists to suggest their efficacy. In addition, although patients with MGUS show significant amounts of bone loss and a higher risk of fracture especially of vertebral bodies, the panel did not recommend treatment of these patients with bisphosphonates. A clinical trial was recently started to evaluate the use of intermittent zoledronic acid (4 mg infused every 6 months) for MGUS patients with osteopenia or osteoporosis (t-score less than −1.0).

also unclear whether MIP-1α indirectly or directly mediates its effects through the MM tumor cells to enhance osteolysis. In tumor-bearing mice, administration of neutralizing anti-MIP-1α antibodies reduced tumor burden, limited the process of osteolysis, and concomitantly reduced tumor growth in bone.[88] This study supports the idea that inhibition of MIP-1α can reduce myeloma bone disease and tumor growth; and, therefore, may offer a potential new treatment strategy for myeloma skeletal-related complications.

Moreover, inhibitors of Src activity recently have shown marked anti-resorptive 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 involved in stimulating bone formation as well as their inhibitory effects on mevalonic acid biosynthesis which results in the lack of prenylation of critical cellular proteins such as the GTPases. These latter proteins are known to play key roles in both bone pathophysiology and myeloma growth.[89]

7. Modification of lifestyle in MM patients

To minimize bone loss, change of daily activity level and diet are recommended. Bone mass and muscle strength can significantly improve with aerobic exercises and weight-bearing workout programs. Routine and moderate exercise not only increases muscle tone but also reduces the risk of falling and improves overall mental health. In addition to exercise, cessation of smoking, avoiding excessive alcohol intake, and reducing caffeine consumption are advised as part of lifestyle measures. In a prospective study, the relationship between physical exercise and various qualities of life (QOL) were examined in post-bone marrow transplant patients. Statistical analysis of this study indicated that exercise during hospitalization significantly correlated with almost all QOL indices, including physical well-being, psychological well-being, depression, anxiety and days hospitalized.[90]

Nutritional factors also play important roles in maintaining bone mass in MM patients. Food with high calcium and vitamin D (i.e. green leafy vegetables, canned fish, nuts, dairy products, milk, cereal, liver, etc.) should be part of a routine diet. Daily supplements of calcium (1200 mg/day) and vitamin D (400–800 IU/day) are recommended. Patients taking calcium and vitamin D supplement may have lower incidences of hypocalcemia and hypophosphatemia while receiving intravenous bisphosphonate treatment. (see Table 3)[91,92] Importantly, outdoor activities with occasional sun exposure for 15–30 min are advised to maintain normal vitamin D levels.

8. Summary

The major clinical problems that arise in myeloma patients relate to the enhanced bone loss that commonly occurs in these patients. Recent development of minimally invasive surgical procedures such as kyphoplasty allows myeloma patients with vertebral compression fractures to have immediate improvement in quality of life and shorter hospital stays. The use of intravenously administered monthly bisphosphonates (zoledronic acid or pamidronate) in two large Phase III clinical trials have shown the safety and efficacy of these drugs in reducing bone complications in myeloma patients. Bisphosphonate treatment, therefore, should now be considered for all myeloma patients with evidence of bone loss. Although pre-clinical studies suggest nitrogen-containing bisphosphonates have potent anti-tumor effects, clinical trials will be necessary, probably at higher doses given more slowly, to establish their anti-tumor effects clinically. Recent advances in the use of bone-seeking radiopharmaceuticals make these attractive therapeutic candidates to combine with bisphosphonates or radiosensitizing drugs (eg. bortezomib). As our understanding of the biology of myeloma bone disease continues to develop, increasing numbers of new potential therapies are emerging. Early clinical development of a variety of new drugs is currently being tested for patients with myeloma bone disease.

Conflict of interest statement

Dr Berenson has received honoraria from Novartis and Millenium for lectures and consultancy and has also received research grants from both companies. Dr Berenson has also received honoraria for consultancy and has received research grants from Amgen.

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