Myeloma Bone Disease: Pathogenesis and Treatment

Elizabeth K. O’Donnell, MD, and Noopur S. Raje, MD

Abstract: Bone involvement manifesting as osteolytic bone disease (OBD) or osteopenia is one of the defining features of multiple myeloma (MM). Osteolytic lesions develop in nearly 90% of patients with MM, and these are frequently complicated by skeleton-related events (SREs) such as severe bone pain, pathologic fractures, vertebral collapse, hypercalcemia, and spinal cord compression. SREs have a negative effect on patients’ quality of life and affect their long-term outcomes, including survival. In MM, the delicate balance between bone formation and bone destruction is perturbed. OBD is a consequence of increased osteoclast activation along with osteoblast inhibition, which alter bone remodeling. Although MM remains incurable, tremendous progress has been made in the treatment of the disease. As such, there is a need to address the symptoms of the disease that affect quality of life and, ultimately, overall survival. Novel agents targeting OBD are promising therapeutic strategies not only for the treatment of MM OBD but also for the treatment of MM itself. In addition to bisphosphonates, several novel agents are currently under investigation for their positive effect on bone remodeling via osteoclast inhibition or osteoblast stimulation. Future studies will look to combine or sequence all of these agents to improve quality of life, decrease the symptoms of MM OBD, and enhance antitumor activity.

Introduction

Multiple myeloma (MM) is a B-cell malignancy characterized by the clonal proliferation of malignant plasma cells in the bone marrow microenvironment, the production of a monoclonal protein present in the blood or urine, and associated organ dysfunction. It is the second most common hematologic malignancy, with approximately 30,330 cases diagnosed in the United States annually.1 Clinically, MM is characterized by osteolytic bone destruction, hypercalcemia, renal failure, anemia, reductions in normal gamma globulins (immunoparesis), and a consequently increased risk for infections. The past 2 decades have seen dramatic advances in the treatment of MM, resulting from an increased understanding of the disease and the evolution of therapies. Despite these advances, MM remains incurable, and there is an ongoing need to address patients’ quality of life and disease-related symptom burden.
Bone destruction, in the form of lytic lesions or osteopenia, is one of the devastating consequences of MM. In one study, 67% of patients had osteolytic bone disease (OBD) at the time of diagnosis, and 20% had osteoporosis, pathologic fractures, or compression fractures of the spine (many patients had both lytic bone lesions and other findings). The severity of bone destruction typically correlates with tumor burden and prognosis.

OBD results from the disruption of interactions among osteoclasts, osteocytes, osteoblasts, and bone marrow stromal cells (BMSCs) in the bone marrow. MM cells stimulate osteoclast function and inhibit osteoblast differentiation, resulting in bone resorption and consequent OBD. The perturbed bone marrow microenvironment in OBD provides a permissive niche that allows MM cell growth. New insights into the pathophysiology of osteoclast-mediated diseases are enhancing our understanding of myeloma cell growth and bone destruction, and it is hoped that these insights will lead to better bone-directed therapies aimed at restoring bone homeostasis by targeting either osteoclast or osteoblast activity, or both. It has been demonstrated that inhibition of osteolysis and stimulation of osteoblast differentiation reduces tumor growth in vivo. Therefore, novel agents targeting OBD are promising therapies for the treatment of MM.

Biology of Bone Metabolism

Osteocytes, osteoclasts, and osteoblasts maintain homeostasis in normal physiologic states by balancing bone formation and bone resorption. In adult bone, osteocytes make up 90% to 95% of all bone cells, and osteoclasts and osteoblasts make up fewer than 10%. Osteocytes serve as the main regulators of bone homeostasis between osteoclasts (responsible for bone resorption) and osteoblasts (responsible for bone formation). Osteocytes can secrete several cytokines that regulate the activity of osteoclasts and osteoblasts. These cytokines include sclerostin, dickkopf WNT signaling pathway inhibitor 1 (DKK1), receptor-activated nuclear factor-κB ligand (RANKL), and osteoprotegerin (OPG). Osteoclast function is regulated by receptor-activated nuclear factor-κB (RANK), its ligand RANKL, and OPG, the decoy receptor of RANKL. RANK-RANKL signaling activates a variety of downstream signaling pathways required for osteoclast development and stimulates osteoclast differentiation and maturation. Interestingly, apoptotic osteocytes release apoptotic bodies expressing RANKL to stimulate osteoclast differentiation. These data suggest that osteocytes can recruit osteoclasts to sites of remodeling. In addition, osteocytes regulate osteoblast differentiation via sclerostin and DKK1, which block canonical WNT signaling by binding to low-density lipoprotein receptor–related proteins 5 and 6 (WNT receptors) on the surface of osteoblasts. Osteoblasts and BMSCs also express OPG and RANKL and regulate osteoclast differentiation. Because OPG is a WNT canonical signaling target, osteocytes also regulate osteoclast differentiation via regulation of WNT signaling activity in osteoblasts. However, osteoclasts express semaphorin 4D (SEMA4D), which inhibits osteoblast differentiation. In healthy bones, these processes are well balanced and serve to maintain bone quality and mass.

Bone Disease in Multiple Myeloma

In MM, the osteocyte-osteoclast-osteoblast axis is disrupted, stimulating bone resorption and inhibiting new bone formation, with the consequent formation of pathognomonic osteolytic lesions.

Osteoclasts

The pathogenesis of OBD in MM is primarily the result of generalized osteoclast activation that leads to bone destruction and characteristic lytic lesions. Bone marrow biopsy specimens from patients with MM show a correlation among tumor burden, osteoclast numbers, and resorptive surface. Osteoclast activity also correlates with disease activity. The cytokines primarily involved in osteoclast differentiation and activity in MM OBD are RANKL/OPG, decoy receptor 3 (Dr3), C-C motif chemokine ligand 3 (CCL3; also known as macrophage inflammatory protein 1α [MIP-1α]), MIP-1β, tumor necrosis factor α (TNF-α), interleukin 3 (IL-3), IL-6, IL-11, stromal cell–derived factor 1α (SDF-1α), B-cell activating factor (BAFF), activin A, and vascular endothelial growth factor (VEGF).

MM cells stimulate osteoclast differentiation through the production of IL-3,17 Dr3,18,19 CCL3, MIP-1β,20-22 VEGF,23 TNF-α,24,25 and RANKL.26-29 MM cells also adhere to BMSCs via very late antigen 4 (VLA-4) and vascular cell adhesion molecule 1 (VCAM-1). These interactions lead to the secretion of cytokines, including RANKL, SDF-1α, IL-6, BAFF, VEGF, and activin A, which in turn promote osteoclast differentiation and activation. In addition to BMSCs and osteoblasts, MM cells stimulate CCL3 and the osteoclastogenic cytokine IL-11 in osteocytes. Osteoclasts also secrete CCL3 in addition to activin A, which stimulates osteoclast differentiation and activation. Collectively, these cytokines stimulate osteoclast differentiation and activity and contribute to the development of MM OBD.
CCL3
CCL3 is a pro-inflammatory cytokine that belongs to the CC chemokine subfamily. High CCL3 levels correlate with OBD and poor survival.\textsuperscript{21} Interestingly, fibroblast growth factor receptor 3 (FGFR3) overexpression in MM with t(4;14) results in upregulation of CCL3 expression, which has been associated with OBD.\textsuperscript{40} CCL3 binds to the G-protein–coupled receptors CCR1 and CCR5 and activates ERK and AKT signaling pathways, thereby modulating osteoclast differentiation. In the tumor niche, MM cells and osteoclasts are the main source of CCL3, which promotes MM cell migration and survival, along with stimulation of osteoclastogenesis.\textsuperscript{41,42} CCL3 also reduces bone formation by inhibiting osteoblast function via ERK activation, which is followed by downregulation of the osteogenic transcription factor osterix.\textsuperscript{22} CCL3-induced osteoclastogenesis and osteoclast support of MM cells can be inhibited by a small-molecule CCR1 antagonist.\textsuperscript{43}

**RANKL:OPG Ratio**
The proteins RANKL and OPG play a central role in the stimulation of osteoclast differentiation. An increase in the RANKL:OPG ratio results in bone loss in several cancers and inflammatory diseases, including rheumatoid arthritis.\textsuperscript{44-46} In patients with MM, bone marrow plasma levels of RANKL are increased, whereas OPG expression is decreased compared with OPG expression in normal volunteers and patients who have monoclonal gammopathy of undetermined significance.\textsuperscript{26} Importantly, low levels of OPG in serum correlate with advanced OBD in MM.\textsuperscript{47} A high RANKL:OPG ratio is associated with a worse prognosis.\textsuperscript{4} Treatment with OPG or OPG-like molecules prevented both bone destruction and MM growth in vivo.\textsuperscript{27,48} Anti-MM therapies, such as thalidomide and autologous bone marrow transplant, reduced OBD by normalizing the RANKL:OPG ratio.\textsuperscript{49,50} Recombinant OPG constructs, soluble RANK, OPG peptidomimetics,\textsuperscript{27,48,51,52} and more recently the anti-RANKL antibody denosumab (Xgeva, Amgen),\textsuperscript{53-56} have been developed to modulate the RANKL:OPG axis and reduce osteoclast activity in myeloma. The RANKL-OPG axis is an important target in the development of novel therapeutic strategies for MM bone disease.
BMSCs and Osteoblasts

BMSCs and the osteoblasts derived from BMSCs play an important role in the development of OBD in the presence of MM cells. MM cells stimulate osteoclast differentiation directly by secreting osteoclast-activating factors and indirectly by stimulating the secretion of osteoclast-activating factors such as RANKL, activin A, and VEGF in BMSCs and osteoblasts.63,64,65 Secretion of MM cells to BMSCs leads to RANKL and VEGF secretion by BMSCs via p38 mitogen-activated protein kinase (MAPK) activation.57,58 Moreover, sequestosome 1/p62 is an upstream regulator of the p38 MAPK and nuclear factor κB (NF-κB) signaling pathway, which is activated in BMSCs by MM cell adhesion. Osteoclast differentiation and MM cell proliferation are repressed by inhibition of p62 in BMSCs.59 As such, p62 is a novel promising target in MM OBD. Adhesion of MM cells to BMSCs and immature osteoblasts also leads to IL-6 secretion via NF-κB signaling33,34,60 and the X-box binding protein 1 (XBP1) signaling pathway. IL-6 stimulates MM cell proliferation, inhibition of MM plasma cell apoptosis,62 and osteoclast differentiation. MM cell adhesion also stimulates BAFF expression in BMSCs via NF-κB signaling.32 BAFF is a MM cell survival factor; it rescues MM cells from apoptosis induced by IL-6 deprivation and dexamethasone via activation of NF-κB, phosphoinositide 3-kinase (PI3K)/AKT, and MAPK pathways in MM cells and induction of strong upregulation of the MCL1 and BCL2 antiapoptotic proteins.63 Secreted IL-6 and BAFF stimulate serine/threonine kinase PIM2 expression in MM cells via activation of NF-κB and the JAK2/STAT3 pathway, resulting in MM cell survival.63 MM cells stimulate activin A expression in BMSCs via c-Jun N-terminal kinase (JNK)–dependent activation.7 Importantly, high levels of activin A in patients with MM are associated with advanced bone disease and advanced features of MM.64 Secreted activin A inhibits osteoblast differentiation in addition to having growth-stimulating effects on osteoclasts. MM cells also stimulate PIM2 expression in BMSCs/osteoblasts by IL-3, IL-7, TNF-α, transforming growth factor β (TGF-β), and activin A secretion and inhibit osteoblast differentiation.67

WNT Canonical Signaling in BMSCs and Osteoblasts

WNT canonical signaling plays an important role in osteoblast differentiation. Activated WNT signaling induces nuclear translocation of β-catenin protein, resulting in stimulation of osteoblast differentiation by activation of major osteoblast transcription factors.68 WNT antagonists, such as DKK1, sclerostin, and secreted frizzled related proteins (sFRPs), inhibit WNT canonical signaling activity by blocking WNT protein binding to WNT receptors. WNT antagonists act as negative regulators for osteoblast differentiation. In MM OBD, osteoblast differentiation is strongly inhibited. MM cells secrete several WNT antagonists, such as DKK1,69 sFRP2,70 and sFRP3,71 and inhibit WNT canonical signaling. High DKK1 levels have been detected in the serum of patients with MM and have been correlated with MM bone lesions.69 Also, high circulating levels of sclerostin, encoded by the SOST gene, have been found in patients with newly diagnosed MM and correlate with advanced MM disease stage and fractures.72 Although MM cells have been reported to produce sclerostin,73 we and others74 detected very little or no sclerostin or SOST messenger RNA expression in primary MM cells from patients or MM cell lines. The source and role of sclerostin in MM OBD therefore remain to be defined. Importantly, WNT antagonists inhibit OPG expression—because OPG is a target of WNT canonical signaling12—and increase the RANKL:OPG ratio. They are responsible not only for the suppression of osteoblast differentiation and activity but also for the stimulation of osteoclast differentiation and activity in MM OBD.

Osteocytes

Osteocytes regulate bone homeostasis in healthy bone.13 A recent study showed that the number of viable osteocytes is significantly lower in patients with MM than in healthy controls, and that osteocyte death correlates with the presence of bone lesions.38 Despite the fact that lower numbers of viable osteocytes have been observed in patients with MM, no significant difference was observed between the expression of sclerostin, an osteocyte marker, in the bone biopsy specimens of patients with MM and expression in the specimens of healthy controls.38 In addition, higher circulating levels of sclerostin have been found in patients with newly diagnosed MM, as mentioned before.72 This suggests that there may be other sources of sclerostin besides osteocytes in MM. MM cells stimulate expression of the osteoclastogenic cytokines CCL3 and IL-11 in pre-osteocytes, leading to increased osteoclast differentiation.38 Further investigation regarding the role of osteocytes in MM OBD is under way.

Osteolytic bone lesions, bone pain, and generalized bone loss (or osteoporosis), along with an increased risk for pathologic fractures, are well-defined features of myeloma.75 With a better understanding of the pathophysiology of the bone marrow microenvironment, better therapies can be developed to address OBD.

Role of Imaging

Imaging studies are an essential part of the diagnosis and management of bone disease in MM. The historical standard of care in the initial staging of newly diagnosed
myeloma is a complete skeletal survey. This includes a posteroanterior view of the chest; anteroposterior and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri, femora, and skull; and an anteroposterior view of the pelvis. Although widely employed, this modality has limitations. Roentgenographic detection of osteolytic lesions requires a loss of bone mass of at least 50% to 70%,76 which is advanced bone destruction. Conventional radiographs have limited sensitivity and consequently may miss from 10% to 20% of early lytic lesions.77 In addition, the reproducibility of skeletal survey results is poor and depends on the expertise of the reviewer.78 Another limitation of plain radiographs is that they cannot be used to assess response to therapy, as lytic lesions seldom show evidence of healing.79 Although skeletal survey remains the gold standard for the initial evaluation of myeloma, the limitations of this modality necessitate the use of additional imaging modalities. This requirement is reflected in the updated International Myeloma Working Group (IMWG) diagnostic criteria.80,81

The consensus statement recommends the use of magnetic resonance imaging (MRI) to define symptomatic MM.82 This recommendation has been incorporated into the new definition of symptomatic MM, which specifies “more than one focal lesion by MRI that is at least 5 mm or greater in size” as a biomarker of malignancy.83 Evidence provided in the recent publication supports the conclusion that patients with lesions detected on MRI are at elevated risk for progression to symptomatic MM84,85 and should be treated for the disease. This is a practice-changing recommendation. The statement further supports the use of MRI as the gold standard method for the detection of bone marrow involvement in MM. MRI is also indicated as the modality of choice for the evaluation of a painful lesion, particularly in the axial skeleton, and for the detection of spinal cord compression. MRI is further recommended to distinguish between benign osteoporotic vertebral fractures and those related to malignant MM. Whole-body MRI can give information complementary to that of a skeletal survey and is recommended in patients with normal results on plain radiography, particularly when symptoms are present.

Numerous studies have demonstrated the superior sensitivity of MRI in comparison with both skeletal survey86,87 and whole-body multidetector row computed tomography (CT).88 MRI has the ability to distinguish between myeloma-affected marrow and normal marrow. Specifically, MRI allows visualization of the medullary cavity and thus direct assessment of the extent of myeloma cell infiltration of the bone.89 In the event of suspected spinal cord compression, MRI is the imaging modality of choice for its ability to provide an assessment of the level and extent of cord compression, the size of the tumor mass, and the extent to which a tumor is compressing the epidural space.90 In the event that MRI is unavailable or contraindicated, urgent CT may be used for the evaluation of potential cord compression.

Positron emission tomography (PET), particularly in combination with CT, also can be used to detect active myeloma. Multiple studies have demonstrated that PET/CT is able to detect lesions at least 1 cm in diameter when a standardized uptake value of 2.5 or higher is used to indicate the presence of disease.91 The limitation of this technology is that subcentimeter lesions may not be detected.92 In a prospective study comparing PET/CT, MRI, and whole-body radiography in patients with newly diagnosed myeloma, PET/CT was superior to radiography in 46% of patients, including 19% with negative radiographic results. However, PET/CT scans of the spine and pelvis failed to show abnormalities in 30% of patients in whom MRI had demonstrated an abnormal pattern of bone marrow involvement. On the other hand, PET/CT identified myelomatous lesions in areas that were out of the field of view of MRI in 35% of patients. The combination of these 2 modalities proved to be the most powerful, with a detection rate as high as 92%.93 In multivariate analysis, the same group also showed that persistent PET/CT positivity before and after primary therapy and subsequent high-dose therapy is a predictor of poor outcome in patients with symptomatic myeloma.94

The IMWG consensus statement provides practice-changing recommendations for MM. Whole-body MRI is an excellent option for diagnostic imaging when available; however, PET/CT is also an effective modality that can be considered for diagnostic evaluation. The choice of imaging modality should be dictated by the risk for disease and the presenting symptoms. The use of advanced skeletal imaging to better classify patients with asymptomatic MM will refine the management of this disease.

**Treatment**

Novel treatment strategies in MM have led to significant improvements in overall survival (OS), but the disease remains incurable. As patients live longer with MM, bone-directed therapy has become increasingly relevant. Bone-directed therapies, including bisphosphonates, radiotherapy, and surgery, are aimed at reducing the development of new osteolytic lesions and preventing skeleton-related events (SREs) such as bone pain, pathologic fractures, vertebral collapse, hypercalcemia, and spinal cord compression. Preclinical trials suggest that restoring bone homeostasis with novel bone-targeted agents may inhibit tumor growth. These promising
results have set the stage for the clinical evaluation of novel strategies targeting MM via the restoration of bone homeostasis.

**Bisphosphonates**

Before the advent of effective bisphosphonate therapy, bone healing occurred uncommonly in myeloma and was delayed in treated patients, despite responses to chemotherapy. In this context, a major effort has been made over the last 30 years to either prevent or inhibit further bone resorption in patients with myeloma. Bisphosphonates are the standard of care for MM OBD. Nitrogen-containing bisphosphonates, such as pamidronate and zoledronic acid, reduce osteoclast activity by inhibiting farnesyl pyrophosphate synthase. In a double-blind randomized trial of clodronate vs placebo in 350 patients, the proportion of patients with progression of osteolytic lesions was twice as high in the placebo group as in the clodronate-treated group. It was then shown in a prospective randomized trial that pamidronate, a more bioactive intravenous bisphosphonate, reduced SREs such as pathologic fractures, the necessity for radiation therapy to bone, and spinal cord compression in patients with Durie-Salmon stage III myeloma and at least 1 lytic bone lesion. This benefit was maintained until 21 months after the initiation of therapy. Pamidronate also significantly improved quality of life, with decreases in pain scores seen within a month. More potent bisphosphonates, such as zoledronic acid, have since undergone clinical evaluation and offer the benefit of shorter infusion times than those required with pamidronate. The IMWG and the National Comprehensive Cancer Network (NCCN) panels advocate the use of either pamidronate or zoledronic acid monthly for patients with MM and lytic bone disease. Both pamidronate and zoledronic acid were considered equally effective for reducing skeletal complications.

These guidelines recommend that pamidronate be delivered at a dose of 90 mg intravenously for at least 4 hours or zoledronic acid at a dose of 4 mg intravenously for 15 minutes every 3 to 4 weeks for patients with MM and lytic bone disease. The IMWG recommends that bisphosphonates be given until disease progression in patients without a complete response or very good partial response. This recommendation is motivated by the Medical Research Council (MRC) Myeloma IX trial findings of improvements in OS and reductions in SREs in patients who received bisphosphonate treatment for more than 2 years. For patients with a complete response or a very good partial response, the optimal duration of bisphosphonates is an active area of investigation, given that prolonged exposure to bisphosphonates may increase the risk for side effects, including osteonecrosis of the jaw (ONJ). Currently, the IMWG panel recommends 12 to 24 months of treatment (timed from the start of treatment) and then continuation at the discretion of the provider.

To better define the duration of bisphosphonate therapy, the Z-MARK study evaluated whether patients with 1 to 2 years of prior intravenous bisphosphonate therapy could be treated safely long term with less frequent administration of zoledronic acid on the basis of markers of bone turnover. Patients with levels of urinary N-telopeptide of type I collagen (uNTX) below 50 nmol/mmol of creatinine received 4 mg of zoledronic acid every 12 weeks, vs every 4 weeks for those with higher levels of uNTX. The patients’ uNTX levels were monitored over the course of treatment, and the dosing of zoledronic acid was adjusted accordingly. Additionally, patients in whom an SRE or disease progression developed were treated on the every-4-weeks schedule thereafter, regardless of uNTX levels. A majority of the patients (79 of 121) were on the every-12-weeks schedule throughout the study. SRE occurred in only 5.8% of patients in year 1 and 4.9% of patients in year 2. The low incidence of SREs in this study vs that in prior studies with zoledronic acid suggests that less frequent dosing of zoledronic acid beyond 1 to 2 years may continue to reduce the risk for SREs. Furthermore, it suggests that more effective treatment of MM with novel therapies may have protective effects on bone.

In addition to their role in OBD, bisphosphonates may have an antitumor effect. The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial showed that the administration of zoledronic acid every 6 months for 3 years reduced the risk for disease recurrence in patients with estrogen receptor–positive breast cancer, although no improvement was seen in the rate of disease-free survival in another study. In MM, the MRC Myeloma IX trial compared zoledronic acid vs oral clodronate in patients with newly diagnosed disease and found that zoledronic acid reduced mortality by 16% and increased median OS from 44.5 to 50.0 months (P= .04).

**Denosumab**

The RANK-RANKL system has been identified as an essential mediator of osteoclast precursors, which stimulate or promote differentiation into osteoclasts and activate mature osteoclasts to resorb bone. Therefore, RANKL is a therapeutic target for diseases associated with increased bone resorption. Denosumab is a fully human monoclonal immunoglobulin G2 (IgG2) antibody to RANKL that binds with high affinity (Kd = 3 × 10⁻¹² M) and specificity to the soluble and cell membrane–bound forms of human RANKL. Denosumab is highly specific because it binds only to RANKL and not to other members of the TNF

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family, including TNF-α, TNF-β, TNF-related apoptosis-inducing ligand, and CD40 ligand. Denosumab binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and cancer-induced bone destruction are reduced.

Denosumab is approved for increasing bone density in patients with osteoporosis and for preventing SREs in patients with metastatic bone disease. Study 20050244 was a phase 3 randomized study of denosumab vs zoledronic acid in patients with advanced cancers, including solid tumors (except breast and prostate tumors), lymphoma, and MM, and radiographic evidence of at least one bone metastasis (or lytic bone lesion in MM). Of the 1140 patients enrolled, 180 had a diagnosis of MM. This study demonstrated that denosumab delayed the time to first on-study SRE (pathologic fracture, radiation therapy to bone, bone surgery, or spinal cord compression) and that it was noninferior to zoledronic acid (hazard ratio [HR], 0.84; 95% CI, 0.71-0.98; \( P=\) .0007).

An ad hoc analysis examining OS for the 3 stratification variables (non–small cell lung cancer, MM, and other solid tumors) demonstrated an HR of 0.79 (95% CI, 0.65-0.95; n=702) for non–small cell lung cancer, 2.26 (95% CI, 1.13-4.50; n=180) for MM, and 1.08 (95% CI, 0.90-1.30; n=894) for “other” solid tumors. For MM, imbalances in baseline disease characteristics, stem cell transplant, and withdrawals (due to consent withdrawal or loss to follow-up) favored zoledronic acid. These baseline and on-study imbalances may partially account for the difference observed between treatment groups. Denosumab is not currently approved by the US Food and Drug Administration for use in patients with MM. To address the discrepancies definitively, a randomized, double-blind, multicenter phase 3 study is currently comparing denosumab with zoledronic acid in the treatment of bone disease in patients with newly diagnosed MM (Denosumab Compared to Zoledronic Acid in the Treatment of Bone Disease in Subjects with Multiple Myeloma; NCT01345019).

It is estimated that 25% to 50% of patients who have MM present with renal insufficiency, and approximately 9% require hemodialysis. There is no current standard of care with respect to bone-targeted therapy in this patient population. Bisphosphonates are renally cleared and are considered contraindicated in oncology patients with a creatinine clearance of less than 30 mL/min. Denosumab is not cleared by the kidneys, so its use is not restricted in patients with renal insufficiency. There exists an unmet need for bone-targeted therapy in patients with MM who have renal insufficiency. A single-arm study of denosumab in such patients (creatinine clearance <30 mL/min) is currently under way to address this unmet need (A Study of Denosumab in Multiple Myeloma Patients With Renal Insufficiency; NCT02833610).

Side Effects

ONJ is one of the most serious complications of bisphosphonate therapy. ONJ is traditionally defined as a condition in which exposed, necrotic bone in the jaw does not heal after 8 weeks and is generally painful. In the MRC Myeloma IX trial, the cumulative incidence of ONJ was 3% to 4% at a median follow-up of 3.7 years. The exact etiopathogenetic mechanism of the development of ONJ is not known, but trauma (including dental extractions), infection, and reduced vascularity can be associated with the development of this condition. Attention to dental hygiene and minimization of invasive procedures may reduce the risk for ONJ. ONJ also has been reported with the use of other antiresorptive agents. For example, the incidence of ONJ was 1.8% in several phase 3 trials of denosumab.

Other important side effects of bone-directed therapy include atypical femoral fractures and hypocalcemia. Atypical, low-energy, or low-trauma fractures of the femur have been reported in patients receiving bisphosphonates or denosumab. These fractures include those of the subtrochanteric femur (bone just below the hip joint) and diaphyseal femur (long segment of the thigh bone). Some patients experience prodromal pain weeks or months before the fracture occurs. Patients receiving long-term (>5-3 years) bisphosphonate therapy may be at an increased risk.

Hypocalcemia (including severe and life-threatening cases) also has been reported with the use of bisphosphonates and denosumab. The incidence of hypocalcemia was higher with denosumab than with zoledronic acid (12.4% vs 5.3%) in the 3 registration trials. Decreases in calcium were mostly mild to moderate and asymptomatic, and they occurred within the first 6 months of therapy in the majority of patients. It is important to measure serum calcium and vitamin D levels before treatment initiation and replete accordingly. Supplementation during therapy with at least 500 mg of calcium and at least 400 IU of vitamin D daily is recommended to prevent hypocalcemia.

Acute kidney injury has also been reported with use of intravenous bisphosphonates. An elevated baseline serum creatinine level appears to be a risk factor for renal injury. In a review of 300 patients with MM treated with zoledronic acid, 34 (11%) showed worsening renal function. In 28 of these patients, zoledronic acid was discontinued and restarted in half of cases following a brief delay. Further worsening of renal function occurred in only 5 of the 34 patients. Pamidronate is also associated with acute kidney injury as well as with...
nephrotic-range proteinuria. The toxicity appears to be both dose-dependent and infusion time-dependent, particularly when the drug is given over less than 2 hours. Acute kidney injury from either drug can lead to renal failure and the need for hemodialysis.

Future Directions

**Activin A Antagonists**

Activin A is secreted by BMSCs and osteoclasts in MM OBD; it stimulates osteoclast differentiation and inhibits osteoblast formation in MM OBD. RAP-011, a chimeric antibody being developed by Acceleron Pharma to target activin A, is derived from fusion of the extracellular domain of type II activin receptor (ActRIIA) and the constant domain of the IgG2a-Fc. RAP-011 has been shown to enhance osteoblast mineralization and increase bone density in an osteoporotic mouse model. In an in vivo humanized MM model, RAP-011 reversed osteoblast inhibition, decreased MM bone disease, and inhibited tumor growth. ACE-011 is the humanized counterpart of RAP-011. It effectively decreased the bone resorption markers C-telopeptide of type I collagen (CTX) and tartrate-resistant acid phosphatase (TRACP-5b) and increased the bone formation marker bone-specific alkaline phosphatase (BSAP) in postmenopausal women. It has been shown in vitro that lenalidomide (Revlimid, Celgene), a well-known and approved treatment strategy for MM, stimulates activin A secretion on BMSCs via an AKT-mediated increase in JNK signaling. Clinical trials with ACE-011 (sotatercept) in combination with lenalidomide/dexamethasone or pomalidomide (Poma-lyst, Celgene)/dexamethasone are ongoing in MM (Sota-tercept [ACE-11] With Lenalidomide or Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma; NCT01562405). Preliminary data from this ongoing study suggest that ACE-011 leads to early increases in hemoglobin levels and bone mineral density, and it is the first agent that may address deficiencies in both of these, which are significant causes of morbidity in MM.

**DKK1 Antagonists**

DKK1 plays one of the key roles in mediating osteoblast inhibition in MM and is therefore an attractive target for MM therapy. In vitro assays show that inhibition of DKK1 via a specific neutralizing antibody promotes osteoblast differentiation and function and reverses the negative effect of MM cells on osteoblast differentiation. Moreover, in vivo studies using both murine and humanized murine models of MM-induced bone disease showed an increase in bone formation and osteoblast numbers and a decrease in osteolytic lesions with DKK1 inhibition. Inhibition of DKK1 also resulted in a reduction of tumor growth, mainly as an indirect effect via modification of the tumor microenvironment. Therefore, DKK1 inhibition with a neutralizing antibody restores bone homeostasis and may have an inhibiting effect on tumor growth. Currently, ongoing clinical trials combining DKK1 neutralizing antibody and bisphosphonates will test these promising preclinical results. In particular, zoledronic acid in combination with the pro-anabolic agent BHQ880, a fully human anti-DKK1 monoclonal antibody, has been studied in a phase 1 clinical trial (A Study to Assess BHQ880 in Combination With Zoledronic Acid in Relapsed or Refractory Myeloma Patients; NCT00741377). BHQ880 also was tested in a phase 2 clinical trial of patients with smoldering MM (Study of BHQ880 in Patients With High Risk Smoldering Multiple Myeloma; NCT01302886), and preliminary results showed that BHQ880 significantly stimulated vertebral strength measured by quantitative CT, with an increase in bone mineral density in some cases exceeding 5% across vertebral vertebrae and vertebral compartments (P=.002).

**Sclerostin Neutralizing Antibody**

Several studies have already demonstrated the importance of sclerostin in osteoporosis, and inhibition of sclerostin is an important strategy in the treatment of bone conditions with a high catabolic rate. Clinical trials with the experimental sclerostin-neutralizing antibodies romosozumab and blosozumab for the treatment of postmenopausal osteoporosis are ongoing. Preliminary results have shown an increase in bone mineral density. Elevated levels of circulating sclerostin have been found in patients with newly diagnosed MM, and levels have been shown to correlate with MM disease stage and number of fractures. Targeting sclerostin may play an important role in the treatment of MM OBD. As previously discussed, the source and role of sclerostin in MM OBD remain unclear. Further studies about the role of sclerostin in MM and application of sclerostin-neutralizing antibody to MM OBD are anticipated and will inform further exploration of this potential target.

**Conclusions**

The treatment of MM has become increasingly more effective over the past decades with the incorporation of novel therapies such as the immunomodulator drugs, proteasome inhibitors, and monoclonal antibodies. A continuing imperative is to develop better supportive strategies that match the effectiveness of these newer anti-MM agents. Bisphosphonates have been a major advance for managing bone disease. Newer drugs, such as denosumab and other bone anabolic agents, are under investigation...
and may be incorporated as therapy for bone disease in the near future. With a better understanding of the biology of bone disease, treatments developed to target the bone marrow microenvironment will be able to preserve bone health and potentially improve disease outcomes. Advances in supportive care will translate into a better quality of life and better overall outcomes for patients.

Disclosures
Drs O’Donnell and Raje have no financial disclosures.


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