Advances in the Biology and Treatment of Bone Disease in Multiple Myeloma

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Abstract

Osteolytic bone disease is pathognomonic of multiple myeloma (MM) and affects more than 80% of patients. Bone disease results in skeletal-related events (SRE) such as vertebral compression fractures, which may cause cord compression, hypercalcemia, pathologic fractures that require radiation or surgical fixation, and severe pain. All of these not only result in a negative impact on quality of life but also adversely impact overall survival. Osteolytic disease is a consequence of increased osteoclast (OC) activation along with osteoblast (OB) inhibition, resulting in altered bone remodeling. OC number and activity are increased in MM via cytokine deregulation within the bone marrow (BM) milieu, whereas negative regulators of OB differentiation suppress bone formation. Bisphosphonates are a well-established treatment of myeloma-related skeletal disease and are the current standard of care. However, complications arising from their long-term use have prompted studies of schedule optimization and alternate strategies. Several novel agents are currently under investigation for their positive effect on bone remodeling via OC inhibition. The identification of negative regulators of OB differentiation has prompted the use of anabolic agents. In addition to restoring bone remodeling, these drugs may inhibit tumor growth in vivo. Future studies will look to combine or sequence all of these agents with the goal of not only alleviating morbidity from bone disease but also capitalizing on the resultant antitumor activity.

Introduction

The last decade has seen rapid advances in our understanding of the biology of multiple myeloma (MM), and therapeutic options have evolved. From our understanding of precursor conditions such as monoclonal gammapathy of undetermined significance (MGUS; ref. 1) to the unraveling of complex oncogenomics (2), we have made advances in the treatment of both newly diagnosed (3) and relapsed and refractory MM (4). Consequent to these advances, MM patients are living longer, and the associated bone disease, although now a more chronic problem, is much better controlled with both anti-MM strategies and bone-directed therapies, including better pharmacologic, appropriate surgical, and minimally invasive interventions.

Osteolytic lesions are a pathognomonic feature of MM. More than 80% of MM patients develop osteolytic bone disease (OBD), frequently complicated by skeletal-related events (SRE) such as severe bone pain, vertebral compression fractures, and pathologic fractures, resulting in a need for radiation or surgical fixation. Importantly, pathologic fractures affect 40 to 50% of MM patients, increasing the risk of death by more than 20% compared with patients without fractures (5, 6). Therefore, OBD negatively impacts both patients’ quality of life and their survival. Here, we discuss the pathogenesis of OBD and focus on advances in our understanding of its biology and therapeutic implications.

The pathogenesis of OBD in MM is primarily associated with generalized osteoclast (OC) activation. Bone marrow (BM) biopsies from MM patients show a correlation between tumor burden, OC number, and resorptive surface (7, 8). Although enhanced OC function is a key player in the development of OBD, a decrease in trabecular thickness and low calcification rate in BM biopsy specimens of MM patients, with osteolysis and decreased osteoblast (OB) numbers and/or surface, suggest that OB activity is also impaired (9). Therefore, bone remodeling in which OC and OB activity are tightly coupled is severely disrupted in MM.

Several novel agents are aimed at restoring bone homeostasis by targeting either OC or OB activity. Interestingly, inhibition of osteolysis and stimulation of OB differentiation lead to reduced tumor growth in vivo (10, 11). Therefore, novel agents targeting bone disease are also promising therapeutic strategies for the treatment of MM.
The Biology of Myeloma Bone Disease

The cross-talk between MM cells and their local BM microenvironment is tightly regulated. Many components of the microenvironment form a supportive microenvironment for the propagation of tumor cells (12–17), which is termed the cancer niche. Malignant cells, in turn, shape their local microenvironment to create a permissive niche for their survival (18–20). MM is an exquisitely niche-dependent cancer and can serve as a model to identify niche-directed therapeutic strategies. Stromal, endothelial, immune, and bone cells, as well as extracellular matrix components, such as osteopontin and fibronectin, constitute the MM niche that supports tumor growth and survival. Under normal physiologic states, OC and OB result in balanced bone resorption and formation maintaining normal homeostasis. In MM, the OC-OB axis is disrupted, favoring bone resorption and suppressing new bone formation with the development of pathognomonic osteolytic lesions (Fig. 1; ref. 21). The main cytokines involved in OC and BM stromal cell (BMSC) interactions with MM cells are interleukin-6 (IL-6), receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG), B-cell activating factor (BAFF), chemokine (C-C motif) ligand 3 (CCL3)/macrophage inflammatory protein (MIP)–1α, and VEGF. Cell adhesion interactions, mainly very late antigen (VLA)–4/vascular cell adhesion molecule (VCAM)–1 and lymphocyte function–associated antigen (LFA)–1/intercellular adhesion molecule (ICAM)–1, result in integrin signaling that activates drug resistance mechanisms (CAM-DR; refs. 17, 22–26). Another recently described MM-derived factor is dickkopf (DKK)–1, a WNT/β-catenin signaling antagonist (27). Highly expressed in BM of MM patients with osteolytic lesions, DKK1 is apparently involved in early stages of bone disease. DKK1 and other cytokines have inhibitory effects on OB and thus promote MM bone disease. Via modulation of receptors such as LRP5/6 and Frizzled, Wnt and its antagonists, such as DKK-1 and soluble frizzled related protein (sFPR)–1,2,3,4 regulate the canonical β-catenin–dependent and noncanonical disheveled or calcium-dependent pathways. In addition to effects on the OB axis, DKK-1 also plays an important role in regulating OC function. Although OBs secrete MM growth factors such as IL-6, they have an overall inhibitory effect on MM cell proliferation (28). In vivo upregulation of OBs, by stimulating the β-catenin signaling pathway, results in significant tumor growth inhibition (11). Although the mechanism is still to be clarified, small leucine-rich proteoglycans are probably involved. Decorin, in particular, is an OB-derived extracellular matrix component regulating bone formation and mineralization. Decorin induces MM cell apoptosis via p21 activation and inhibits angiogenesis and osteoclastogenesis (29).

**Rankl to osteoprotegerin ratio in multiple myeloma.** The receptor activator of NF-κB (RANK), its ligand RANKL, and the decoy receptor of RANKL, osteoprotegerin (OPG), play a pivotal role as central regulators of OC function. RANK-RANKL signaling activates a variety of downstream signaling pathways required for OC development. RANK mRNA is expressed widely in bone and BM. It has a significant role in stimulating OC differentiation and maturation, and also in preventing apoptosis. Deregulation of the RANKL to OPG ratio results in bone loss in cancer and inflammatory disease (30, 31). In MM patients, BM plasma levels of RANKL are increased, whereas OPG expression is reduced compared with normal volunteers and patients with MGUS (32). Importantly, low serum levels of OPG correlate with advanced OBD in MM (33). The relevance of the RANKL/OPG pathway in mediating OC activation in MM has been further confirmed in several murine models of MM OBD. Treatment with OPG and OPG-like molecules prevented both bone destruction and MM growth in vivo (34, 35). Interestingly, specific anti-MM strategies such as thalidomide and autologous BM transplantation inhibited bone resorption by normalizing the RANKL to OPG ratio (36, 37). Therefore, the RANKL-OPG axis is an important target in the development of novel therapeutic strategies for MM bone disease.

**CCL3/CCR1 pathway in multiple myeloma.** CCL3 is a chemokine binding to G-protein–coupled receptors, CCR1 and CCR5, to activate AKT and mitogen-activated protein kinase (MAPK) signaling pathways. High BM serum levels
of CCL3 correlate with osteolytic lesions and survival in MM patients (38). CCL3 is secreted by OCs and MM cells. Interestingly, fibroblast growth factor receptor 3 (FGFR3) overexpression in MM with t(4;14) results in upregulation of CCL3 expression (39). The CCL3/CCR1 pathway has multiple roles in MM, including induction of growth and survival and chemotaxis of malignant plasma cells (23). It also induces osteoclastogenesis by promoting OC precursor cell migration and fusion into multinucleated TRAP positive cells (40). The dual activity of CCL3 has been targeted in vivo with different strategies; both antisense sequence and neutralizing antibody against CCL3 effectively inhibited tumor growth and restored bone remodeling in a mouse model of MM bone disease (10, 41). Importantly, CCR1 inhibition was associated with impairment of osteoclastogenesis and OC-induced tumor cell proliferation in vitro, suggesting that the CCL3/CCR1 pathway is a relevant target in MM bone disease (42).

Other osteoclast-activating factors in multiple myeloma.
In addition to RANKL and CCL3, several OC-activating factors such as IL-1, IL-6, IL-3, IL-7, CCL20, and activin are highly expressed in the BM of MM patients (43–46). More recently, activin A, a TGF-β family member, has been identified as a key player in the pathogenesis of OBD in MM. Activin modulates bone remodeling by dual activity as OC promoter and inhibitor of OB differentiation. In MM, high activin A levels are associated with advanced bone disease. BMSC and OCs are the main sources of activin, and MM cells further upregulate BMSC expression of activin (47). Other factors such as hepatocyte growth factor, IL-8, VEGF, and M-CSF may regulate MM-related bone disease.

Multiple myeloma–induced osteoclast differentiation via bone marrow stromal cells and osteoblasts. MM cells stimulate OC differentiation directly by secreting OC-activating factor and, indirectly, by stimulating BMSC secretion of RANKL and activin. Furthermore, inhibiting OB differentiation decreases OPG expression in the marrow microenvironment, because mature OBs are a primary source of OPG.

Adhesion of MM to BMSC leads to RANKL and VEGF secretion by BMSC via p38 MAPK activation (48, 49). The sequestosome p62 is a recently discovered upstream regulator of p38 MAPK and the NF-κB signaling pathway, activated in BMSC by MM cell adhesion. Inhibition of p62 in BMSC represses OC differentiation and MM cell proliferation, therefore p62 is a novel promising target in MM-OBD (50).

MM-derived DKK1 inhibits wingless (Wnt)3a–induced OPG expression in OBs and stimulates RANKL secretion (51).

Treatment of Multiple Myeloma–Related Bone Disease
Current treatment strategies in MM have resulted in improved patient overall survival, but patients continue to relapse, and no definitive cure has been as yet achieved. Given the improved survival of MM patients, treatment of OBD has taken on a new relevance as the focus is now largely on quality of life. Until recently, therapeutic options for MM-OBD included bisphosphonates, radiotherapy, and surgery. These therapies are aimed at preventing SREs and reducing the development of new osteolytic lesions and bone pain. Other strategies, such as vertebral augmentation procedures, are mainly useful for symptom control. Interestingly, several studies using novel bone-targeted agents suggest that restoring bone homeostasis may lead to tumor growth inhibition. These promising preclinical results have set the stage for clinical evaluation of novel strategies targeting MM via restoring bone homeostasis (Fig. 2). Table 1 provides a list of bone-directed agents, their targets, and stage of clinical development.

Bisphosphonates
Prevention of skeletal-related events. Bisphosphonates represent the standard of care for MM-related bone disease. The anticasabolic effects result from enhanced OC apoptosis partly because of inhibition of the mevalonate pathway (52). In the clinical setting, treatment with either pamidronate (PAM) or zoledronic acid (ZA) significantly reduces pain related to bone disease and prevents SRE (53). Monthly infusion of PAM reduces bone pain and SRE and improves quality of life, compared with placebo. For intravenous bisphosphonates, the 1996 pivotal randomized trial and extension study tested the effect of 90 mg of PAM versus placebo in 392 patients with stage III MM. In 2001, in a noninferiority randomized trial, escalating doses of ZA were tested in comparison with 90 mg of PAM, in 280 patients, 108 of them affected by MM. The study showed equivalence of both drugs, except ZA at 0.4 mg. These studies established the role of PAM and ZA as standard of care as supportive treatment in patients with symptomatic MM.

Antimyeloma effects. In vitro data also suggest that a high concentration of bisphosphonates may have a direct cytotoxic effect on tumor cells as well as inhibit tumor-stromal cell interactions (54). For example, ZA improves disease-free survival in breast cancer patients when combined with adjuvant endocrine therapies (55). However, despite the positive results in vitro and in vivo, major clinical trials failed to show both reduction in the evolution of asymptomatic to symptomatic MM (56) and prolongation of survival in patients with MM. This trial was flawed, however, because of the limited duration of ZA treatment of 1 year, as opposed to an average time to progression of more than 3 years. A meta-analysis of 18 randomized clinical trials in cancer patients, including 4 trials in MM (53, 57–60), confirmed prevention of SRE by bisphosphonate without any impact on patients’ survival. This result is likely because of the trial design, with the bisphosphonate always considered a supportive care therapy, and data for antitumor activity always gathered in a post hoc analysis. Interestingly, a recent analysis of the Medical Research Council (MRC) Myeloma IX study
showed, after a median follow-up of 3.7 years, that ZA impacts overall survival and progression-free survival in MM patients (61), confirming the observations in patients with breast cancer (55). Importantly, response rates were also higher in the ZA-treated patients, suggesting their antitumor effects and the survival advantage persisted despite correcting for SREs. These results are most likely a consequence of the fact that the type of anti-MM therapy was also randomized and was not left to investigator choice as with the older studies. These results suggest that tumor growth may be negatively affected by targeting bone in patients or that bisphosphonates enhance the effects of the antimyeloma therapy or have direct antimyeloma activity.

Safety and adverse events. The most serious adverse events associated with bisphosphonates are renal impairment and osteonecrosis of the jaw (ONJ; ref. 62). These events are relatively rare but are significant.

In patients treated with bisphosphonate at recommended doses and infusion rates, an increase in serum creatinine is seen in less than 10% of cases and severe renal toxicity is rare. Kidneys are particularly sensitive to bisphosphonates, being responsible for 40% of their excretion via glomerular filtration and active tubular excretion. The nephrotoxicity is related to the dose, infusion time, and maximum plasma concentration (C_{max}) that affects the intracellular bisphosphonate concentration. Furthermore, a bisphosphonate with prolonged renal tissue half life, such as ZA, can potentially accumulate in renal tissue, contributing to renal damage.

ONJ is characterized by exposed bone, severe localized pain, and increased risk of secondary infections at the site of the ONJ. The lesion can be preceded or accompanied by pain, swelling of the mucosa, ulcer, and loose teeth or can manifest as a nonhealing socket after tooth extraction. Although the association between ONJ and bisphosphonate has been reported by several authors, the causality and the patho-physiology are still a matter of investigation. New strategies for the use of bisphosphonates are being explored with the view to reduce some of these complications, as well as maintaining their well-established efficacy. It had been hypothesized, in fact, that excessive inhibition of bone remodeling is the result of the very long half life of aminobisphosphonates and their possible accumulation with a 3- to 4-week administration schedule. The observations that animals treated with high doses of ZA show accumulation of microdamage (63, 64) and impaired bone strength secondary to hypermineralization (65, 66) support this theory and suggest that reduced frequency might avoid these unwanted side effects. The observation that ONJ is also reported with the use of denosumab lends credence to the theory that this is not necessarily a bisphosphonate-related issue, but rather a consequence of profound effects on bone remodeling due to potent antiresorptive agents.

The Z-MARK study, a phase IV clinical trial, will estimate the effectiveness and safety of 4 mg of ZA every 4 weeks or...
every 12 weeks in MM patients, on the basis of urinary NTx levels. An ongoing phase II clinical trial will assess the effect of the administration of a single dose of ZA and a 6-month observation period with evaluation of urinary NTx to determine whether this is, indeed, a good surrogate to predict bone disease (67). Additional biomarkers will also be studied in order to determine what the best predictors would be, as NTx in the context of bisphosphonates has certain limitations. Research is also focusing on lowering doses of bisphosphonates. An ongoing trial is comparing 30 mg of PAM versus 90 mg every month in newly diagnosed patients with MM. Data available on 505 patients, after a median follow-up of 3.7 years, did not show any difference in SREs between the 2 doses tested (68). Bisphosphonates are also under investigation in combination with other compounds in a multidrug approach for MM bone disease. In particular, clinical trials are testing ZA in combination with the proanabolic agent BHQ880, an anti-Dkk1 monoclonal antibody, and bortezomib (69). Finally, bisphosphonates are currently in clinical trials for asymptomatic MM.

**Denosumab**

Denosumab, a RANKL-neutralizing antibody (AMG165, Amgen Pharmaceutical), has been successfully used in MM and breast cancer patients to inhibit bone resorption markers. Compared with bisphosphonates, a single subcutaneous administration of denosumab induces a sustained inhibition of bone resorption markers lasting about 80 days versus 30 days of bisphosphonates. Denosumab displayed limited toxicity, consisting mainly of asthenia and peripheral edema (70). Interestingly, a recent randomized clinical trial showed that denosumab inhibited bone resorption and prevented SREs even in patients refractory to bisphosphonate therapy (71). A recently completed phase III trial comparing the effectiveness of ZA with denosumab suggests that RANKL inhibition is as efficacious as ZA in terms of decreasing SRE. Denosumab continues to remain in clinical development for MM.

**Other novel bone targets**

**CCR1 inhibitors.** The CCL3/CCR1 pathway mediates OC differentiation and is involved in MM cell survival and migration, making it an appealing therapeutic target. In vitro and in vivo studies showed that inhibition of CCL3 by antisense strategies prevents the development of osteolytic lesions and inhibits tumor growth (10). Similar results have been shown with MLN3897 (Millennium Pharmaceuticals), a specific orally available CCR1 inhibitor. MLN3897 inhibits osteoclastogenesis and overcomes the proliferative advantage conferred by OC to MM cells (42). Future clinical trials using CCR1 inhibition strategies in patients with MM-OBD will test these promising preliminary results.

**Anti-BAFF–neutralizing antibody.** OC and MM cells interact by stimulating each others’ growth and survival, and a critical mediator in this interplay is the TNF family member, B-cell activating factor (BAFF). BAFF is a MM growth factor derived from OC and BMSC that mediates both MM cell survival and MM-BMSC adhesion (24, 26). In vivo–neutralizing antibodies against BAFF (Ely Lilly) significantly inhibit tumor burden and, importantly, reduce the number of lytic lesions and OC differentiation (72). Certainly, the impact on osteolysis could be a secondary effect due to its anti-MM activity. On the basis of these results, a clinical trial combining BAFF-neutralizing antibody with bortezomib is currently ongoing.

**RAP-011/ACE-011.** Activin is a novel cytokine upregulated in MM patients with advanced bone disease. It has a dual activity on bone remodeling, both stimulating OC differentiation and inhibiting OB formation. Activin can be targeted by a chimeric antibody RAP-011 (Acceleron Pharma), derived from the fusion of the extracellular domain of activin receptor IIA and the constant domain of the murine IgG2a (73). Inhibition of activin A via both RAP-011 and neutralizing antibody against activin leads to increased OB differentiation and inhibits OC development in vitro. In murine models of osteoporosis and MM-OBD, RAP-011 treatment improved bone density and prevented osteolytic lesions. Moreover, RAP-011 effectively reduced tumor growth (47). The humanized counterpart of RAP-011, ACE-011, effectively inhibited bone resorption markers and stimulated bone formation parameters in postmenopausal women. Ongoing clinical trials are evaluating its role in MM.

**Table 1. Novel Bone-Directed Therapies for Multiple Myeloma**

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**DKK1 antagonists.** As recently shown, DKK1 plays a key role in mediating OB inhibition in MM (27). Therefore, treatment strategies to block DKK1 activity have been developed. In vitro assays show that DKK1 inhibition via a specific neutralizing antibody promote OB differentiation and function and reverse the negative effect of MM cells on OB differentiation (74, 75). Moreover, in vivo studies using both murine and humanized models of MM-induced bone disease showed increased bone formation, OB number, and improvement of osteolytic lesions by DKK1 inhibition (75–77). Importantly, blocking DKK1 also resulted in reduction of tumor growth, mainly as an indirect effect via modification of the tumor microenvironment (75). Therefore, DKK1 inhibition via a neutralizing antibody restores bone homeostasis and may have an inhibitory effect on tumor growth. Currently, ongoing clinical trials combining DKK1-neutralizing antibody and bisphosphonates will test these promising preclinical results. In particular, ZA in combination with the proangiogenic drug bortezomib, an anti-Dkk1 monoclonal antibody, is being studied in a phase I clinical trial (69). BHQ880 is also being tested in smoldering MM.

**Thalidomide analogs.** Thalidomide derivatives with immunomodulatory functions such as lenalidomide or pomalidomide display a direct inhibitory effect on MM growth (78). Moreover, they affect the microenvironment by regulating the immune response and inhibiting angiogenesis (79, 80). Recent studies also suggest a role for these agents as inhibitors of OC development. Both lenalidomide and pomalidomide downregulate PL1 expression in OC precursor cells. PL1 is an early transcription factor involved in monocytic cell commitment to OC differentiation (81, 82). Lenalidomide also inhibits RANKL secretion by BMSCs, and the RANKL-OPG balance is restored in patients treated with lenalidomide. Immunomodulatory derivatives of thalidomide, therefore, have a broad range of effects affecting tumor growth directly and indirectly by alteration of the tumor microenvironment.

**Bortezomib.** Bortezomib is a proteasome and NF-kB signaling pathway inhibitor with potent anti-MM activity. Bortezomib also inhibits MM-BMSC interactions, impairs osteoclastogenesis, and stimulates mesenchymal stem cell differentiation to OB and, therefore, actively modulates bone remodeling in MM (83–85). The anabolic effects of bortezomib are mediated by p38 inhibition at early timepoints and, at later timepoints, by impairment of NF-kB signaling and AP1 inhibition (84). These effects have been confirmed in the clinical setting by upregulation of OB activation markers and downregulation of bone-resorption markers in patients treated with bortezomib (87).

**Signaling pathway inhibitors.** Several signaling pathways are involved in MM cell growth and survival but also modulate MM-BMSC interactions and OC differentiation. Therefore, specific inhibition of these pathways leads to both antitumor effects and alterations in the MM niche. MAPK inhibitors, such as extracellular signal regulated kinases (ERK) and p38 inhibitors, block early OC differentiation, and in in vivo models of MM, they control tumor growth and reduce OCs number (49, 88).

HSP 90 inhibitors, in particular SNX-2112, showed a broad range of effects on the MM microenvironment (89). Importantly, the anti-OC effects of SNX-2112 were mediated by downregulation of ERK signaling and the transcription factors c-fos and PL1.

**Future Directions**

Although OCs are a critical player in the pathogenesis of bone disease, other cell types such as OBs and BMSCs are affected in MM and contribute to the development of osteolysis. Therefore, effective therapeutic strategies to overcome MM-induced bone disease should target the OB-OC axis, combining bone-anabolic with anticatabolic agents. Current clinical trials are studying the benefits of combination strategies such as BAFF inhibitors and bortezomib, or DKK1-neutralizing antibodies and bisphosphonates. Novel agents with dual activity on bone remodeling, such as ACE-011, may also result in improvement of bone disease besides prevention of osteolytic lesions. Therefore, agents restoring bone balance in MM represent a novel strategy to overcome osteolytic disease and, more provocatively, to create a hostile niche for MM tumor growth.

**Disclosure of Potential Conflicts of Interest**

N. Raje, commercial research grant, Acetylone, AstraZeneca; consultant, Celgene, Amgen, Novartis. G. D. Roodman disclosed no potential conflicts of interest.

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