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NEWS

Multiple myeloma bone disease: targeting osteoclasts and osteoblasts

Neil A Andrews

International Bone and Mineral Society, Chicago, IL, USA.

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Multiple Myeloma Bone Disease: Novel Insights into Pathogenesis and Management, *IBMS BoneKEy's* eleventh overall and third cancer and bone-themed webinar, stressed the importance of targeting both the bone-resorbing and bone-forming cells of the skeleton

Introduction

Good bone health depends on a balance between bone formation carried out by osteoblasts and bone resorption carried out by osteoclasts. Of the many factors that can tilt this equilibrium, two key molecular signaling pathways stand out. On one side is the receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL) pathway. Here, osteoblasts produce RANKL that binds to its receptor, RANK, on the surface of osteoclast precursors, which stimulates those precursors to develop into mature, bone-resorbing osteoclasts. The activity of osteoprotegerin (OPG), a decoy receptor for RANKL, keeps this process in check by inhibiting the binding of RANK to RANKL. Meanwhile, on another side is the Wnt-signaling pathway in which the binding of Wnt to its low-density lipoprotein receptor-related protein 5/6 receptor on the surface of osteoblast precursors pushes those cells to develop into mature, bone-forming osteoblasts. Like the RANK/RANKL pathway, the Wnt-signaling pathway also has its own inhibitors. In this case, the sclerostin and Dickkopf-1 (DKK-1) proteins serve as the brakes.

That serious bone disease is seen frequently in multiple myeloma should come as no surprise, considering that myeloma cells affect both the RANK/RANKL and Wnt-signaling pathways through effects on the natural inhibitors of those pathways and via additional mechanisms as well. In 'Multiple Myeloma Bone Disease: Novel Insights into Pathogenesis and Management', *IBMS BoneKEy's* eleventh overall webinar (http://www.nature.com/bonekey/webinars/index.html?key=webinar11) and third to focus specifically on cancer and bone, presenter Evangelos Terpos (University of Athens School of Medicine, Greece), described how RANK/RANKL and Wnt-signaling are upset in the bone marrow microenvironment during multiple myeloma, pointing to evidence from patients that confirms what laboratory studies of multiple myeloma bone-disease pathogenesis suggests. Dr Terpos also discussed the management of multiple myeloma patients, with a focus on the clinical trials supporting the use of bisphosphonates, the bone field's mainstay of treatment for osteoporosis, as well as on evidence favoring treatment with the bone field's newest approved anti-resorptive, denosumab. However, because multiple myeloma cells adversely affect both bone resorption and bone formation, treatments that target only the osteoclast address just one facet of the problem. Consequently, multiple myeloma investigators are looking to new agents that target the osteoblast, and Dr Terpos described the potential that such bone-building agents may eventually have in the treatment of multiple myeloma bone disease. Moderated by Philippe Clézardin (INSERM and the University of Lyon, France), *IBMS BoneKEy* Associate Editor for cancer and bone content, and featuring panelists David Roodman (Indiana University, US) and Massimo Massaia (University of Torino and CERMS, Italy), the webinar concluded that the combination of anabolic agents with anti-resorptive drugs is the future of multiple myeloma bone-disease treatment.

Multiple Myeloma Bone Disease: Pathogenetic Mechanisms

The data are clear that bone disease is a very serious problem in multiple myeloma patients, causing great pain and suffering.[1] 'Bone disease is the most frequent complication of multiple myeloma, present in up to 80% of patients at diagnosis,' Dr Terpos began his presentation. 'The bone disease seen in multiple myeloma is characterized by osteolytic bone lesions secondary to increased bone resorption and impaired bone formation, which leads to pathological fractures, osteoporosis, hypercalcemia, bone pain and spinal cord compression,' Dr Terpos said. Considering the effect of myeloma cells on the RANK/RANKL pathway in the bone marrow microenvironment, it is no wonder. First, multiple myeloma cells express the $\alpha 4\beta 1$ integrin, a receptor that allows the cancerous cells to bind to vascular cell-adhesion molecule-1 (VCAM-1) on the surface of bone marrow stromal cells. This binding stimulates the latter to produce many growth factors, chemokines and cytokines, including RANKL, that push osteoclast precursors to develop into mature, activated cells. Meanwhile, myeloma cell binding to bone marrow stromal cells decreases OPG levels, as does

the binding of myeloma cells directly to OPG through the cell surface receptor CD138. This decrease in OPG levels means that RANK/RANKL binding, with its consequent effects on osteoclast precursors, continues apace. Ultimately, it is the activation of osteoclastic bone resorption that releases growth factors from the bone matrix, which further fuels myeloma cell growth in a 'vicious cycle' taking place in the bone marrow microenvironment.

Clinical studies of multiple myeloma patients bolster the case for an important role of deleterious changes in the relative levels of RANKL and OPG, alterations that occur not just in the bone marrow microenvironment but in the serum as well. For instance, serum RANKL/OPG ratios correlate with the extent of lytic bone disease observed in multiple myeloma patients, with higher ratios seen in those with more extensive bone disease. In addition, these ratios also predict survival, with higher serum RANKL/OPG ratios being associated with poorer survival. As with the relative levels of RANKL and OPG, changes in the levels of other molecules in the bone marrow microenvironment have also been found in multiple myeloma patients. For instance, expression of MIP-1α, a chemokine released by myeloma cells that activates osteoclasts, is correlated with the extent of bone disease. Indeed, biopsies of bone marrow plasma cells taken from multiple myeloma patients reveal that the greater the expression of MIP-1, the worse the bone disease. Finally, as with the relative levels of RANKL/OPG, serum MIP-1α levels also correlate with survival, with higher levels associated with poorer survival.

However, bone-resorbing cells are not the only ones influenced by myeloma cells in the bone marrow microenvironment; bone-forming osteoblasts are affected too. Indeed, myeloma cells express Dickkopf-1 and sclerostin, as well as other inhibitors like activin A, all of which blunt the activity of osteoblasts. Here too, clinical data support the insights gained from studying the pathogenesis of myeloma cell function during laboratory investigations. For instance, Dr Terpos pointed to the reduced levels of bone alkaline phosphatase, an enzyme and marker of bone formation made by osteoblasts, in multiple myeloma patients, indicating a reduction in bone formation. This effect can be attributed to increased expression of Dickkopf-1, as multiple myeloma patients show high levels of this inhibitor in marrow and blood plasma. Meanwhile, circulating sclerostin levels are also increased in patients, with those suffering from relapse exhibiting the highest levels of this protein. Along these lines, Dr Terpos noted the interesting finding that sclerostin levels are elevated even in patients who are at the plateau phase of their disease. 'This may be one of the reasons why we see strong inhibition of osteoblast function even in patients who have responded to therapy,' Dr Terpos said.

Finally, in a perfect illustration of how both aspects of bone remodeling, formation and resorption, are affected in multiple myeloma, Dr Terpos presented data submitted for publication demonstrating a role for activin A, a member of the TGF-β superfamily of proteins, in the pathogenesis of the disease. Indeed, in multiple myeloma, activin A, which is produced mainly by bone marrow stromal cells, both stimulates osteoclasts and inhibits osteoblasts. Furthermore, clinical studies show that multiple myeloma patients with osteolytic lesions exhibit increased bone marrow plasma levels of the protein, and circulating levels of activin A are also increased at the time of diagnosis, and are highest in patients who have relapsed.

Managing Multiple Myeloma Patients with Anti-resorptive Drugs and Bone Anabolics

Considering the effects of myeloma cells on both osteoblasts and osteoclasts, bone disease is common in multiple myeloma patients, with about 50% of patients exhibiting skeletal-related events (SREs) such as pathological fractures (affecting about 37% of patients), the need for radiation or surgical intervention (34% and 5%, respectively) or spinal cord compression (3%). One approach to managing these patients is to inhibit the osteoclast with anti-resorptive drugs. Bisphosphonates have become the standard treatment in this regard, with double-blind, placebo-controlled clinical trials of clodronate, pamidronate and zoledronic acid having demonstrated the ability of these agents to reduce SREs and pain.[2] Double-blind, randomized clinical trials comparing one bisphosphonate to another have also provided clinical investigators with important data. For example, results indicate that zoledronic acid and pamidronate are equally good at reducing SREs in multiple myeloma patients, though a larger reduction from baseline in levels of serum N-telopeptide, a marker of bone resorption, was seen with zoledronic acid (and a non-prospective study from Dr Terpos' group found that higher baseline N-telopeptide levels in multiple myeloma patients were associated with poorer survival). Another double-blind, randomized controlled trial that compared 30–90 mg of pamidronate in multiple myeloma patients suggests that the lower dose is sufficient to manage their bone disease.

With regard to bisphosphonate comparison trials, Dr Terpos focused much of his attention on the randomized, controlled MRC Myeloma IX trial, the largest trial of its kind, including nearly 2000 patients.[3] This study randomized patients to receive 4 mg of zoledronic acid every 3–4 weeks or 1600 mg of oral clodronate daily, with patients in one arm of the trial receiving intensive inductive chemotherapy and patients in the other arm receiving non-intensive inductive chemotherapy. In terms of SREs, zoledronic acid was significantly better than clodronate, as patients taking the former exhibited a statistically significant 24% relative reduction in SREs compared with those taking the latter. Sub-analyses of the overall study population revealed that the zoledronic acid group had statistically significant decreases in vertebral and other fractures, as well as in new bone lesions, though no statistically significant differences were found in the need for radiotherapy or surgery to bone or spinal cord compression.

Myeloma experts were also heartened to see what earlier placebo-controlled trials of clodronate and pamidronate had hinted at in subgroup analyses: a direct anti-cancer effect of bisphosphonates. Indeed, in MRC Myeloma IX, patients receiving zoledronic acid exhibited a statistically significant 5.5-month increase in overall survival, compared with those taking clodronate. Recent unpublished data from a subgroup analysis also show that, compared with placebo, zoledronic acid produced a nearly 10-month overall survival advantage in patients suffering from bone disease at baseline, whereas there were no such statistically significant differences in patients who had no bone disease at baseline. 'This survival advantage is probably due to an indirect effect on osteoclast support of myeloma cell growth, which sends the message that inhibition of osteoclast function is very important in multiple myeloma treatment,' Dr Terpos explained. Meta-analysis data also show the superiority of zoledronic acid to clodronate in terms of overall survival and SREs. Finally, Dr Terpos noted that although osteonecrosis of

the jaw was more common in the zoledronic acid group, this complication can be avoided with preventive measures such as the use of antibiotics before dental procedures.

Currently, recommendations from the American Society of Clinical Oncology, the European Myeloma Network, the International Myeloma Working Group and the National Comprehensive Cancer Network all state that all multiple myeloma patients exhibiting osteolytic lesions, or osteopenia or osteoporosis, should be treated with a bisphosphonate at the time of diagnosis, with the European Myeloma Network recommending that patients undergoing chemotherapy also receive one as well. Furthermore, because the MRC Myeloma IX trial found that zoledronic acid was superior to clodronate in reducing SREs, both in patients with bone lesions at baseline and in patients without such lesions, it is important to treat all multiple myeloma patients with a bisphosphonate, regardless of lesion status, as is stated in guidelines from the British Society for Haematology. However, Dr Terpos did caution that careful thought must be given to this recommendation, because the number of patients with no lytic disease in MRC Myeloma IX was much higher than clinical investigators are accustomed to seeing. As a result, Dr Terpos noted that for patients who exhibit no bone lesions upon skeletal radiography, his clinical practice is to use bisphosphonates only when other imaging techniques do detect bone lesions. Furthermore, because of the effect of zoledronic acid on survival, the British Society for Haematology recommendations also say that this powerful bisphosphonate should be the physician's first choice. Finally, with regard to how long multiple myeloma patients should be treated with bisphosphonates, although there is no consensus on this question, unpublished data from MRC Myeloma IX show that 2 years of treatment may be warranted because zoledronic acid continues to exhibit a cumulative reduction in SREs at 2 years of follow-up, compared with clodronate. Investigators hope that future results from MRC Myeloma IX will provide some guidance for treatment decision-making beyond 2 years.

Is there a role for the bone field's newest antiresorptive therapy, denosumab, in the treatment of multiple myeloma bone disease? In this regard, investigators were disappointed in the results of a randomized, double-blind, phase-3 trial published last year that compared denosumab to zoledronic acid in patients with advanced cancer and bone metastases (excluding breast and prostate cancer) or multiple myeloma.[4] In the entire study population, no statistically significant differences between the two drugs were found for time to first on-study SRE or for time to first-and-subsequent SREs. One cause for concern was a *post-hoc* analysis of the multiple myeloma patients from this trial, who exhibited a 2.3-fold increased risk of death with denosumab, compared with zoledronic acid. Dr Terpos cautioned, however, that the study was not powered to show a difference in survival, nor did it stratify patients according to the multiple myeloma therapy they were receiving. Experts are looking to a larger clinical trial (soon underway) comparing denosumab to zoledronic acid, one that will stratify patients according to therapy, to provide more reliable data that will clarify the role of denosumab in the multiple myeloma setting.

The Future

In the final part of his presentation, Dr Terpos turned to bone anabolics that hold promise in treating multiple myeloma bone disease; future therapies are likely to combine anti-resorptive drugs with these bone-building agents. One such anabolic is bortezomib, a proteasome inhibitor that prevents the activation of NF-κB, a crucial osteoclast transcription factor. In research published in 2010 by Dr Terpos and colleagues, a subset of relapsed multiple myeloma patients with low bone mineral density and non-extensive lytic disease who received bortezomib, along with dexamethasone and zoledronic acid, at the time of first relapse showed a statistically significant increase in bone mineral density compared to before they started bortezomib. Meanwhile, a 2011 prospective study of relapsed or refractory myeloma patients who received bortezomib found that such patients exhibited increased anabolic activity, as seen in large increases in the bone volume/total volume ratio. Finally, *post-hoc* data from a phase-3 study that investigated the effects of adding bortezomib to standard chemotherapy in newly diagnosed multiple myeloma patients documented striking improvements in lytic lesions of the skull, providing further evidence of an anabolic effect.

In addition to bortezomib, anti-DKK-1 antibodies may also have great potential as an anabolic agent for the treatment of multiple myeloma bone disease. Dr Terpos presented results from mouse studies showing increased bone formation and reductions in lytic lesions in animals that received the antibodies. The multiple myeloma field also keenly awaits results from a phase-1/2 study of anti-DKK-1 antibodies in multiple myeloma patients. A final candidate anabolic agent is sotatercept, an activin A antagonist; unpublished data show positive effects on bone mineral density. 'Novel agents in combination with zoledronic acid seem to be the future for the management of multiple myeloma-related bone disease,' said Dr Terpos, concluding the webinar on an optimistic note.

Conflict of Interest

The author declares no conflict of interest.

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