Scientific & Clinical

BONE DISEASE IN MULTIPLE MYELOMA

Myeloma Today in conversation with Dr. Matthew T. Drake

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Please tell us about your medical background.

The 2010 annual meeting of the American Society of Clinical Oncologists I studied biology at Harvard and worked at the Massachusetts General Hospital with a group interested in bone biology, so my interest in bone started in college. I received my medical degree and completed my doctoral work in Molecular and Cell Biology at Washington University (St. Louis, MO). Subsequent to that, I did my residency and fellowship in Internal Medicine/Endocrinology at Duke University (Durham, NC), followed by two more years there as a Postdoctoral Fellow. In 2006, I came to Mayo Clinic (Rochester, MN) as a Postdoctoral Clinical and Research Fellow in Endocrinology. Since 2007, I have been Senior Associate Consultant (Endocrinology) and Assistant Professor of Medicine (College of Medicine) at Mayo Clinic.

Recently you were invited to join the IMF's International Myeloma Working Group (IMWG). How did you develop an interest in myeloma?

Endocrinology can be subdivided into several sub-specializations, and my primary interest is in metabolic bone disease. It was not until I came to Mayo in 2006 that I started to work in myeloma. Clinically, I spend about a quarter of my time seeing patients with metabolic bone diseases, including myeloma and MGUS (monoclonal gammopathy of undetermined significance).

In brief, please describe myeloma bone disease.

In a healthy individual, there is a balanced continuous process of removal of old bone by osteoclasts and replacement with new bone by osteoblasts. This process is normally well coupled, so that on average we completely replace our skeletons every 6-7 years. In a number of bone diseases, there is increased bone breakdown (resorption), but myeloma bone disease is rather distinct from other bone diseases because it also involves decreased bone formation

(remodeling). In myeloma, there is both increased activation of osteoclasts and suppression of osteoblasts. Thus in myeloma, bone is being destroyed at an accelerated rate *and* not being then actively rebuilt.

How is myeloma bone disease diagnosed and assessed?

In myeloma, bone scans can be misleading because they are based on the bone formation process. However, in myeloma, the bone building cells are not working properly. As a result, it is easy to underestimate the extent of myeloma bone disease. Thus in myeloma, plain X-rays and MRIs are more accurate than bone scans.

What other options are there?

In myeloma, biochemical bone turnover markers of bone metabolism may be helpful in assessing both bone formation and resorption, and may provide useful information on myeloma disease activity in bone. Bone turnover markers have also been used for the early diagnosis of bone lesions, for evaluating the extent of myeloma bone disease, and to measure response to anti-myeloma therapies. However, there has been no consensus for the use of bone turnover markers in myeloma. The recent IMWG report, published in Leukemia, summarizes the current data for the use of markers of bone remodeling to assess the extent of myeloma bone disease and to monitor bone turnover during anti-myeloma treatment, proposes markers that may have a role in caring for patients with myeloma, and presents novel markers that may be of interest in the future.

Is there a correlation between myeloma bone disease and the myeloma itself?

It does not appear that the myeloma cells are the direct cause of bone loss, but they affect the bone cells that, in turn, cause the bone loss. In general, patients who have more extensive myeloma tend to have more bone damage. Approximately 85-90% of myeloma patients have some sort of lytic (destructive) bone disease as a complication of their myeloma. The majority of myeloma patients have bone lesions that result in skeletal-related events (SREs).

It is also known that patients with MGUS, even those who never progress to myeloma, are at a higher risk for osteoporotic fractures than individuals who do not have MGUS. I think it is reasonable for MGUS patients to have their baseline bone mineral density determined.

Patients with MGUS or myeloma may experience fractures, radiation or surgery to bone, spinal cord compression, and hypercalcemia (elevated calcium levels in the blood). Bone lesions rarely heal even in those myeloma patients who have achieved a complete remission (CR). Without

therapy for their bone disease, more than half of myeloma patients with stage III disease will experience at least one SRE over the span of two years. On average, patients who do not have myeloma bone disease have a better prognosis than those who do.

Please give us some examples of bone markers and their use in myeloma.

Bone markers help assess bone turnover. In myeloma the bone resorption markers are more useful than the bone formation markers in assessing bone disease, and they have also been shown to correlate with stage of myeloma. The bone resorption markers that appear to be more useful in myeloma include urinary NTX, serum CTX, and serum ICTP. In my practice, I frequently use the serum CTX marker with myeloma patients because it's a simple blood test done fasting in the morning, and it gives me a some sense of whether the disease is active or not, especially if I track the patient over an extended time.

What about anti-resorptive therapy?

Biochemical bone turnover markers have been used in studies of myeloma patients to monitor response to bisphosphonate therapy, and in studies aimed at determining those patients who would most benefit from bisphosphonate therapy to decrease bone resorption. Data from such studies demonstrate that while the majority of patients have a good clinical response to bisphosphonate therapy and decrease their bone resorption markers, there are some myeloma patients who do not respond to, or who stop responding to bisphosphonate therapy over time.

How would you assess the risk of ONJ?

With improved recognition of osteonecrosis of the jaw (ONJ), and improved dental care, the risk of developing ONJ has significantly decreased. The rate of ONJ is currently about 2-4%. In addition to our heightened awareness and improved dental care efforts up front, we look forward to studies aimed at determining if decreased cumulative bisphos phonate dosing and decreased dosing frequency will further decrease the incidence of ONJ.

What about denosumab, a bisphosphonate currently in clinical trials?

Denosumab is a potent new osteoclast inhibitor. It targets the same cells but uses a completely different mechanism of action than the bisphosphonates Zometa® (zoledronic acid) and Aredia® (pamidronate). It has a much shorter duration of action, staying in the bones approximately 3-6 months, not 5-10 years like we believe some other bisphosphonates do. Also, it does not seem to have an adverse effect on renal function. In a recent study of 1776 patients with solid tumors or myeloma who had not previously received intravenous bisphosphonates,

those who were randomized to receive 120 mg of subcutaneous denosumab attained results similar to the patients who received intravenous zoledronic acid every 4 weeks. Denosumab also reduced urinary NTX levels by more than 80% within the first month. However, in the subgroup of patients with myeloma (approximately 10% of the total study population), denosumab was associated with significantly worse survival. As a result, the FDA did not approve the drug for treatment in myeloma. Further studies are needed to evaluate the safety and efficacy of denosumab in myeloma.

What is the effect of novel anti-myeloma agents on bone markers?

The effect of novel drugs – thalidomide (Thalomid®), lenalidomide (Revlimid®), and bortezomib (Velcade®) – on bone metabolism in myeloma has been evaluated in several studies. The available data indicate that immunomodulatory drugs have more effect on osteoclast activity than on osteoblast activity. Two clinical phase II trials have studied the effect of thalidomide on bone metabolism in myeloma. One study of relapsed/refractory patients showed that after six months of therapy with thalidomide plus dexamethasone (TD) there was a significant reduction of serum levels of some bone markers. The other study of newly diagnosed myeloma patients showed that the combination of TD and zoledronic acid (Zometa®) for four months produced a significant reduction of urinary NTX and serum CTX in patients who responded to therapy. There is limited data on the effects of lenalidomide on myeloma bone disease. Studies have shown that bortezomib may decrease bone resorption and increase bone formation, but data suggest that the beneficial effect of bortezomib may be reduced when it is combined with other anti-myeloma agents.

What do you anticipate in your field in the near future?

Better understanding bone disease and the bone marrow microenvironment, the area within the bone where myeloma cells grow, is crucial to controlling and/or curing myeloma. Clinical trials are needed before biochemical markers of bone remodeling become part of the routine clinical care of myeloma patients. There are ongoing studies with breast cancer patients and in patients with other forms of cancer and bone metastases, and trials in myeloma are anticipated in the future.