Despite the significant progress that has occurred in recent decades in the treatment of many advanced malignancies, skeletal morbidity remains a major problem for patients affected by cancers that metastasize to or grow primarily within bone.[1] Thus as patients with a variety of malignancies survive longer, therapies to limit cancer-associated as well as treatment-associated skeletal complications have become increasingly important for the provision of optimal patient care.

Multiple Myeloma Bone Disease: The Nature of the Problem

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal expansion of malignant plasma cells within the bone marrow. In the United States, nearly 20,000 patients are diagnosed with MM each year, with roughly 11,000 cancer-related deaths occurring annually.[2] Although median survival of MM patients is only 3 to 4 years from the time of diagnosis, the recent development of novel chemotherapeutic agents has resulted in an increasing proportion of patients who achieve prolonged periods of survival, including some with survival of greater than 10 years.[3,4] Accordingly, improving quality of life by limiting disease-associated complications is an important aspect of caring for all patients with MM.

For many patients, a pathologic fracture or severe bone pain resulting from the lytic destruction of bone within the marrow cavity is the sentinel event that precipitates a diagnosis of MM.[5] Indeed in the year preceding diagnosis, MM is associated with a 16-fold increased risk for fracture.[6] Bone pain (which is usually worsened by movement and improved by rest) is present in approximately 60% of patients at the time of MM diagnosis.[7] Roughly 90% of MM patients will ultimately suffer from osteolytic lesions[8] and approximately 60% will develop a fracture at some point during the course of their disease.[6]

Further, the presence of a pathologic fracture in MM patients is associated with at least a 20% increased risk of death.[9] Skeletal-related complications cause significant morbidity and mortality in affected patients. Although osteolytic lesions may occur at any skeletal site, those most commonly affected include the central skeleton (spine, ribs, and pelvis), skull, and proximal long bones (humeri and femora). Frequent skeletal-associated complications include pathologic fractures (particularly vertebral), intractable bone pain, hypercalcemia of malignancy, and spinal cord compression.[10] Importantly, even a significant MM cell response to chemotherapy may not prevent the progression of skeletal disease,[11] and patients in complete remission generally do not demonstrate any radiographic evidence of bone lesion healing.[12]

Within the adult skeleton, there is normally a balanced bone-remodeling sequence as osteoclast-mediated resorption of fatigued or damaged bone is followed both spatially and temporally by osteoblast-mediated new bone formation. Disruption of this balance leads to bone loss, impaired bone structural integrity, and the potential for skeletal complications. It is now clear that MM bone disease results from both an increase in osteoclast-mediated bone resorption and a reduction in osteoblast-mediated new bone formation.[13] Together, this imbalance of bone cell activity results in the development of lytic bone lesions, and also likely contributes to the systemic bone loss and approximately twofold increased risk of osteoporotic fractures found in MM patients.[6,14]

In recent years, our understanding of the altered osteoclast and osteoblast activity that underlies MM bone disease has increased markedly, due to the identification of factors made by MM cells or within
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the local bone marrow microenvironment that affect bone cell function. Localization of MM cells adjacent to sites of lytic bone destruction suggests that locally produced factors play an important role in the development of osteolytic lesions, whereas the generalized bone loss that also occurs suggests that systemic factors are also likely important. Increases in osteoclast activity appear to result at least in part from increased levels of factors such as RANK ligand[15] and macrophage inflammatory protein (MIP)-1alpha.[16,17] Likewise, the most prominent osteoblast inhibitory factor identified to date in subjects with osteolytic MM is dickkopf 1 (DKK1), with increases in DKK1 levels correlating with the extent of MM bone disease.[18] Clinical trials are currently underway to evaluate the effects of modulating each of these molecules, as well as other identified molecular targets, and may yield important approaches to the future treatment of MM bone disease. Finally, it is important to note that several recently approved agents used for the treatment of MM also appear to affect bone cell function. Thus, an immunomodulatory drug has recently been shown to inhibit osteoclast formation,[19] while a proteasome inhibitor has been shown to both induce osteoblast differentiation and suppress osteoclast function.[20,21] Thus, it will be important that future studies assessing therapies for MM bone disease be evaluated in the setting of these bone-active molecules now widely used as chemotherapeutic agents for the treatment of multiple myeloma.

Skeletal Imaging

As noted above, bone disease in MM reflects both regions of localized osteolytic destruction as well as generalized bone loss resulting in osteopenia/osteoporosis. Indeed, the identification of osteolytic lesions is one of the criteria used to diagnose MM. As such, skeletal imaging is an essential component in the evaluation of any patient either suspected or confirmed to have MM. As recently articulated in guidelines developed by the International Myeloma Working Group (IMWG), a metastatic bone survey with plain radiographs is the initial imaging modality of choice at the time of diagnosis. This survey should provide images of all areas of possible myeloma involvement including the entire spine, skull, chest, pelvis, humeri, and femora.[7,22] However, it is important to recognize that plain radiographs do have limitations, including the ability to detect osteolytic lesions only after the loss of at least 30% of trabecular bone, and the inability to differentiate between malignant and nonmalignant (corticosteroid-associated or senile) causes of generalized bone loss.[23] Despite these limitations, however, conventional skeletal surveys demonstrate some form of skeletal involvement (lytic lesions, fractures, or diffuse bone loss) in nearly 80% of patients. The most commonly affected sites are those with active hematopoiesis, and include the vertebral bodies, ribs, skull, shoulders, pelvis, and proximal humeri and femora. Notably, the IMWG recommends that even in the absence of skeletal symptoms, radiographic identification of lytic bone disease categorizes MM patients as “symptomatic” and warrants the initiation of MM therapy.[24] Despite the high rate at which skeletal lesions are identified by plain radiographs, approximately 10% to 20% of patients with complete skeletal surveys do not reveal any evidence of skeletal disease.[25] Particularly in subjects with bone pain but no radiographic correlate identified on plain films, the use of alternative imaging methods, such as magnetic resonance imaging (MRI), can be very helpful for the detection of bone involvement. As recently reported, MRI permits the detection of both diffuse and focal bone marrow infiltration even in the absence of bone loss or local osteolysis on standard skeletal surveys, and detected focal lesions (in the spine, pelvis, and sternum) with a higher frequency than found by plain radiographs.[26] Importantly, however, the same study demonstrated that standard metastatic bone surveys were able to detect some focal lesions (particularly in the ribs and proximal long bones) at a higher frequency than found by MRI. As such, the clinical utility of routinely using MRI to evaluate for skeletal involvement in subjects with myeloma remains to be determined.

However, as recommended by the recent IMWG guidelines, patients with an apparent solitary plasmacytoma should receive an MRI of the entire spine in addition to a standard skeletal survey.[22] Finally, MRI is the method of choice for evaluating suspected spinal cord and/or nerve compression, although computed tomography (CT) can be used in situations in which MRI is not available.

Lastly, because bone scans assess new bone formation by osteoblasts (whose activity is severely suppressed in MM patients), bone scans frequently underestimate the extent of MM bone disease and are of little clinical use for either the initial diagnostic evaluation or in following MM patients longitudinally.[27] Likewise, the routine use of positron emission tomography (PET) imaging is not recommended at this time, although trials assess the utility of PET-based techniques are currently underway.[22]
Treatment

The frequency, severity, and impact on quality of life and overall survival of skeletal-related complications suffered by patients with MM make efforts to treat MM bone disease of paramount importance. For patients with established skeletal disease, incident or impending fractures, or spinal cord compression, appropriate care is necessary to limit the risk for future complications. As will be discussed below, intravenous bisphosphonate therapy is the current cornerstone of therapy. However, radiation therapy, orthopedic or neurosurgical intervention, and kyphoplasty or vertebroplasty are all important components that are at times necessary for the treatment of MM-associated bone disease, and must be decided upon on a case-by-case basis.

As noted, current clinical approaches aimed at limiting skeletal-related complications in patients with MM involve the use of intravenous bisphosphonates. Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate. Due to their affinity for hydroxyapatite (the major constituent of bone), bisphosphonates are incorporated into sites of active osteoclast-mediated bone resorption on the bone surface. This allows bisphosphonates to achieve a high local concentration and thereby affect osteoclast activity. Bisphosphonates not bound to the skeleton are rapidly cleared from the circulation via renal elimination. Skeletal retention is believed to reflect host factors (including the prevalent rate of bone turnover which determines binding site availability, and renal function which determines clearance of unbound bisphosphonate) and bisphosphonate potency for bone matrix.[28,29]

Worldwide, three bisphosphonates are approved for treatment of bone disease in MM, although only two are available in the United States. One early-generation oral bisphosphonate differs from the later-generation intravenous bisphosphonates due to the lack of a nitrogen-containing side chain. This difference accounts for the ability of nitrogen-containing bisphosphonates to much more potently limit osteoclast-mediated bone resorption. This is achieved through inhibition of the enzyme farnesyl pyrophosphate synthase following osteoclast endocytosis of bisphosphonate from the bone surface, resulting in osteoclast apoptosis. Although the precise biologic half-lives of the different nitrogen-containing bisphosphonates in bone remain unknown, they are estimated to be at least 10 years.[30]

Despite bisphosphonate therapy, approximately 50% of patients with myeloma experience a skeletal-related event at the time of relapse.[31]. This may in part reflect the capacity of bisphosphonates to indirectly target only mature osteoclasts and not to halt the production of osteoclast progenitor cells. Further, bisphosphonates do not appear to affect osteoblast activity, and thus do not induce new bone formation.

Bisphosphonate therapy is not without risk, as MM patients who receive bisphosphonates have the highest incidence (among all groups of patients with malignancies receiving bisphosphonate therapy) of avascular osteonecrosis of the jaw (ONJ), exceeding 10%.[32,33]. Both intravenous bisphosphonates are effective at reducing skeletal related events in MM, and either may be considered as first-line therapy. Specific practice guidelines regarding the frequency and duration of bisphosphonate use, optimization of treatment in specific patient populations (including patients with renal impairment), the necessity of monitoring renal function prior to repeated bisphosphonate dosing, and the potential for the development of ONJ have recently been published. These guidelines provide practical recommendations for the use of bisphosphonates for the prevention and treatment of bone disease in MM,[34,35]

Complications Associated With Bisphosphonate Use

No potential adverse effect of bisphosphonate therapy has been more widely reported in the popular and clinical literature than ONJ. While current estimates of ONJ related to oral bisphosphonate therapy for osteoporosis are approximately 1 in 10,000 to 1 in 100,000 patient treatment years,[32] the incidence of ONJ in oncology patients (and in particular patients with MM) has approached 10% in some case series. Risk factors for ONJ development include poor oral hygiene, invasive dental procedures or denture use, and prolonged exposure to high doses of intravenous bisphosphonates.[36] Whether concomitant chemotherapy or glucocorticoid use increases the risk for ONJ is unknown.[37]

Care for ONJ is largely supportive, with antiseptic oral rinses, antibiotics, and limited surgical debridement as necessary. Performance of a careful oral examination for active or anticipated dental issues, and discussion of the importance of maintaining good oral hygiene after starting treatment, may be helpful in limiting the risk for ONJ development. Intriguingly, a reduction in the dosing schedule, with intravenous bisphosphonate therapy given monthly for 1 year and then every 3 months thereafter, was recently shown to significantly decrease the incidence of ONJ in MM patients when compared to a schedule in which patients received monthly infusions.[38] Further, a recent
A retrospective study suggested that antibiotic prophylaxis before invasive dental procedures may also be an effective approach to reducing the incidence of ONJ in MM patients receiving intravenous bisphosphonate therapy.[39] Additional prospective studies, however, will be necessary to validate these provocative findings.

Recently, measurement of the bone resorption marker carboxy-terminal collagen crosslinks (CTx) has been postulated to predict the risk of developing ONJ. In a report of 30 cases of ONJ associated with oral bisphosphonate use, Marx and colleagues suggested that patients receiving bisphosphonate therapy can be stratified as low, moderate, or high risk for the development of ONJ based upon a serum CTx levels.[40] Unfortunately, control subjects receiving bisphosphonates but who did not have ONJ were not included, nor were any indices of bone remodeling on any subject prior to bisphosphonate initiation available. Thus, while it is possible that measurement of bone resorption markers may be helpful in guiding decisions about the management of patients who present with ONJ, the data as presented do not support serum CTx testing to help identify patients at increased risk.[41] Accordingly, at present it is not recommended that measurements of serum markers for either bone resorption or formation be used to guide bisphosphonate therapy in patients with MM.[34,35]

Finally, it has recently been recognized that in some patients, prolonged bisphosphonate use appears to be associated with an increased risk for the development of atypical fractures (particularly subtrochanteric femoral fractures), a result which may be due to oversuppression of the normal bone remodeling process. Although first described in patients receiving oral bisphosphonate therapy,[42] similar cases have now been reported in MM subjects receiving intravenous bisphosphonate therapy.[43,44] Although uncommon, several consistent clinical features for these fractures have been described. These include the following: (1) fracture occurrence in the proximal or mid-femoral diaphysis, typically either spontaneously or as a result of low energy trauma; (2) a transverse or oblique (≤ 30º) appearance of the fracture on radiographs; (3) delayed healing; (4) a history of prolonged bisphosphonate therapy; and (5) the frequent occurrence of a prodrome of thigh pain, discomfort, or subjective weakness at the site of the subsequent fracture.[45,46] Importantly, plain radiographic imaging obtained prior to fracture may show thickened cortices and the presence of a localized cortical stress reaction, which may also be present in the contralateral femur. Thus, although bisphosphonates serve as the central pharmacologic approach to limit bone loss and skeletal-related events in MM, many questions regarding their optimal use for the treatment of multiple myeloma bone disease remain.

Conclusions

Bone disease in MM imposes a tremendous burden on patients in terms of both morbidity and mortality. At present, the standard of care for limiting progressive skeletal disability in patients with radiographically documented skeletal disease involves the use of intravenous bisphosphonate therapy, which can limit osteoclast-mediated skeletal resorption but does not lead to any replacement of lost bone. The identification of multiple factors dysregulated in MM bone disease, including RANK ligand and its soluble decoy receptor osteoprotegerin, MIP-1alpha, and the Wnt pathway inhibitor DKK1, has provided novel targets that are all being actively examined in trials designed to assess clinically relevant skeletal endpoints in MM patients. Lastly, the recent development of immunomodulatory agents and proteasome inhibitors with significant activity against MM tumor cells, but which also appear to affect bone cell function, may lead to improvements in the treatment of MM bone disease. Although much work has been done, new strategies to improve skeletal-related outcomes are necessary if we are to lessen the skeletal morbidity synonymous with MM, and ultimately provide our patients with the highest quality of care possible for the treatment of all aspects of their disease.

Financial Disclosure: The author has no other significant financial interest or relationship with the manufacturers of any products or providers of any service mentioned in this article.

This article was conceived of and fully funded by Amgen, and Amgen provided background direction for the article.

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