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Review Article

Myeloma bone disease: Pathophysiology and management

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ABSTRACT

Multiple myeloma bone disease is marked by severe dysfunction of both bone formation and resorption and serves as a model for understanding the regulation of osteoblasts (OBL) and osteoclasts (OCL) in cancer. Myeloma bone lesions are purely osteolytic and are associated with severe and debilitating bone pain, pathologic fractures, hypercalcemia, and spinal cord compression, as well as increased mortality. Interactions within the bone marrow microenvironment in myeloma are responsible for the abnormal bone remodeling in myeloma bone disease. Myeloma cells drive bone destruction that increases tumor growth, directly stimulates the OCL formation, and induces cells in the marrow microenvironment to produce factors that drive OCL formation and suppress OBL formation. Factors produced by marrow stromal cells and OCL promote tumor growth through direct action on myeloma cells and by increasing angiogenesis. Current therapies targeting MMBD focus on preventing osteoclastic bone destruction; however regulators of OBL inhibition in MMBD have also been identified, and targeted agents with a potential anabolic effect in MMBD are under investigation. This review will discuss the mechanisms responsible for MMBD and therapeutic approaches currently in use and in development for the management of MMBD.

1. Introduction

Multiple myeloma (MM) is the most frequent cancer to involve the skeleton with 80–90% of patients developing bone lesions during their disease course [1]. Myeloma bone lesions are purely osteolytic and are associated with severe and debilitating bone pain, pathologic fractures, hypercalcemia, and spinal cord compression, as well as increased mortality [2]. It is estimated that 20% of MM patients present with pathologic fractures, 40% develop a fracture in the first year after diagnosis, and up to 60% develop pathologic fractures over the course of their disease [3]. Additionally, patients with pathologic fractures have a 20% increase in mortality when compared to patients without pathologic fractures [4]. The bone destructive lesions can be extensive and severe [5] and bone pain, frequently centered on the chest or back and exacerbated by movement, is present in more than two-thirds of patients at diagnosis [6].

Multiple myeloma bone disease (MMBD) is distinct from the bone disease caused by other types of tumors that metastasize to bone and is marked by dysfunction of both bone formation and bone resorption [5]. While osteolytic metastases from MM and other malignancies induce osteoclastic (OCL) bone resorption, myeloma bone lesions are unique in that osteoblast (OBL) activity is severely decreased or absent [7,8]. Thus, bone scans in patients with MM frequently underestimate the extent of bone disease [9]. Furthermore, bone lesions in patients with myeloma rarely heal, even when a patient is in prolonged complete remission. MMBD can affect any bone, with predominant areas of involvement occurring in sites of red marrow, such as the vertebral bodies and ribs.

Current therapies targeting MMBD focus on preventing osteoclastic bone destruction. OCL activity is responsible for the bone destruction in myeloma and plays a pivotal role in MMBD through release of growth factors from the bone matrix during the bone resorptive process that enhance tumor growth. Recently, regulators of OBL inhibition in MMBD have also been identified, and targeted agents with a potential anabolic effect in MMBD are under investigation. In this review, mechanisms responsible for MMBD and therapeutic approaches based on these mechanisms will be discussed.

2. Prevalence and presentation of myeloma bone disease

The clinical presentation of myeloma is variable and approximately 11% of patients are initially asymptomatic [10]. (Disease in these patients is generally identified through routine laboratory studies.) Of symptoms reported at presentation, the most common is bone pain, which is present in more than two-thirds of patients

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[6]. The American Cancer Society estimates that there will be 21,700 new cases of myeloma diagnosed in 2012, including 12,190 in men and 9510 in women, with an estimated 4690 deaths [11]. The majority of myeloma patients are elderly, with a median age at diagnosis of 69 years and a median age at death of 74 years [12]. Treatment of MM has improved markedly over the past 30 years, with an increase in 5-year survival from 25% in 1975 to 41% in 2007, however the disease remains incurable and MMBD remains a major contributor to the morbidity and mortality of myeloma patients.

Up to 90% of MM patients have evidence of osteolysis in the form of generalized osteopenia or discrete lytic lesions over the course of their disease [13], and approximately 80% have radiologic evidence of bone involvement on skeletal survey [14]. Approximately 40% of patients with MM will develop a fracture in the first year after diagnosis, and up to 60% will develop pathologic fractures [3]. The bone destructive lesions in myeloma can be extensive and can affect any bone [5]. The predominant areas of involvement occur in sites of red marrow, such as the vertebral bodies (49%), skull (35%), pelvis (34%) and ribs (33% of patients) [15]. While there is an association between a patient's tumor burden and the number of lytic lesions present [16], and tumor burden, OCL number, and OCL resorptive surface area are correlated in bone marrow biopsies from MM patients [17,18], an individual's degree of bone disease does not have significant utility in predicting clinical outcomes. Additionally, bone lesions in patients with myeloma rarely heal, even when a patient is in prolonged complete remission.

Approximately 15% of newly diagnosed MM patients are hypercalcemic due to increased bone resorption, decreased bone formation, and impaired renal function, all of which are often exacerbated by immobility. Unlike other malignancies with metastatic bone involvement, parathyroid hormone related protein (PTHrP) is rarely over-produced by myeloma cells. Thus, the severity of hypercalcemia in patients with myeloma is not correlated with serum PTHrP levels and instead reflects tumor burden [6]. Symptomatic hypercalcemia can result in anorexia, nausea, vomiting, confusion, fatigue, constipation, renal stones, depression and polyuria, and is suggestive of a high tumor burden.

Finally, MM patients have accelerated bone loss when compared to age-matched controls. Bone mineral density is decreased in patients with MM as well as in patients with monoclonal gammopathy of undetermined significance (MGUS) [19,20], a clinically benign condition defined by a low level of monoclonal protein production and the absence of skeletal lesions [19].

3. Mechanisms of myeloma bone disease

MMBD is characterized by purely osteolytic bone destruction due to increased OCL activity and suppressed or absent OBL activity, and myeloma bone lesions have a characteristic “punched-out” appearance on x-rays. The bone marrow microenvironment in myeloma includes both extracellular and cellular elements, including osteoblasts, osteoclasts, endothelial cells, immune cells and MM cells that contribute to tumor growth and the bone destructive process. Multiple interactions within the bone marrow microenvironment in myeloma are responsible for the abnormal bone remodeling of MMBD (Fig. 1, panels A and B). Myeloma cells drive bone destruction that in turn increases tumor growth; highlighting the critical role that bone disease plays in myeloma. In addition, myeloma cells both directly stimulate OCL formation and induce cells in the marrow microenvironment to produce factors that drive OCL formation and suppress OBL formation. Immune cells contribute to the bone destructive process through production of cytokines and adhesion molecules that increase myeloma cell growth and enhance myeloma cell chemoresistance, increase osteoclastogenesis, suppress osteoblastogenesis, and drive T cell polarization from a predominantly Th1 phenotype to Th17 [21–24]. Factors produced by marrow stromal cells and OCL promote tumor growth through direct action on myeloma cells [25] and indirectly by increasing angiogenesis (Fig. 1, panel C). [26–28]. Finally, the bone resorption process itself releases immobilized growth factors such as TGFβ from the bone matrix that also drive tumor growth [29].

4. Pathogenesis of the increased osteoclast activity in myeloma

Histologic studies of bone biopsies from patients with MM demonstrate that increased OCL activity occurs adjacent to MM cells, suggesting that bone destruction in MM is a local event. This has led to the hypothesis that local cytokines produced or induced by MM cells are responsible for the increased OCL formation and subsequent bone resorptive activity in MM. These osteoclastogenic activating factors, (OAFs), directly increase OCL formation and activity and decrease production of osteoprotegerin (OPG), a soluble decoy receptor for receptor activator of NF-kB ligand (RANKL), a critical differentiation factor for OCLs produced by marrow stromal cells and OBL [30]. OAFs were initially identified in conditioned media from myeloma cell lines and found to stimulate bone resorption in bone organ culture systems [31]. Additional factors identified as OAFs important in MMBD include RANKL, MIP-1α, TNF-α, Interleukin 3 (IL-3), and IL-6. Interestingly, several of these OAFs also suppress OBL formation and/or support myeloma cells directly, indicating that they play multiple roles in MMBD.

Myeloma cells also stimulate cells in the marrow microenvironment, particularly marrow stromal cells and T cells, resulting in increased production of OAFs and decreased production of OCL inhibitory factors. Adhesive interactions between myeloma cells and bone marrow stromal cells via binding of surface VLA-4 ($\alpha_4\beta_1$ integrin) to VCAM-1 on stromal cells results in production of osteoclastogenic cytokines such as RANKL, M-CSF, IL-11, and IL-6 by marrow stromal cells and osteoclastogenic cytokines including macrophage inflammatory protein-1α (MIP-1α) and IL-3 by MM cells [32–35,36].

Additionally, OCLs themselves secrete factors that support myeloma cells [37], including IL-6 [38], annexin II [39], osteopontin [40], fibroblast activation protein [41], BAFF, and APRIL [42].

RANK/RANKL: The RANK/RANKL signaling pathway is a critical component of both normal and malignant bone remodeling. RANK is a transmembrane signaling receptor and a member of the tumor necrosis receptor (TNF) superfamily that is found on the surface of OCL precursors [43,44]. RANK ligand (RANKL) is expressed as a membrane-bound protein on marrow stromal cells and OBL that is secreted by activated lymphocytes. RANKL expression is induced by cytokines that stimulate bone resorption [45] such as PTH, 1,25-OH Vitamin D_3, prostaglandins [46,47], and myeloma cells themselves both produce and induce production of RANKL by marrow stromal cells via adhesive interactions described above, as well as by soluble factors produced by myeloma cells such as Dickkopf1 (DKK1) [48] and TNF-α [49]. In addition, RANKL further increases OCL formation and survival by binding to RANK [50].

OPG, the soluble décor receptor for RANKL, is critical for the regulation of lytic activity in both normal and myelomatous bone [51]. OPG is produced by OBL in the marrow and blocks the interactions of RANKL with RANK, limiting osteoclastogenesis. The RANKL/OPG ratio in the marrow microenvironment in MM is skewed in favor of RANKL [30], and the ratio of RANKL to OPG in the sera of myeloma patients impacts prognosis. Patients with high RANKL:OPG ratios have inferior survival as compared to