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Biology and management of myeloma-related bone disease

Evangelos Terpos [1,*], *Nikolaos Kanellias* [1], *Krzysztof Giannopoulos* [2,3,4]

[1] *Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece*
[2] *Experimental Hematooncology Department, Medical University of Lublin, Poland*
[3] *Department of Hematooncology and Bone Marrow Trasplantation, Medical University of Lublin, Poland*
[4] *Polish Myeloma Consortium, Poznan, Poland*

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ABSTRACT

Bone disease is one of the most common complications of multiple myeloma. It is the result of increased osteoclast activity which is not compensated by osteoblast activity and leads to osteolytic lesions characterized by bone pain and increased risk for pathological fracture, spinal cord compression and need for radiotherapy or surgery to the bone. Recent studies have revealed novel pathways and molecules that are involved in the biology of myeloma bone disease including the receptor activator of nuclear factor-kappa B ligand/osteoprotegerin pathway, the Wnt signaling inhibitors dickkopf-1 and sclerostin, macrophage inflammatory proteins, activin A, and others. A thorough study of these pathways have provided novel agents that may play a critical role in the management of myeloma related bone disease in the near future, such as denosumab (anti-RANKL), sotatercept (activin A antagonist), romosozumab (anti-sclerostin) or BHQ-880 (anti-dickkopf 1). Currently, bisphosphonates are the cornerstone in the treatment of myeloma related bone disease. Zoledronic acid and pamidronate are used in this setting with very good results in reducing skeletal-related events, but they cannot be used in patients with severe renal impairment. Furthermore, they have some rare but serious adverse events including osteonecrosis of the jaw and acute renal insufficiency. This review paper focuses on the latest advances in the pathophysiology of myeloma bone disease and in the current and future treatment options for its management.

Introduction

Multiple myeloma (MM) is a plasma cell malignancy which is characterized by the presence of bone destruction due to an elevated function of osteoclasts that is not balanced by a comparable elevation of osteoblast function. This bone destruction develops lytic lesions that lead to bone pain, hypercalcemia and skeletal-related events (SREs) such as pathological fractures, requirement for surgery and/or radiation

* *Corresponding author at*: Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528 Athens, Greece. Tel.: +30 213 2162846; fax: +30 213 2162511.
E-mail address: eterpos@med.uoa.gr (E. Terpos).
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to the bone and spinal cord compression (SCC) [1]. At diagnosis 70% of the patients present with bone pain, while during the course of the disease 50% of the patients develop at least one SRE if they do not receive a bone-targeted agent [2]. In two studies, Melton et al. has shown that MM patients have generalized bone loss and osteoporosis that make them vulnerable to osteoporotic fractures [3]. They also showed that even patients with monoclonal gammopathy of undetermined significance (MGUS) have a >2-fold increase in fracture rate of the axial skeleton [4]. Bone disease has a serious impact on the quality of life and survival of MM patients [5] and affects both clinical and economic aspects of their life [6]. The risk of death in MM patients who develop a pathologic fracture increases by 20% in comparison with MM patients without pathologic fractures [7]. Thus, it is important to diagnose early and treat properly bone disease and its complications. This paper reviews the latest available details of pathophysiology and treatment of myeloma related bone disease.

Biology of multiple myeloma bone disease

In the adult skeleton, skeletal integrity is coordinated by the synchronized activity of three cell types. Osteoblasts create new bone matrix; osteoclasts are responsible for bone resorption and osteocytes regulate bone turnover. In multiple myeloma patients, bone disease is the result of an uncoupling in bone remodeling. It consists of an increase in the osteoclast-mediated bone resorption, which is combined with suppression in the osteoblast, mediated bone mineralization and defects in osteocyte functions [8]. Until today, several direct and indirect interactions between myeloma and stromal cells in the bone marrow microenvironment have been recognized. The fact that osteolytic lesions occur close to MM cells suggests that factors secreted by tumor cells lead to direct stimulation of osteoclast mediated bone resorption and inhibition of osteoblast mediated bone formation [9]. In addition, the increased bone resorptive progress leads to the release of growth factors that increase the growth of MM cells, leading to a vicious cycle of tumor expansion and bone destruction. Apart from this, interactions via adhesion between MM cells and bone marrow cells result in the production of factors that promote angiogenesis and make the myeloma cells resistant to chemotherapy [10, 11]. One example is that of T-regulatory and T-helper cells. In MM patients the stimulated T-regulatory cells by myeloma cells up-regulate pro-osteoclastic molecules and have been implicated with disease progression, whereas T-helper cells secrete IL-17 which promotes osteoclast formation [12–14]. On the other hand, Yaccoby et al. showed that osteoblasts inhibit MM cell growth in most of the patients [15].

Increased osteoclast activity

The main regulator of the osteoclast stimulation and activation is the system of the receptor activator of nuclear factor-kappa B (RANK), its ligand (RANKL) and its decoy receptor, osteoprotegerin (OPG). An important step in the osteoclast stimulation is the binding of myeloma cells to the bone marrow stromal cells (BMSCs). This adhesion is mediated by interactions between α4β1 on myeloma cells and vascular cell adhesion molecule 1 (VCAM-1) on BMSCs, and leads to the up-regulation of a variety of pro-osteoclastic cytokines and chemokines which directly or indirectly stimulate osteoclast formation differentiation and activity. These factors include interleukin-6 (IL-6), IL-1α, IL-1β, IL-11, macrophage-colony stimulating factor (M-CSF), tumor necrosis factor alpha and beta (TNF-α and TNF-β), macrophage inflammatory proteins-1 alpha and beta (MIP-1α and β), parathyroid hormone-related peptide (PTHrP), vascular endothelial growth factor (VEGF) and others [16–18]. These factors are excreted by MM cells directly, or indirectly after stimulation of bone marrow cells by the MM cells.

TNF Superfamily members – the RANK/RANKL signaling pathway

RANK is a transmembrane signaling receptor. It is located on the surface of osteoclast precursors [19, 20]. RANKL is expressed by a range of cell types, including marrow stromal cells and osteoclasts. Its expression is stimulated by cytokines that stimulate bone resorption [21] such as parathyroid hormone (PTH), 1,25-dihydroxy vitamin D3 and prostaglandins [22, 23]. RANKL binds to its receptor on osteoclast precursors and stimulates osteoclast differentiation formation and survival. These functions are mediated through the nuclear factor kappa-B (NFκB) and p38 MAP-kinase pathways. Apart from this, RANKL has direct enhancement effects on mature osteoclasts that inhibit their apoptosis. The importance of the role of RANKL in osteoclastogenesis has been shown in RANKL or RANK gene knockout mice. These animals lack osteoclasts and as a result they develop osteopetrosis [24–27]. In the absence of RANKL almost no chemokine with osteoclast activity can act.

OPG, another member of the TNF receptor superfamily, is a soluble decoy receptor for RANKL [28]. It is produced by several cells, including osteoblasts, and interacts with RANKL, causing inhibition of its action, thereby reducing osteoclastogenesis. The important role of OPG has been shown in studies with knock-out mice. OPG deficient mice develop severe osteopenia and osteoporosis [29–31]. An abnormal RANKL/OPG ratio is found in the majority of malignant bone disorders [32].

Myeloma cells turn the balance of the RANKL/OPG ratio in favor of RANKL. In the bone marrow microenvironment, MM cells play a double role: they induce the expression of RANKL from stromal cells, while they directly express RANKL, although in low amounts [33–37]. Apart from this they decrease the OPG availability within the bone marrow microenvironment. This is maintained in two different ways .The MM cells reduce OPG secretion from osteoblasts and stromal cells. In addition, they remove the remaining OPG by lysosomal degradation [38, 39]. The up-regulation of RANKL, in combination with down-regulation of OPG, leads to the formation and activation of osteoclasts. Levels of RANKL and OPG have been shown to correlate with clinical activity of MM, severity of bone disease and poor prognosis[40]. In individuals with MGUS, the RANKL/OPG is also increased when compared to that in control subjects but remains significantly lower than that in patients with myeloma [41],