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Review Article

The effects of proteasome inhibitors on bone remodeling in multiple myeloma

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ABSTRACT

Bone disease is a characteristic feature of multiple myeloma, a malignant plasma cell dyscrasia. In patients with multiple myeloma, the normal process of bone remodeling is dysregulated by aberrant bone marrow plasma cells, resulting in increased bone resorption, prevention of new bone formation, and consequent bone destruction. The ubiquitin–proteasome system, which is hyperactive in patients with multiple myeloma, controls the catabolism of several proteins that regulate bone remodeling. Clinical studies have reported that treatment with the first-in-class proteasome inhibitor bortezomib reduces bone resorption and increases bone formation and bone mineral density in patients with multiple myeloma. Since the introduction of bortezomib in 2003, several next-generation proteasome inhibitors have also been used clinically, including carfilzomib, oprozomib, ixazomib, and delanzomib. This review summarizes the available preclinical and clinical evidence regarding the effect of proteasome inhibitors on bone remodeling in multiple myeloma.

Contents

1. Introduction

Bone disease, defined as the presence of at least 1 osteolytic bone lesion or diffuse osteoporosis with compression fractures, is a characteristic feature of multiple myeloma (MM) [1]. Bone disease occurs in MM because of dysregulated bone remodeling, a process in which MM cells interacting with the bone marrow microenvironment disrupt the normal balance between bone resorption and bone formation [2,3]. This disruption of bone homeostasis results in the prevention of new bone formation and leads to bone destruction [2,3].

Abbreviations: ALP, alkaline phosphatase; Cbfa1, core-binding factor subunit alpha-1; DKK, dickkopf; MM, multiple myeloma; MP, melphalan with prednisone; OPG, osteoprotegerin; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; PTHR1, parathyroid hormone 1 receptor; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; Runx2, runt-related transcription factor 2; SRE, skeletal-related event; Wnt, wingless-type; VMP, bortezomib with melphalan and prednisone; VTD, bortezomib with thalidomide and dexamethasone.

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As a consequence of altered bone remodeling, up to 90% of patients with MM develop bone lesions that can, in turn, cause a sequelae of skeletal-related events (SREs) such as bone pain, pathologic fractures, spinal cord compression, and hypercalcemia [2,4]. The occurrence of SREs has been linked to inferior survival [5,6], reduced quality of life [7], and increased healthcare costs for patients with MM [8,9].

Treatment with bisphosphonates is the current standard of care for the management of myeloma-related bone disease and is recommended for all patients with MM receiving frontline therapy [9]. Bisphosphonates inhibit osteoclasts and thereby prevent bone resorption [10]. Although bisphosphonates have been shown to reduce the incidence and severity of SREs, improve quality of life, and prolong survival (in the case of zoledronic acid) compared with placebo [9], these agents do not restore bone formation [11]. In addition, bisphosphonates have been associated with renal toxicities and osteonecrosis of the jaw, which may limit their long-term use [2,10]. These drawbacks have spurred investigations into other agents that could simultaneously prevent bone resorption and promote bone formation, while also being safe and tolerable [10,11].

There is evidence that proteasome inhibition may be an effective strategy to improve bone remodeling in patients with MM. In contrast to bisphosphonate therapy, proteasome inhibition has been found to simultaneously inhibit bone resorption and promote bone formation [11–13]. The first-in-class proteasome inhibitor bortezomib and the next-generation proteasome inhibitor carfilzomib are established anti-MM agents, having been already approved for use in treating patients with MM. Preclinical and clinical data demonstrate that bortezomib has significant beneficial effects on bone metabolism [2,11,14–17]. Agents such as proteasome inhibitors, which combine anti-MM activity with improved bone remodeling, may be a particularly attractive treatment option for patients with myeloma-related bone disease [14]. Herein, we review data from preclinical and clinical studies that have examined the effects of bortezomib and next-generation proteasome inhibitors on bone remodeling in patients with MM.

2. Overview of abnormal bone remodeling in MM

The structure and integrity of the skeleton are maintained by a tightly coordinated process of bone remodeling [18,19]. In this process, osteoclasts continually resorb damaged bone, which is replaced by new bone synthesized by osteoblasts [18–20]. The tight control of bone resorption, once thought to be driven by osteoblasts, has now been shown to be the domain of osteocytes, the most abundant cells in bone that are encased in the mineralized matrix [21,22]. The process of bone remodeling and bone homeostasis is disrupted in patients with MM. Either directly or through complex interactions with the bone marrow microenvironment, MM cells stimulate the bone-resorptive activity of osteoclasts and suppress the bone-forming activity of osteoblasts, ultimately causing significant bone destruction [2,3,23]. The control of both resorption and formation is the realm of the osteocyte and it seems likely that these cells are also dysregulated in myeloma [24].

In recent years, key signaling pathways and cytokines that regulate osteoclast and osteoblast activity, both in normal and abnormal bone remodeling, have been identified and elucidated, as reviewed by Zangari et al., Silbermann and Roodman, Raje and Roodman, and Terpos et al. [2,3,11,23]; importantly, MM cells have been found to dysregulate many of these pathways. Under normal conditions, the coordinated and balanced signaling between the receptor activator of NF-κB (RANK), its ligand RANKL, and the decoy receptor of RANKL, osteoprotegerin (OPG), helps to maintain healthy levels of osteoclast activity and bone resorption [3,23,24]. The binding of RANKL to RANK promotes the formation, activation, and survival of osteoclasts; in contrast, the blockade of RANKL–RANK binding by OPG inhibits the activity of osteoclasts [3,23,25]. MM cells disrupt the RANK/RANKL/OPG axis by enhancing RANKL expression, promoting the binding of RANKL with RANK, and by decreasing the expression of OPG [3,23,25]. Patients with MM have an increased ratio of RANKL to OPG [26,27], the magnitude of which has been found to correlate with markers of bone resorption and the number of osteolytic bone lesions [27].

In addition to RANK, the expression and/or activity of many other osteoclast-activating factors are altered by MM cells including parathyroid hormone-related protein (PTHrP) [28], activin [29], macrophage inflammatory protein-1α [30], macrophage colony-stimulating factor [31], monocyte chemoattractant protein 1 [32], stromal derived factor-1α [33], tumor necrosis factor-α [34,35], and interleukin-3 [36]. MM cells may also affect the activity of osteoclasts through their deregulation of the Notch signaling pathway, as pharmacologic inhibition of the Notch pathway has been found to result in the abrogation of RANKL-induced osteoclast differentiation in vitro and a reduction in the number of osteolytic lesions in a murine model of MM [37].

The differentiation and activity of bone-forming osteoblasts are primarily mediated by the transcription factor runt-related transcription factor 2 (Runx2)/core-binding factor subunit alpha-1 (Cbfa1) and the wingless-type (Wnt) signaling pathway [2,23]. MM cells have been shown to down-regulate Runx2/Cbfa1 activity in osteoblast progenitor cells, which has been shown to suppress the formation and differentiation of osteoblasts [38]. Interestingly, MM cells themselves have been demonstrated to have a higher level of Runx2 expression than normal plasma cells; this overexpression of Runx2 in MM cells has been associated with tumor growth and bone metastasis [39]. In addition, it has been demonstrated that MM cells inhibit the Wnt pathway by overexpressing or producing Wnt inhibitors such as Dickkopf-1 (DKK-1) [40], secreted frizzled related proteins [41], and sclerostin [42]. The serum concentrations of DKK-1 and sclerostin have been correlated with the level of abnormal bone modeling in patients with MM [42,43].

An additional bone cell shown to play a key role in abnormal bone remodeling is the osteocyte. Osteocytes are osteoblast-derived cells that have become embedded within mineralized bone matrix [44]. In one study, patients with MM who had bone lesions were found to have significantly fewer viable osteocytes compared with healthy controls and patients with MM who did not have bone lesions [45]. This study demonstrated that MM cells induced apoptosis in osteocytes and altered their transcriptional profiles, resulting in the up-regulation of osteoclastogenic cytokines [45]. In patients with MM, apoptotic osteocytes may also reduce bone formation through their secretion of sclerostin, an inhibitor of Wnt-dependent osteoblast differentiation and survival [46].

3. Proteasome inhibitors and bone remodeling in MM

Proteasome inhibitors are hypothesized to normalize bone remodeling in patients with MM based on research demonstrating that the ubiquitin–proteasome system controls the catabolism of several proteins (e.g. IκB [13], bone morphogenetic proteins [47], Jak1 [48], zinc-finger transcription factor Gli2 [49], β-catenin [50], and DKK-1 [51]) that regulate bone remodeling (Fig. 1) [2,25]. Supporting this hypothesis, early preclinical studies demonstrated that proteasome inhibition reduced bone resorption and increased bone formation [12,13,52].

3.1. Bortezomib

The results described earlier provided the impetus to investigate the effect of bortezomib, a boronate-based proteasome inhibitor, on bone remodeling in preclinical models of myeloma-related bone disease and in patients with MM. To date, the effect of bortezomib on bone remodeling in MM has been extensively investigated in the preclinical and clinical settings (Tables 1 and 2). The results from these investigations have recently been reviewed by Qiang et al., Zangari et al., Terpos et al., and Mohty et al., [2,14,15,25] and are summarized below.

In preclinical models, bortezomib has been shown to have varied and substantial effects on the activities of osteoclasts, osteoblasts, and osteocytes. Studies have found that bortezomib inhibits the