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Bone Targeted Therapy in Multiple Myeloma

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Abstract The interaction between multiple myeloma (MM) cells and cellular components and its (BM) microenvironment promotes MM cell growth and osteolytic bone destruction. Osteolytic bone disease, characterized by bone pain, increased risk of pathologic fractures, tumor-induced hypercalcemia, is a frequent complication of MM patients. These skeletal-related events (SREs) decrease their quality of life and reduce their survival. Therefore, therapeutic strategies targeting the interplay between MM cells and the BM cellular components, including osteoclasts (OCs), stromal cells as well as MM cells themselves are necessary not only to attain tumor regression but to reduce its associated bone disease. The goal of bone-targeted therapy in MM is to reduce or delay the incidence of SREs and to improve the quality of life in affected patients. Currently, several novel agents are in the clinical trials.

Keywords: *multiple myeloma, bone marrow microenvironment, osteoclast, skeletal-related events, bone-targeted therapy*

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1. Introduction

The bone is a common site of metastasis in patients with advanced cancer such as breast cancer, lung cancer, prostate cancer, osteosarcoma and multiple myeloma (MM) [1,2,3]. MM is hematological malignancy, characterized by the accumulation of monoclonal plasma cells in the bone marrow (BM). In the BM microenvironment of MM, the cellular interaction promotes MM cell growth and devastates its associated osteolytic bone disease, characterized by bone pain, increased risk of bone fracture, which leads to the skeletal related events (SREs). The frequency of SREs depends on the characteristics of bone lesions, locations, the number of lesions, or the treatment complications and its occurrence is reported to be about 85-90% of MM patients [4,5]. Moreover, their severity depends on MM disease activity and high risk MM results in decreased quality of life and poor prognosis. MM cells promote osteoclast (OC) formation in association with BM stromal cells, whereas inhibits osteoblast (OB) formation, leading to the bone destruction. OCs, BM stromal cells (BMSCs) and endothelial cells supply a microenvironment, suitable for MM cell expansion. Thus, the interaction between MM cells and cellular components in the BM leads to the vicious cycle to expand MM cells and destructive bone lesions [6,7,8]. Therefore, novel therapeutic strategies targeting the interaction between MM cells and BM microenvironment is necessary not only to attain tumor regression but also to reduce bone destruction and improve patient outcome [9,10].

This review focuses on the mechanism of the interaction between MM cells and their surrounding cells in the BM microenvironment of MM and assesses bone targeted therapy to treat its associated bone disease to prevent the occurrence of SREs and tumor progression in affected patients [10]. In addition, several potential novel therapeutic strategies will be also discussed for the purpose of providing clues further to develop novel therapeutic approach to improve the survival and quality or life of MM patients.

2. The Mechanism of Bone Disease in MM

The interaction between MM cells and BM microenvironment plays an important role in the pathogenesis of MM. Soluble factors or physical contacts within the cellular components of BM microenvironment promote MM cell growth, survival and drug resistance. It is composed of various kinds of cellular components, including BM stromal cells (SCs), vascular endothelial cells, osteocytes, and OCs with decreased OBs.

BMSCs induces various cytokines or growth factors, such as interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), stromal cell-derived factor 1α (SDF1α), insulin-like growth factor 1 (IGF1) as well as physically contact with MM cells for MM cell proliferation [11,12,13]. They simultaneously secrete RANKL to enhance osteoclastgenesis in MM. RANKL enhances OC apoptosis and leads to decrease the production of osteoprotegerin (OPG), a decay receptor for RANKL, which inhibits RANKL-RANK signaling [14]. The marked imbalance exists between RANKL and OPG levels in the BM microenvironment of MM and it promotes OC activation. Vascular cell adhesion molecule 1 (VCAM-1) expressed on BMSCs binds to very late antigen 4 (VLA-4) on MM cells. Its interaction upregulates RANKL but downregulates OPG in BMSCs

and induces osteoclastgenesis [15]. It also increases the secretion of chemokines such as MIP1α and MIP1β by MM cells, which acts on monocytic progeniters and stimulate osteoclastgenesis [16].

Osteoclastgenesis is enhanced in the BM of MM. Factors produced by MM cells including RANKL, MIP1α, Interleukin-3 (IL-3) enhance bone destruction and suppress bone formation. Tumor necrosis factor α (TNFα), stromal cell-derived factor 1α (SDF1α), insulin-like growth factor 1 (IGF1), a proliferation inducing ligand (APRIL) and B cell activating factor (BAFF), secreted by OCs play an important role in MM cell growth. MM cells and OCs also contact directly [16,17,18,19]. These cells promote their growth each other and form a vicious cycle to lead to MM cell expansion and extensive bone destruction.

Angiogenesis is enhanced in the BM of MM. MM cells and BMSCs secrete angiogenetic factors such as VEGF, basic fibroblast growth factor (bFGF) [13,20]. Endothelial cells express VEGF receptor which interacts with $\alpha_v\beta_3$ integrin. OCs secrete osteopontin, a ligand of $\alpha_v\beta_3$ integrin, which acts on endothelial cells with VEGF, secreted by MM cells and enhance angionegesis. MMP-9, produced by OCs is also involved in angiogenesis and enhances osteoclastgenesis [21]. MM cells and various cells including OCs and endothelial cells in the BM microenvironment are closely related to tumor progression, bone destruction and angiogenesis in MM.

Osteoblastic differentiation inhibits MM cell growth as well as restores bone formation in MM bone lesions. However, the inhibition of osteoblastic formation was observed in MM. The WNT signaling pathway plays an important role in OB differentiation and its functions. DKK1 is a soluble inhibitor of the WNT pathway and is upregulated in MM cells and is more intensely expressed in MM patients with more severe lytic bone distruction, suggesting a role of DKK1 in MM bone disease [22,23,24]. DKK1 increases RANKL and decrease OPG, secreted by OBs. Thus, it induces osteoclastgenesis and inhibits osteoblastgenesis in MM and its suppression results in bone loss.

3. Bone Targeting Therapy in MM

MM is incurable disease with novel anti-tumor agents including immunotherapy or high-dose chemotherapy with stem cell transplantation. Patients with MM frequently experience pathological fractures, spinal cord compression or hypercalcemia, known as SREs, which lead to pain and a decreased quality of life [4,5,7,8]. Current therapeutic options of MM-associated bone disease include intraveneous bisphosphonates, surgical procedures, radiotherapy and the treatments towards MM itself.

Bisphosphonates are currently administrated as the part of the treatments in MM with anti-tumor agents to delay or prevent the occurrence of SREs and hypercalcemia [25,26,27,28]. They also increase the apoptosis of MM cells. The mechanism of action is to keep high affinity for bone mineral through their similarity to pyrophosphates. Nitrogen containing bisphosphonates such as zoledronic acid and pamidronates suppress farnesyl pyrophosphate synthetase (FPPS), the enzyme in the mevalonate pathway. Moreover, they block prenylate GTPase signaling and induce OC apoptosis. In addition, they have anti-angiogenetic effects via inhibiting the expression of VEGF or platelet derived growth factor (PDGF) in endothelial cells. It was also demonstrated that bisphosphonates inhibit tumor cell adhesion to the extracellular matrix and prevent invasion or metastasis in solid tumors [25,26,27,28]. Recent reports suggest that zoledronic acid has been to be effective in prolonging time to the first SRE in advanced cancer and bone metastasis [29,30,31].Rosen et al. demonstrated that compared with pamidronate, zoledronic acid (4mg) was shown to be reduce overall risk of developing skeletal complications including hypercalcemia by an additional 16 % in patients (n=1648) with bone lesions with MM or advanced breast carcinoma [26,27]. However, in other cases, SREs still occur after the treatment with zoledronic acid. Moreover, renal dysfunction frequently occurs in patients with MM and zoledronic acid exacerbate their renal impairment [32]. It also causes the osteonecrosis of the jaw (ONJ) [33]. Therefore, in several cases, alternative therapeutic approach is needed, further to reduce the occurrence of SREs without these drug toxicities.

Recently, several clinical trials have demonstrated that anti-RANKL monoclonal antibody, denosumab can significantly reduce SREs associated with osteolytic metastatic cancers [34]. Denosumab is a fully human monoclonal antibody which binds RANKL with high specificity and inhibit RANKL-RANK signaling and suppress OC activity, which leads to reduced bone resorption and the incidence of SREs caused by the bone destruction. Several trials showed that denosumab was superior to zoledronic acid in delaying or preventing the occurrence of SREs in metastatic breast cancer [35,36,37]. Initial dose adjustments of zoledronic acid is necessary for patients who had baseline creatinine clearance lower than 60mL/min. In contrast, dose adjustments or dose withholding for renal function are not required for denosumab. Henry et al. demonstrated that in patients with a baseline creatinine clearance lower than 60 ml/min, renal adverse effects occurred in 21.6% of patients receiving zoledronic acid, compared with 11.3% receiving denosumab [41]. Changes in serum calcium was occurred because of the mechanism of action of denosumab. Hypocalcemia was seen more frequently with denosumab than with zoledronic acid. However, it is manageable with appropriate supplementation with oral calcium and vitamin D [35,38,41]. Denosumab has an efficacy with little toxicities, but not be superior to zoledronic acid in patients with bone metastasis of other advanced cancer or MM [35-41]. Moreover, it does not significantly decrease tumor burden in MM [37,41].

A RANKL inhibitor, RANKL-Fc decreases bone resorption induced by RANKL as well as reduces tumor burden in animal models of MM [42]. Antagonists to MIP-1α receptor, CCR1 blocks OC formation and inhibits the adhesion between MM cells and BMSCs [43]. Several novel anti-tumor agents including proteasome inhibitors inhibits OC differentiation via the blockade of NFκB signaling pathway [44,45].

CD26 is expressed in normal OCs and is intensely expressed in OCs in osteolytic bone metastasis including

breast cancer, osteosarcoma, adenocarcinoma such as lung cancer, and MM [46]. Humanized anti-CD26 monoclonal antibody blocks OC differentiation *in vitro* during the early phase of human OC development via the blockade of MKK3/6-p38MAPK-mi/Mitf signaling pathway in OC precursor cells. Therefore, anti-CD26 antibody may have therapeutic potential for the treatment of osteolytic lesions following metastasis including MM to alleviate bone destruction and reduce the occurrence of total SREs [46].

Anti-DKK1 monoclonal antibody enhances osteoblastic differentiation and currently used in clinical trials and attains the promising results in MM bone disease [47,48]. Transforming growth factorβ(TGFβ) secreted by OBs and osteotcytes inhibits terminal OB differentiation and minerarlization [49]. TGFβ level is high in the bone lesions of MM and is involved in the bone remodeling. Activin A inhibitor, TGFβinhibitor induces OB differentiation and leads to decrease destructive bone lesions and tumor progression [50].

4. Future Directions

In addition to anti-tumor agents for MM cells, novel agents targeting osteolytic bone lesions seem to be promising therapeutic strategies to delay or prevent SREs for the treatment of MM. Further study of the molecular mechanism of cellular interactions in the BM microenvironment of MM will provide us with novel therapeutic approaches which have dramatic effects on MM-associated bone disease as well as MM cell expansion.

5. Conclusions

MM cells and cellular components interact closely with each other in the BM microenvironment of MM. Bone-targeted therapy is important therapeutic strategies in combination with cytotoxic agents for the treatment of MM. Further studies elucidating the mechanism responsible for the increased OC activity and decreased OC activity in MM will lead to the development of novel therapeutic targets to treat both bone destruction and MM progression.

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