



Therapeutic Approach in Bone Metastasis

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Abstract

The interaction between tumor cells and their surrounding cells in the bone marrow (BM) microenvironment promotes tumor cell growth and its associated bone destruction in osteolytic bone metastasis. Osteolytic bone disease, characterized by bone pain, increased risk of pathologic fractures, tumor-induced hypercalcemia, is a frequent complication of patients with advanced cancer including breast cancer, prostate cancer, lung cancer and multiple myeloma (MM). These skeletal-related events (SREs) decrease their quality of life (QOL) and reduce their survival. Understanding pathogenesis of bone metastasis has resulted in the development of bone-targeted therapy including bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor. Therapeutic strategies targeting the interaction between tumor cells and cellular components including osteoclasts (OCs) in the BM microenvironments is necessary not only to attain tumor regression but to prevent or delay the incidence of SREs and to improve the QOL in affected patients.

Keywords: Osteolytic Bone Metastasis; Skeletal-Related Events; Quality of Life; Osteoclast; Bone-Targeted Therapy

Abbreviations: BM: Bone Marrow; SREs: Skeletal-Related Events; MM: Multiple Myeloma; QOL: quality of Life; RANKL: Receptor Activator Of Nuclear Factor Kappa-B Lligand; OC: Osteoclast; OB: Osteoblasts; FFPS: Farnesyl Pyrophosphate Synthetase; ONJ: Osteonecrosis of the Jaw

Introduction

The bone is a common site of metastasis in patients with advanced cancer such as breast cancer, prostate cancer, lung cancer and multiple myeloma (MM) [1-3]. Patients with osteolytic bone metastasis frequently experience pathological fractures, spinal cord compression or hypercalcemia, known as skeletal related events (SREs), which lead to bone pain and a decreased quality of life (QOL) [1-3]. 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 80-90% of patients with breast cancer or MM and 30-40% of lung cancer patients [4-6]. Tumor cells promote osteoclast (OC) formation in association with BM stromal cells, whereas inhibits osteoblast (OB) formation, leading to the bone destruction. Thus, the interaction between tumor cells and their surrounding cells in the bone marrow (BM) leads to the vicious cycle to expand tumor cells and destructive bone lesions [1-3]. Therefore, novel therapeutic approach targeting the interaction between tumor cells and BM microenvironment is necessary not only to attain tumor regression but also to reduce bone destruction and improve patient outcome [1-3].

Bone Targeting Therapy in Osteolytic Bone Metastasis

Current therapeutic options of bone destruction in osteolytic bone metastasis include intravenous bisphosphonates, surgical

procedures, radiotherapy and the treatments towards the tumor itself.

Bisphosphonates are currently administrated as the part of the treatments in osteolytic bone metastasis including breast cancer, prostate cancer, lung cancer and MM to delay or prevent the occurrence of SREs and hypercalcemia [7-10]. The mechanism of action of nitrogen containing bisphosphonates such as zoledronic acid and pamidronates suppress farnesyl pyrophosphate synthetase (FPPS), the enzyme in the mevalonate pathway and block prenylate GTPase signaling. As a result, they keep high affinity for bone mineral through their similarity to pyrophosphates and inhibit bone resorption mainly by inducing apoptosis of mature OCs [11]. In addition, They are shown to inhibit tumor cell adhesion to the extracellular matrix and prevent invasion or metastasis in solid tumors [7-10]. Recent reports suggest that zoledronic acid has been to be effective in prolonging time to the first SRE in advanced cancer and bone metastasis [12-14]. However, in other cases, SREs still occur after the treatment with zoledronic acid. Zoledronic acid exacerbate the renal impairment [15] and causes the osteonecrosis of the jaw (ONJ) [16]. Therefore, in several cases, alternative therapeutic approach is needed, further to reduce the occurrence of SREs without these drug toxicities.

Denosumab is a fully human monoclonal antibody which binds RANKL with high specificity and inhibit RANKL-RANK signaling. It acts on BM microenvironment and suppress OC bone resorptive activity by interfering with OC development from OC precursor cells, which leads to the incidence of SREs. Recently, several trials have shown that denosumab was superior to zoledronic acid in delaying or preventing the occurrence of SREs, with median progression free and overall survival similar to zoledronic acid in osteolytic bone disease including advanced breast cancer, prostate cancer and lung cancer [17-24]. Initial dose adjustments of zoledronic acid is necessary for patients who had baseline creatinine clearance lower than 60mL/min. On the other hands, they are not required for denosumab. Hypocalcemia is seen more frequently with denosumab than with zoledronic acid. However, it is manageable with appropriate supplementation with oral calcium and vitamin D [17,20,21].

CD26 is preferentially expressed in normal OCs and is intensely expressed in OCs with osteolytic bone metastasis including breast cancer, osteosarcoma, adenocarcinoma such as lung cancer, and MM [25]. Humanized anti-CD26 monoclonal antibody blocks OC differentiation during early phase of human OC development via the blockade of MKK3/6-p38MAPK-mi/Mitf signaling pathway in OC precursor cells. In the future, anti-CD26 antibody may have therapeutic approach for the treatment of osteolytic metastasis to reduce the occurrence of total SREs [25].

Conclusion

Novel agents targeting osteolytic bone lesions seem to be promising therapeutic strategies to delay or prevent SREs for the treatment of MM. Further elucidation of the molecular mechanism of cellular interactions between tumor cells and BM microenvironment will provide us with novel therapeutic approaches which have dramatic effects on the bone destruction with osteolytic bone tumors.

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