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Mini Review

Potential of Targeting Bone Metastases with Immunotherapies

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Abstract

Cancer-related bone metastases are incurable and cause high mortality in patients. Immunotherapies have been evaluated in large-scale clinical trials with advanced cancer patients, but effects on bone metastases have not been specified. This mini review introduces case reports where patients with bone metastases have been treated with immunotherapies and local effects on tumor growth have been assessed. Potential skeletal-related adverse effects of immunotherapies are also discussed.

Keywords: Metastatic cancer; Bone metastasis; Immunotherapies

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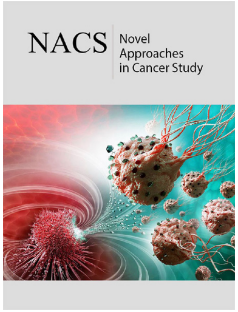

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Introduction

Cancer metastases cause high morbidity and mortality in patients. Bone metastases are most common in breast and prostate cancer, but they are also observed in many other cancers such as lung and renal cancer and melanoma [1]. In breast cancer the formation of metastases depends on the tumor subtype, and the major site for metastasis is the skeleton [2]. Patients with bone metastases have a 5-year survival rate of only 21% and a median survival time of 3 years. Prostate cancer is currently described as a bone disease due to high incidence of skeletal metastases. In prostate cancer patients with bone metastases, the 5-year survival rate is about 30% and the median survival time is 3 years [3]. Metastatic cancer patients are treated with conventional cancer therapies that are usually ineffective against bone metastases. Tumor-induced bone loss can also be treated with bone-targeting therapies. Bone marrow is an important immune organ that contains many immune cells, such as myeloid-derived suppressor cells, T cells, B cells and natural killer cells, and it is a cytokine rich microenvironment [4-6]. Immune cells can regulate many aspects of formation and growth of bone metastases [4]. Bone marrow is an immunosuppressive microenvironment, and immune suppressive cells in bone may promote tumor progression [5]. On the contrary, cytotoxic T cells and NK cells can be activated by immunomodulators to mediate anti-tumor effects. In addition, immune cells directly interact with bone cells, promoting tumor-induced effects on bone [6].

Immunotherapies, agents that activate patient's own dampened immune system to fight cancer, have also been applied to patients with metastases. Currently, programmed cell death 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) targeting therapies are approved for treatment of many advanced cancers. Information of immunotherapies' effects on bone metastases is still scarce but data is emerging from ongoing clinical investigations. It is important to understand that metastases differ from primary tumors, and there can be differences in metastases growing in different locations of the body. For example, a study of renal cell carcinoma indicated that expression of PD-1 and PD-L1 was increased in metastases compared to primary tumor [7]. Furthermore, a recent study showed discrepancy in the response to immunotherapy between metastases growing in different locations, with a poor overall response [8]. However, the expression of PD-L1 in different metastases, including bone metastases, was similar in non-small cell lung cancer [9].

Some reports show promising cases where individual patients with bone metastases have been cured with immunotherapies. One recent report showed that anti-PD-1 treatment decreased the growth of bone metastases in a patient with metastatic anorectal amelanotic melanoma [10]. Some bone metastatic prostate cancer patients treated with anti-CTLA-4, experienced a complete remission [11]. Similarly, a melanoma patient with bone metastases obtained a complete remission after treatment with PD-1 [12]. A prostate cancer patient with

bone metastases undergoing alloreactive cytotoxic T lymphocyte therapy showed decreased serum prostate specific antigen levels, and the bone metastatic lesions diminished after two years of treatment [13]. Cancer-induced bone loss in patients with bone metastases is treated with bone-targeting therapies, typically with the receptor activator of nuclear factor kappa-B ligand (RANKL) antibody denosumab. Furthermore, targeting the RANKL-pathway can have immunological effects on tumors that may enhance the antitumor activity of immunotherapies [14]. Denosumab has been combined with immunotherapies in melanoma patients with bone metastases [15]. All of these patients responded to the treatments, showing promising efficacy.

Importantly, it should be recognized that immune activation may also have harmful effects on the skeleton. A recently published case series showed that immunotherapies were associated with skeletal related adverse effects including spinal cord compression, fractures and lesions caused by increased bone resorption [16]. Considering the biological relationship between immune and bone cells, it is likely that immunotherapies cause skeletal adverse effects, and bone safety evaluation should be considered especially before treating patients with bone metastases.

Conclusion

Even though there are promising case reports of patients with bone metastases successfully treated with immunotherapies, it is still controversial if these findings can be seen in large patient cohorts. There can be discordance between the expression of immune checkpoint markers and the response to immunotherapies in primary and metastatic tumors, which should be taken into consideration in patient selection and treatment planning. Also, possible skeletal-related adverse effects of immunotherapies should be carefully monitored and reported to recognize potential risk factors.

Conflict of Interest

Authors declare no conflicts of interest.

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