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Letter to the Editor

Immune checkpoint inhibitors: friend or foe for osteoporosis

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Dear Editor,

Immune checkpoint inhibitors (ICIs) are enabling long-term survival in patients with cancer, as well as new therapeutic indications in the early stages of cancer,[1] but the potential effect on skeletal disease, especially osteoporosis, remains unclear.

Researchers found that osteoclast hyperactivity was associated with activation of the programmed death 1 (PD-1)/ programmed death ligand 1 (PD-L1) pathway.[2] It was found by Xiu-Ping Cai *et al.* that PD-1 levels were significantly higher in the peripheral blood mononuclear cells (PBMCs) of postmenopausal osteoporosis (PMOP) patients compared with healthy controls. They suggested PD-1/PD-L1 signaling is involved in osteoporosis pathogenesis by regulating inflammation, stimulating osteoclasts, and inhibiting osteoblasts,[3] indicated that PD-1 may be involved in the pathogenesis and development of PMOP.[3] Nagahama *et al.*[4] found that osteoclast formation was inhibited in mice with PD-1 deficiency, leading to mild osteopetrosis. According to Kaiyuan Wang *et al.*, mice lacking Pdcd1 were found to be protected against bone destruction induced by femoral inoculation of Lewis lung cancer cells. Deficit of PD-1 or treatment with nivolumab-inhibited osteoclastogenesis without affecting tumor burden. As a result of suppressing osteoclastogenesis by anti-PD-1 immunotherapy, they concluded that long-term benefits could be obtained in preventing bone destruction.[5] These studies indicates that the anti-PD-1 might be the potential therapy for the osteoporosis.

However, several clinical studies have reported that the ICIs have potential skeletal adverse effects. Data from the United States Food and Drug Administration Adverse Event Reporting System showed compression fractures, fractures at various skeletal sites (rib, thoracic vertebral, and humerus) were recorded after the treatment of ICIs,[6] but the effect of other systemic treatments like glucocorticoids should be considered. One of the retrospective case series examined clinical, laboratory, and imaging data collected from patients who developed new fractures or resorption of bone lesions while taking drugs targeting PD-1, CTLA-4, or both. Vertebral compression was present in all patients, and two of the three fractured at multiple locations. Resorbtive lesions were found in the shoulder, hand, and clavicle. Five of the six patients had elevated or high-normal biochemical markers of bone resorption.[7] According to Filippini *et al.*,[8] four patients received systemic treatment with ICIs in combination or alone and ended up with new osteoporotic fractures. The potential mechanism is that ICI therapy triggers cytokine-secreting T-cells, which are responsible for bone remodeling in proinflammatory states. When activated T-cells produce proinflammatory cytokines and upregulate the nuclear factor-κB ligand, osteoclast differentiation and maturation are favored over osteoblastogenesis, resulting in bone loss and fracture risks.[8–10] Based on these analyses, adverse skeletal events such as fractures may be precipitated by ICIs.

Additional research is required to clarify the potential effect of ICIs on osteoporosis.

It is important to risk stratify patients who begin treatment with ICIs, monitor them for skeletal lesions, and perform laboratory tests (calcium/phosphorus metabolism, PTH and biochemical markers of bone turnover) and imaging tests.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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Competing interests
The author declares that there is no conflict of interest.

Availability of data and material
Not applicable.

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References

1. Johnson DB, Nebhan CA, Moslehi JJ, *et al.* Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022; 19: 254–267.
2. Tai YT, Cho SF and Anderson KC. Osteoclast immunosuppressive effects in multiple myeloma: role of programmed cell death ligand 1. *Front Immunol* 2018; 9: 1822.
3. Cai XP, Zhao Q, Guo ZD, *et al.* Potential diagnostic value of PD-1 in peripheral blood mononuclear cells of postmenopausal osteoporosis patients. *J Clin Lab Anal* 2020; 34: e23223.
4. Nagahama K, Aoki K, Nonaka K, *et al.* The deficiency of immunoregulatory receptor PD-1 causes mild osteopetrosis. *Bone* 2004; 35: 1059–1068.
5. Wang K, Gu Y, Liao Y, *et al.* PD-1 blockade inhibits osteoclast formation and murine bone cancer pain. *J Clin Invest* 2020; 130: 3603–3620.
6. Pundole XN, Sarangdhar M and Suarez-Almazor ME. Rheumatic and musculoskeletal adverse events with immune checkpoint inhibitors: data from the United States Food and Drug Administration adverse event reporting system. *J Immunother Precis Oncol* 2019; 2: 65–73.
7. Moseley KF, Naidoo J, Bingham CO, *et al.* Immune-related adverse events with immune checkpoint inhibitors affecting the skeleton: a seminal case series. *J Immunother Cancer* 2018; 6: 104.
8. Filippini DM, Gatti M, Di Martino V, *et al.* Bone fracture as a novel immune-related adverse event with immune checkpoint inhibitors: case series and large-scale pharmacovigilance analysis. *Int J Cancer* 2021; 149: 675–683.
9. Walsh MC, Takegahara N, Kim H, *et al.* Updating osteoimmunology: regulation of bone cells by innate and adaptive immunity. *Nat Rev Rheumatol* 2018; 14: 146–156.
10. Showalter A, Limaye A, Oyer JL, *et al.* Cytokines in immunogenic cell death: applications for cancer immunotherapy. *Cytokine* 2017; 97: 123–132.