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CASE REPORT

Combination of Sintilimab and Anlotinib for Metastatic Osteosarcoma: A Case Report

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Background: As one of the most common types of primary bone sarcomas in adolescents and young adults, osteosarcoma has a high probability of local invasion and distant metastasis with a poor prognosis.

Case Presentation: Here, we report the case of a 34-year-old patient with advanced metastatic osteosarcoma. Considering the high expression of PD-L1 and the inability of the patient to tolerate chemotherapy, anti-PD-1 antibody (sintilimab 200 mg, q3w) and anti-angiogenesis drug (anlotinib 8 mg D1-14, q3w) were administered. The metastatic lesions were treated with local radiotherapy. The patient obtained an 11.7-month-sustained remission period, and he also enjoyed a better quality of life.

Conclusion: This case demonstrates that sintilimab plus anlotinib may be a feasible treatment regimen for osteosarcoma patients.

Keywords: osteosarcoma, sintilimab, anlotinib, immunotherapy, anti-angiogenesis

Introduction

Osteosarcoma is the most common type of primary bone sarcoma in adolescents and young adults.[1] Current clinical management of osteosarcoma involves surgery, neoadjuvant chemotherapy or adjuvant chemotherapy. Nevertheless, osteosarcoma has a high opportunity for local invasion and distant metastasis is more likely to the lung.[2] The 5-year relative survival rate of people with localized osteosarcoma is 70%, but only 20–30% in those who present with distant metastasis.[3,4] Considering the poor prognosis of patients with unresectable metastases, it is urgent to establish novel therapeutic strategies at this stage.

Herein, we reported an advanced metastatic osteosarcoma patient with high PD-L1 expression. The patient reached disease control (about 11.7 months) after immunotherapy combined with an anti-angiogenesis agent. To the best of our knowledge, this case was the first report that investigated the efficacy of anti-PD-1 antibody (sintilimab) and angiogenesis inhibitor (anlotinib) for adult patients with metastatic advanced osteosarcoma.

Case Presentation

The current case reports a 34-year-old man diagnosed with metastatic osteosarcoma originating in the proximal part of the left humerus. In June 2019, the patient entered the local hospital with pain in the upper left arm and a magnetic resonance imaging (MRI) scan showed a large mass of the left humerus. The patient underwent palliative operation of curettage, bone-grafting and internal fixation of the left proximal humerus in August 2019, and the histological examination of the excised specimens showed high-grade osteosarcoma. After 3 months, positron emission tomography/computed tomography (PET/CT) showed lung lesions and suspicious of multiple bone metastases, multiple lymph node and intramuscular metastases, and multiple soft tissue metastases to the axilla and abdomen and pelvis, and then he was referred to our hospital for further treatment. He had a poor ECOG performance status of three presented with recurrent high fever and systemic pain and therefore could not tolerate chemotherapy. CT-guided biopsy was performed against the left-iliac mass and the histologic examination showed poorly differentiated

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osteosarcoma (Figure 1A) and immunohistochemical stains suggested positivity for PD-L1 expression (TPS ≥ 95%) (Figure 1B).

Considering the patient's poor physical condition and high PD-L1 expression, sintilimab 200 mg was administered every 3 weeks, along with anlotinib 8 mg, once daily, 2 weeks on, 1 week off in December 2019. Meanwhile, 60 Gy of radiotherapy was given to the patient over 20 fractions, 3 Gy daily, to the lateral soft tissue mass of the left humerus from December 2019 to January 2020. On January 5, 2020, after 2 cycles of this regimen, a stable disease (SD) with 20% shrinkage of volume was observed (Figure 2A–H). Twelve cycles of treatment later, a CT scan showed partial response (PR) of the mass, especially in the lung, mediastinal lymph nodes, right pubic and subcutaneously left iliac region (Figure 2I–L). Meanwhile, ECOG PS recovered from 3 to 1. On account of the toxicity profile, grade 1 rash and oral mucositis were the only adverse event observed during treatment. The patient was dead at the time of writing this article but written informed consent was obtained from the patient's wife for the publication of any potentially identifiable images or data included in this article.

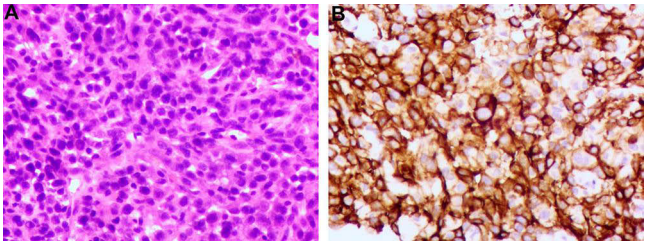

Figure 1 Hematoxylin-eosin (HE) staining and immunohistochemistry (IHC) of CT-guided biopsy of the left iliac mass. (**A**) HE staining showed poorly differentiated osteosarcoma (×200); (**B**) IHC examination revealed the left iliac mass was positive for PD-L1 (×200).

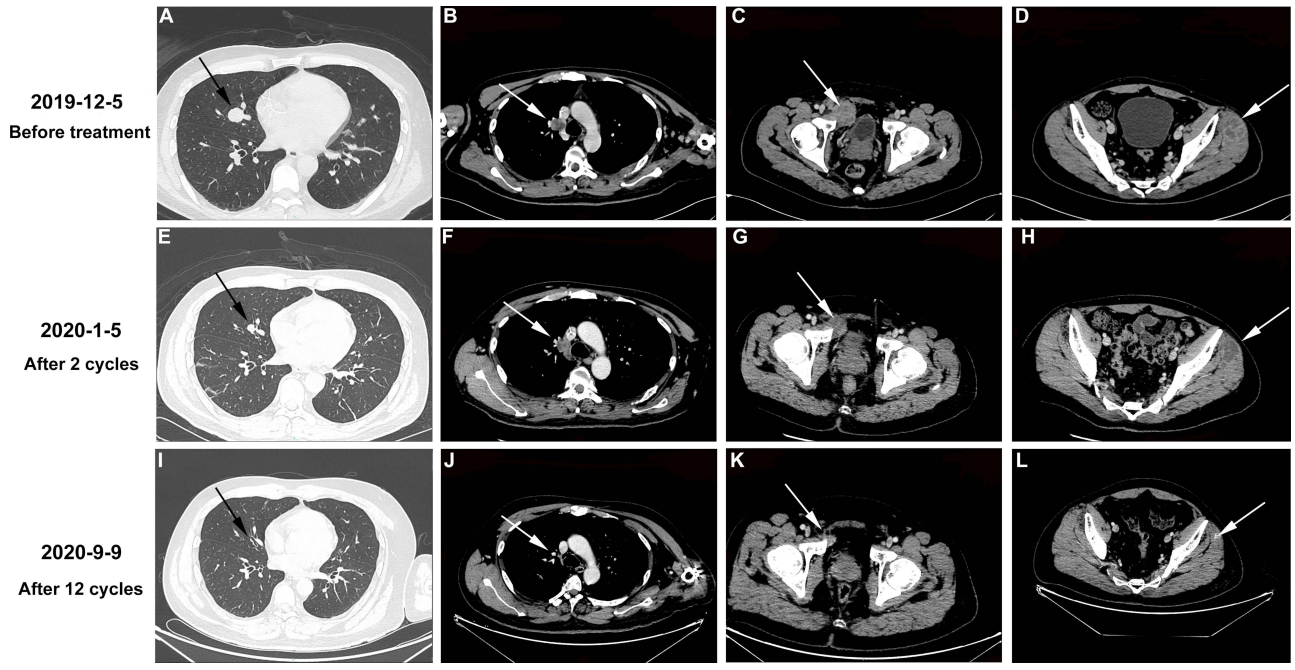

Figure 2 Computerized tomography (CT) was performed before and after sintilimab plus anlotinib therapy. (**A–D**) CT scan of the mass in the right lung, the mediastinal lymph nodes, the mass in the right pubic and the mass in the subcutaneously left iliac region before the treatment, respectively (arrow); (**E–H**) CT scan of the mass in the right lung, the mediastinal lymph nodes, the mass in the right pubic and the mass in the subcutaneously left iliac region after 2 cycles of sintilimab plus anlotinib therapy, respectively (arrow); (**I–L**) CT scan of the mass in the right lung, the mediastinal lymph nodes, the mass in the right pubic and the mass in the subcutaneously left iliac region after 12 cycles of sintilimab plus anlotinib therapy, respectively (arrow).

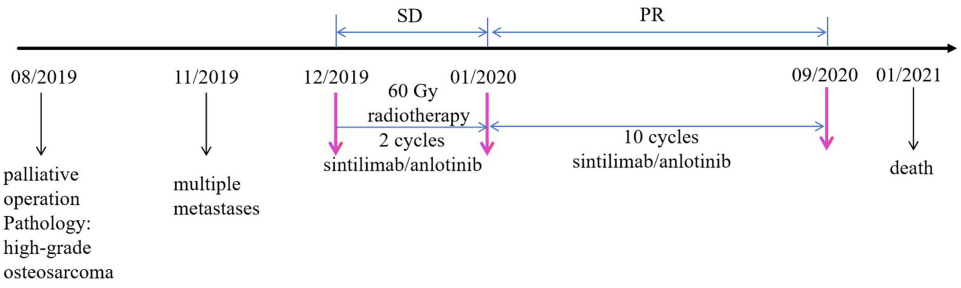

Figure 3 Timeline of the clinical course of the patient.

Discussion

The prognosis for advanced osteosarcoma has not improved over the decades, with median progression-free survival (PFS) and overall survival (OS) of only 4 (95% CI, 3.0 to 5.7) weeks and 5.9 (95% CI, 1.4 to 16.4) months, respectively.[5,6] With first-line chemotherapy, including high-dose methotrexate, doxorubicin, cisplatin and ifosfamide, producing limited efficacy, there is no established treatment for advanced osteosarcoma patients who progress after chemotherapy.[7] In recent years, immunotherapy and antiangiogenic therapy have both brought advances in the treatment of solid tumors. A single-arm, open-label, Phase II trial revealed that apatinib plus camrelizumab demonstrated advantages over chemotherapy in patients with advanced osteosarcoma progressed after chemotherapy with a median PFS of 6.2 months.[8] Although immunotherapy plus antiangiogenic therapy is a promising strategy, dual drugs often cause considerable toxicity and the toxicity of different PD-1 antibodies and tyrosine kinase inhibitors (TKIs) varies. Therefore, it is urgent to utilize novel chemo-free combination therapy to maximize antitumor efficacy while minimizing toxicity.

Sintilimab, an IgG4 monoclonal human anti-PD1 antibody, has been approved for the treatment of classical Hodgkin's lymphoma and non-small cell lung cancer (NSCLC) in China.[9,10] Anlotinib is a multikinase inhibitor that has been approved for the treatment of NSCLC, small cell lung cancer, soft tissue sarcoma, and medullary thyroid carcinoma in China.[11–14] In osteosarcoma, Wang et al reported that anlotinib could increase chemosensitivity and inhibit tumor growth, migration and invasion in vitro and in vivo models.[15] A case report of a patient with delayed pulmonary metastasis of osteosarcoma who reached disease-control of 27 weeks after treatment with anlotinib can be found.[16] Besides, anlotinib was proved to improve immunotherapeutic response and has exhibited synergistic antitumor effects with immune checkpoint inhibitors in several cancer types including endometrial cancer, cervical cancer and hepatocellular carcinoma, having advantageous toxicity.[17–19] In this case, as a result of the combination of sintilimab and anlotinib treatment, the tumor shrank dramatically and has continued to shrink for over 11 months with a manageable safety profile (Figure 3).

To our knowledge, this is the first reported case where an advanced osteosarcoma patient with high expression of PD-L1 achieved PR and was stable for over 11 months using sintilimab in combination with anlotinib as first-line therapy. This case indicates that advanced osteosarcoma patients with high PD-L1 expression, especially those who cannot tolerate chemotherapy may be available with sintilimab plus anlotinib as a new promising option. The main limitation of this study is that we did not explore biomarkers such as tumor mutational burden (TMB) and microsatellite status (MS) for predicting response to combined immunotherapy and antiangiogenic therapy.

In summary, sintilimab along with anlotinib have exhibited encouraging efficacy and acceptable safety in this case, providing an option for patients with advanced osteosarcoma, especially for those who cannot tolerate chemotherapy.

Abbreviation

PD-L1, programmed cell death ligand-1.

Date Availability Statement

The raw data supporting the conclusions of this article was made available by the corresponding author (Yuanling Qi), without undue reservation.

Ethics Statement

The study involving human participant was reviewed and approved by Weifang People's Hospital. The patient's wife provided her written informed consent to participate in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no conflict of interest to disclose for this work.

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