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Letter to the Editor

Eltrombopag treatment for severe refractory thrombocytopenia caused by pembrolizumab

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To the Editor,

In the past decade, immune-related adverse events (irAEs) caused by immune checkpoint inhibitors (ICIs) have been an important issue for oncologists in the clinic. With the widespread use of ICIs in cancer therapy, in addition to the data provided by prospective clinical trials, new data regarding toxicity are emerging. Herein, we report the first case of refractory thrombocytopenia caused by pembrolizumab, ineffective treatment of hormones and immunoglobulins and effective treatment with eltrombopag.

Case report: a 65-year-old male patient was admitted to the hospital with frequent cough. Contrast-enhanced computed tomography of the chest and abdomen showed a left upper lung–occupying mass, accompanied by pulmonary artery and pericardial involvement. Bronchoscopy showed a new mass in the left upper lobe. Biopsy histopathology showed atypical immunohistochemistry suggestive of non–small-cell lung cancer, which is difficult to further classify. Tissue and peripheral blood gene test results were negative. There was no abnormality on contrast-enhanced magnetic resonance imaging of the head and bone imaging. After administering 2 cycles of paclitaxel plus carboplatin, the efficacy was assessed to be stable. In the third cycle, paclitaxel and carboplatin were combined with pembrolizumab, and partial remission was evaluated after 2 cycles. Pembrolizumab monotherapy was initiated from cycle 5. Before the administration of the 7th cycle of pembrolizumab, the blood cell count was normal (platelet [PLT] count: 326×10^9/L). On the 5th day after treatment, the patient presented with bleeding in the gums in the morning and did not seek medical attention. On the 10th day after treatment, the patient was admitted to the hospital owing to severe nosebleed, and the PLT count was 0×10^9/L (normal value: $125–350 \times 10^9$/L). Results were negative for autoimmune antibodies, viruses and bacteria and positive for anti-PLT antibodies; bone marrow smears suggested maturation of the megalaryngeal system, and bone marrow biopsy suggested the presence of myeloproliferative changes. During the period, the patient did not take other drugs or special foods, and it was considered that the thrombocytopenia was caused by pembrolizumab. The patient was administered with a sufficient dose of dexamethasone for 5 days (equivalent to prednisone: 1 mg/kg/d), combined with sufficient immunoglobulin for 5 days on the 6th day of admission, with an intermittent PLT infusion three times during the period. A repeated review of the patients' PLT count revealed an increase to 14×10^9/L (Fig. 1). The patient still exhibited epistaxis, with absolute bed rest. We consulted a haematologist, who recommended discontinuing the administration of hormones and immunoglobulins and to orally administer

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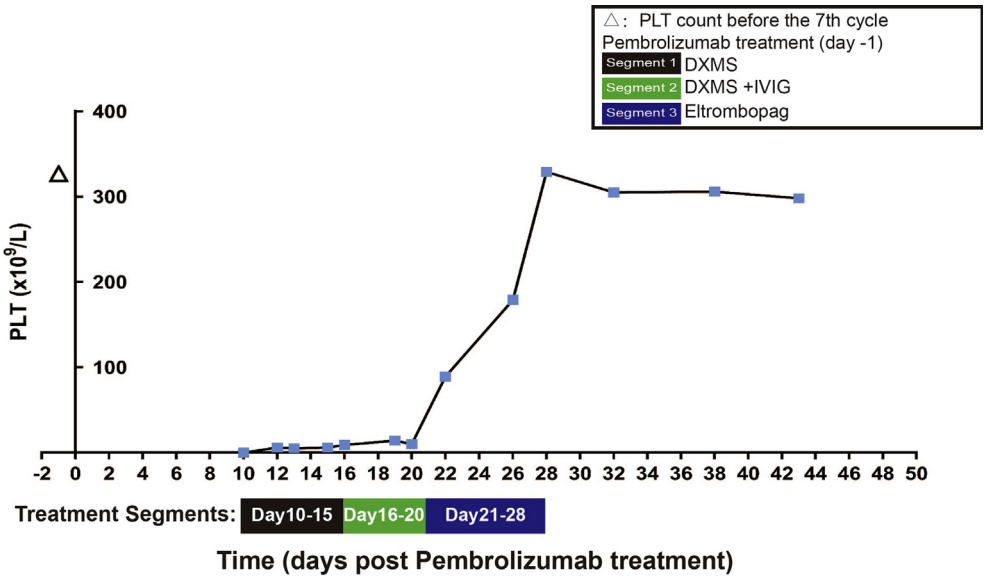

Fig. 1. Platelet count and response to therapy. PLT, platelet; DXMS, dexamethasone; IVIG, immunoglobulin.

eltrombopag (50 mg once a day). On the 11th day of admission, the patient started taking eltrombopag. The PLT count was 127 × 10^9/L after 2 days of taking eltrombopag, 181 × 10^9/L after 6 days and 321 × 10^9/L after 8 days (Fig. 1). The PLT count achieved a normal high value, and eltrombopag was discontinued. The PLT count remained stable on the 15th day after the patient stopped taking eltrombopag. Pembrolizumab treatment was not reinitiated, considering that severe thrombocytopenia was life-threatening.

Discussion: according to a literature review, severe thrombocytopenia associated with ICIs is very rare, with an incidence of about 0.8% [1]. Its emergence can lead to further delays in antitumour treatment and increase the risk of life-threatening bleeding in patients; therefore, oncologists should be highly vigilant. The guidelines by the American Society of Clinical Oncology [2], European Society for Medical Oncology [3] and Society for Immunotherapy of Cancer Toxicity Management Working Group [4] and other guidelines recommend hormone and immunoglobulin treatment for ICI-related thrombocytopenia and do not recommend the use of immunosuppressive agents. Based on a search in PubMed, there are currently 12 reported cases of ICI-related thrombocytopenia. Except for one case involving romastatin combined with hormones and immunoglobulins, the other cases involve effective treatment with hormones and immunoglobulins [5,6].

The mechanism by which ICIs cause thrombocytopenia is currently unclear. Although Aster *et al* [7]. have proposed six potential mechanisms for drug-induced immune thrombocytopenia, ICIs do not seem to correspond to any of these mechanisms. Pembrolizumab stimulates antibody production and cell-mediated immunity by blocking the action of programmed cell death protein-1 on T cells, which may cause an autoimmune response. Therefore, identifying drug-induced antibodies may clarify the mechanism of ICI-related thrombocytopenia.

This patient was definitively diagnosed with severe refractory thrombocytopenia caused by pembrolizumab with obvious bleeding symptoms. After a sufficient dose of hormones combined with immunoglobulin treatment, the patient's PLT count did not increase significantly, and the symptoms of nose bleeding did not improve. Following the recommendation of a haematologist, PLT counts increased rapidly after oral administration of eltrombopag. After 10 days of continuous administration, the PLT count achieved a normal value and remained stable after 15 days of withdrawal. Eltrombopag is an oral thrombopoietin receptor agonist that is primarily intended for patients with chronic immune thrombocytopenia who have not responded well to glucocorticoids, immunoglobulin or spleen treatment. Atratropa is a treatment option for refractory thrombocytopenia caused by ICIs, and more relevant data are expected.

This case suggests that tumour treatment is extremely complex and immune-related toxic reactions are diverse. The correct management of strong irAEs requires fast and efficient responses and decision-making, which rely on the efficient collaboration of multidisciplinary teams. This is the only way through which patients with cancer can benefit the most from the rapid development of immunotherapy.

Conflict of interest statement

None declared.

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