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Running title: Treatment of EBV-PTLD with nivolumab

Keywords: Epstein-Barr virus, PTLD, allogeneic hematopoietic stem cell transplantation, nivolumab, immune checkpoint inhibitors

Type of manuscript: Letter to the Editor

Figure: 1

Reference count: 8

Dear Editor,

Epstein-Barr virus (EBV)-associated post-transplantation lymphoproliferative disorders (PTLD) represent a heterogeneous group of EBV-driven abnormal lymphoid proliferations occurring after allogeneic hematopoietic stem cell transplantation [1-3]. Although several therapeutic strategies, such as reduction of immunosuppressive agents, rituximab monotherapy, multiagent chemotherapy, and infusion of EBV-specific cytotoxic T-lymphocytes (CTLs) have somewhat improved the outcome of patients with PTLD, there is a concern that PTLD is still significantly associated with high mortality. The use of immune checkpoint inhibitors (iCPIs) has emerged as a promising strategy because of its potential effectiveness in enhancing anti-tumor immunity.

Recently several case reports have been published describing the use of iCPIs to treat patients with aggressive hematological malignancies such as Hodgkin lymphoma [4-6]. However, there is a paucity of data on the safety and efficacy regarding the use of iCPIs before or after allo-HSCT. Although iCPIs can induce an anti-tumor immune response, there is also a risk of graft-versus-host disease (GVHD). Ijaz A et al. have reported that 14% of the patients who receive iCPIs after allo-HSCT develop acute GVHD and 9% develop chronic GVHD [7]. Therefore, development of GVHD should be considered while applying these agents in the pre- or post-allo-HSCT settings. Despite the

abundant data on the use of iCPIs for the treatment of cHL, only one pediatric case report is available on the use of iCPIs for PTLD [8]. Here we report the first case of successful iCPI use for the treatment of an adult patient with cHL-like PTLD following allo-HSCT.

A 58-year-old woman was diagnosed with myelodysplastic syndrome and refractory cytopenia with multilineage dysplasia (MDS-RCMD) with complex karyotype in June 2013. She received bone marrow transplantation from an HLA8/8 allele-matched unrelated donor in March 2014. In March 2018, ^{18}F fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) revealed left supraclavicular and abdominal paraaortic lymphadenopathies (Figure 1a and b). Biopsy of the supraclavicular lymph node was performed for diagnosis, and the histology showed EBV-associated cHL-like PTLD with the presence of CD15, CD30, and EBER-positive tumor cells.

We started administering brentuximab vedotin (BV) every three weeks. After six courses of BV, ^{18}F-FDG-PET/CT showed complete remission. After four months, follow-up CT study showed paraaortic lymphadenopathy of 20 mm in diameter. The CT-guided biopsy of the lymph node demonstrated the relapse of cHL-like PTLD. ^{18}F-FDG-PET/CT revealed no other lymph node involvement (Ann Arbor stage I). Following the regulatory approval, biweekly administration of nivolumab was started.

The starting dose was set to 240 mg/every other week. After four courses, liver toxicity (grade 3) developed, thus we postponed the next course. One month later, the liver function was improved. Therefore, we restarted administering nivolumab at the same dose. After six courses, cutaneous pruritus developed as an immune-related adverse event (irAE) of nivolumab, and thus we started administering 15mg prednisolone. Final evaluation with ^{18}F-FDG-PET after ten courses of nivolumab administration showed complete remission of PTLD (Figure 1c, d).

Although nivolumab is considered as a rational treatment option in cHL-like PTLD, to the best of our knowledge, this is the first case report of its use in an adult patient of EBV-associated PTLD after allo-HSCT. Ijaz A et al have demonstrated the high risk of acute and chronic GVHD among patients who received iCPIs after allo-HSCT [7]. In fact, a treatment for skin rash and liver damage after using iCPIs is needed, although it is difficult to distinguish between GVHD and irAE.

In conclusion, this case report shows the effectiveness of iCPIs on EBV-associated cHL-like PTLD after allo-SCT. However, the high risk of GVHD and irAE should be carefully considered while treating with iCPIs. To evaluate the efficacy and safety of iCPIs for PTLD, further analysis with a larger number of patients must be conducted.

Acknowledgments

We are grateful to the medical, nursing, and laboratory staff of the participating departments for their contributions to this study.

Compliance with ehical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Funding: none

Conflict of interest: The authors declare no conflicts of interest.

Informed consent: Informed consent was obtained from the patient included in the study.

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Figure. 1

Response to nivolumab in a patient with Hodgkin lymphoma-like PTLD after alloSCT. ^{18}F-FDG-PET obtained before (a and b) and after 10 courses of nivolumab administration (c and d). The maximum intensity projections (a and c) and axial reconstructions of the CT/PET fusions (b and d) are shown. The pre-treatment images (a and b) show a metabolically active lymph node in the left inner hilum of the kidney. The post-treatment scans (c and d) reveal the complete resolution of the metabolic activity in the lesion.