Nivolumab for treatment of progressive multifocal leukoencephalopathy in Sézary syndrome

N. Grassl 1, L. Bunse 1, T. Beutel, M. Klockziem, A. Gass, M. Platten and P. Eisele

Department of Neurology, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim, Germany

doi:10.1111/ene.14433

Progressive multifocal leukoencephalopathy (PML) is a rare but severe opportunistic central nervous system infection caused by John Cunningham (JC) polyomavirus (JCPyV) in immunosuppressed patients. Immune checkpoint blockade stimulates immune function and has been suggested to reinvigorate viral clearance in PML patients by expanding JCV-specific T cells [1]. Among the first 13 published PML patients treated with programmed cell death 1 inhibitors (PD1I) eight showed a mild to marked treatment response [2–7]. The underlying conditions ranged from chronic lymphocytic leukemia, AIDS, non-Hodgkin lymphoma, idiopathic lymphopenia, variable immune deficiency, Hodgkin lymphoma, B-cell lymphoma to primary and combined immunodeficiency. Here, we present a patient with Sézary syndrome (SS) who developed PML and did not benefit from treatment with nivolumab.

A 69-year-old man was diagnosed with SS stage IVa in December 2016. Treatment consisted of 46 cycles of extracorporeal photopheresis combined with interferon alfa-2a injections resulting in stable disease. In September 2019, the patient developed progressive non-fluent aphasia and right-sided hemiparesis. Brain magnetic resonance imaging showed a left-sided T2-hyperintense frontotemporal lesion with reduced apparent diffusion coefficient along the margin of the lesion (Fig. 1a). Polymerase chain reaction amplification of JCPyV DNA revealed 4505 copies/ml in the cerebrospinal fluid (CSF). Clinical, neuroimaging features and presence of JC virus DNA in CSF were diagnostic of PML.

The patient’s surrogate decision-maker gave consent to an off-label treatment with the PD1I nivolumab. Extracorporeal photopheresis and interferon alfa-2a were discontinued before administering nivolumab at a dose of 240 mg biweekly. Programmed cell death protein 1 (PD-1) was expressed on 7.4% of peripheral CD4-positive and 0.4% of peripheral CD8-positive T cells at baseline and reduced further after two infusions of nivolumab (Fig. S1). Lymphocyte subset status was characteristic of SS stage IV (Table S1). Over 5 weeks, the patient deteriorated clinically with worsening hemiparesis, global aphasia and seizures. Consistently, magnetic resonance imaging showed progression of PML lesions and new lesions in both cerebellar hemispheres and peduncles (Fig. 1a). While the CSF and serum JCPyV copy number initially stabilized, it subsequently increased (Fig. 1b). The patient’s SS remained stable under the new therapeutic regime. Treatment with nivolumab was stopped due to neurological deterioration after three doses, and the patient died the following week.

In summary, nivolumab therapy did not prevent the detrimental clinical course of PML in a patient with SS, nor was a viral clearance induced. In synopsis with previously published cases [2–7] neither viral load in CSF at baseline nor patient age nor the number of months between PML onset and start of PD1I seem to correlate with clinical improvement. It is tempting to speculate that the comparatively low PD-1 expression at baseline and overall lymphopenia prevented a more favorable response in this case. Further investigations into immune checkpoint inhibition for the treatment of PML are needed.

Acknowledgement

Open access funding enabled and organized by Projekt DEAL.

Disclosure of conflict of interest

All authors declare that they have no conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. PD-1 was predominantly expressed on peripheral CD4-positive T cells (7.4%) and less so on CD8-positive T cells (0.4%) at baseline. No relevant CTLA-4 expression on peripheral CD8 and CD4 T cells was observed. Interestingly, PD-1 expression was reduced to 1.6% on CD4-positive T cells after two infusions of nivolumab.

Table S1. Immune status of a 69-year-old patient with SS and PML at baseline (week 0) and after two infusions of nivolumab (week 4).

References

1. Tan CS, Bord E, Broge TA, et al. Increased program cell death-1 expression on T lymphocytes of patients with progressive multifocal leukoencephalopathy. *J Acquir Immune Defic Syndr* 2012; 60: 244–248.
2. Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med* 2019; 380: 1597–1605.
3. Pawlitzki M, Schneider-Hohendorf T, Rolfes L, et al. Ineffective treatment of PML with pembrolizumab: exhausted memory T-cell subsets as a clue? *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e627.
4. Küpper C, Heinrich J, Kamm K, Bäcklein V, Rothefusser S, Straube A. Pembrolizumab for progressive multifocal leukoencephalopathy due to primary immunodeficiency. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e628.
5. Walter O, Treiner E, Bonneville F, et al. Treatment of progressive multifocal leukoencephalopathy with nivolumab. *N Engl J Med* 2019; 380: 1674–1676.
6. Hoang E, Bartlett NL, Goyal MS, Schmidt RE, Clifford DB. Progressive multifocal leukoencephalopathy treated with nivolumab. *J Neurovirol* 2019; 25: 284–287.
7. Rauer S, Marks R, Urbach H, et al. Treatment of progressive multifocal leukoencephalopathy with pembrolizumab. *N Engl J Med* 2019; 380: 1676–1677.