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O1115 Control of progressive multifocal leukoencephalopathy by programmed cell death protein-1 blockade

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Background:

New therapeutic strategies aiming at the restoration of immune functions against JC virus (JCV) in patients suffering from progressive multifocal leukoencephalopathy (PML) are urgently needed. We report the efficacy of nivolumab, a monoclonal antibody targeting Programmed cell death-1 (PD-1) in a patient with idiopathic primary immunodeficiency presenting with PML.

Materials/methods:

Clinical, virological (JCV PCR in cerebrospinal fluid (CSF), blood and urine), brain MRI and immunological monitoring (Flow cytometry analysis of T cell subpopulations in blood and CSF) were performed before and during the course on nivolumab therapy (3 mg/kg IV every 2 weeks).

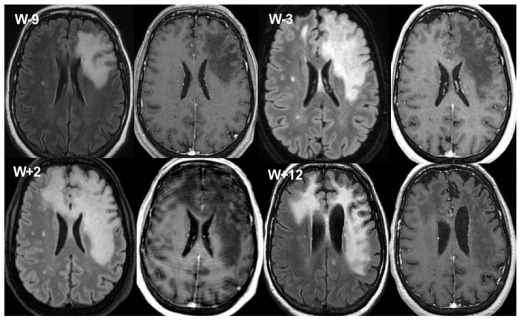
Results:

A 60-year-old woman presented on April 2018 with a diagnosis of PML based on brain MRI and CSF analysis (figure 1 A and B). She had no history of immunosuppression or infection. Extensive investigations concluded to idiopathic primary immunodeficiency. Clinical status progressively deteriorated with complete aphasia, right hemiplegia, left eye ptosis, and epilepsy. In the absence of specific therapeutic strategy and because of high PD-1 expression on CD4+ and CD8+ T cells (figure 1 C and D), we started a compassionate use of nivolumab on June 2018 (Week 0). Clinical status continued to progressively worsen until July 2018, with severely disturbed vigilance (Glasgow coma scale 7). Brain MRI repeated 2 weeks after nivolumab initiation (Figure 1A W+2) showed appearance of contrast-enhancing lesions suggestive of PML-immune reconstitution inflammatory syndrome (IRIS). CSF and blood JCV load drastically decreased (Figure 1B) concomitantly to a sharp decline in PD-1-expressing CD4+ and CD8+ T cells and increase in CD4+ T cells producing IFN-γ, granzyme B or perforin (Figure 1E). Her clinical status finally stabilized and then improved since August 2018 (Glasgow coma scale 12) while brain MRI on October 2018 showed global stabilization of PML and appearance of brain atrophy (Figure 1A W+12).

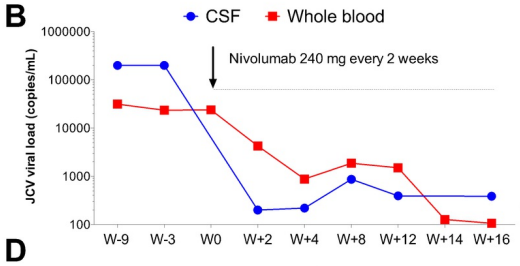
Conclusions:

Immune checkpoint molecules are inhibitory receptors expressed on immune cells limiting effector immune responses in cancer and chronic infections. In this patient nivolumab blockade of the PD-1/PDL-1 axis led to control of JCV replication, radiological IRIS and clinical improvement. Immune checkpoint blockade by re-invigorating exhausted immune cells represents a potential relevant strategy for treating PML.

A



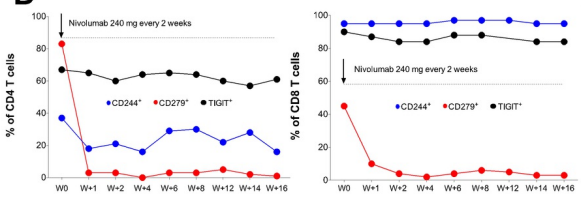
B



C

Blood	CD4 T cells	CD8 T cells
Number /mm³ (% of T cells)	5 (3%)	43 (21%)
Phenotype		
Naïve (%)	7	1
Central memory (%)	12	1
Effector memory (%)	75	44
Effector memory RA⁺ (%)	7	55
Activation markers		
CD25⁺ (%)	8	3.6
HLADR⁺ (%)	55	21
CD38⁺ (%)	75	89
Intracellular staining		
Perforine⁺ (%)	4.8	86
Granzyme B⁺ (%)	8.9	85
IFN-γ⁺ (%)	39	89
TNF-α⁺ (%)	89	91
IL-2⁺ (%)	51	38
IL-17⁺ (%)	2.7	0.25
IFN-γ⁺ TNF-α⁺ IL-2⁺ (%)	23	29

D



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