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Can Immune Checkpoint Inhibitors Keep JC Virus in Check?

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Three groups are now reporting in the *Journal* descriptions of the clinical course of 10 patients with progressive multifocal leukoencephalopathy (PML) who were treated with the immune check-point inhibitor pembrolizumab or nivolumab,[1–3] both of which are monoclonal antibodies that target programmed cell death protein 1 (PD-1). This protein is an inhibitory T-cell surface receptor that keeps the immune system from attacking the body's own tissues and organs (often called self-tolerance) and is a marker of T-cell exhaustion. When PD-1 binds with its ligand, it inhibits T-cell proliferation and cytokine production. Pembrolizumab and nivolumab block this inhibitory reaction and have been used to re-invigorate antitumor T-cell activity.

The rationale for the use of these drugs in patients with PML is based on the observation that PD-1 expression is elevated on the CD4+ and CD8+ T lymphocytes of patients with PML and is particularly elevated on JC virus–specific CD8+ T cells. Blocking the PD-1 receptor in vitro increases the cellular immune response to JC virus in healthy volunteers but only if detectable JC virus–specific CD8+ T cells are present at baseline. PD-1 blockade does not affect JC virus– specific CD8+ T cells in patients who have PML but whose disease is inactive. However, PD-1 blockade was shown to increase JC virus–specific CD8+ T cells in a patient with human immunodeficiency virus (HIV) infection who had active PML.[4]

Although pembrolizumab and nivolumab tar-get different epitopes of the PD-1 protein, their preclinical and clinical pharmacologic features are very similar. They are both IgG4 molecules that are small enough to cross the blood–brain barrier. They both have a half-life of 26 days, and they both reach a steady-state concentration after 6 doses, with nivolumab administered intravenously at a dose of 3 mg per kilogram of body weight every 2 weeks and pembrolizumab administered intravenously at a dose of 2 mg per kilogram every 2 weeks. In addition, the clinical indications of the two drugs overlap.[5]

Currently, there is no specific medication for the treatment of PML, an often deadly demyelinating disease of the brain caused by the JC virus in persons with T-cell immunosuppression. Therefore, the only available means of managing the disease is to foster recovery of the immune system, either by treating the underlying cause of immunosuppression or by discontinuing the use of immunosuppressive medications.[6]

Did pembrolizumab and nivolumab achieve viral clearance of the central nervous system and improve imaging and clinical outcomes? The patients for whom results are now

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reported in the *Journal* had various underlying conditions and had received various previous immunosuppressive treatments; in addition, the time elapsed since the onset of PML varied among them, as did the number of injections administered (which ranged from one to nine). Not surprisingly, the two HIV-infected patients were among those who had better outcomes, because their antiretroviral medications led to HIV suppression, which is associated with recovery of the immune system. Also, a patient with chronic lymphocytic leukemia who had presented with symptoms of PML 15 months before receipt of the pembrolizumab injection had already had spontaneous stabilization of PML before the injection and showed no clear incremental benefit from the medication.

As expected, treatment with the immune checkpoint inhibitors resulted in a decrease in the percentage of PD-1–binding CD4+ and CD8+ T cells in blood and, to a lesser degree, in cerebrospinal fluid. Furthermore, among six patients with PML who had available data, four who had a low but detectable number of JC virus–specific CD4+ T cells at baseline showed increases in the number of these cells after treatment and had better clinical outcomes, whereas the other two patients who had an undetectable number of JC virus–specific cells at baseline did not have a response and died from PML. However, no data were presented on the effect of PD-1 blockade on JC virus–specific CD8+ cytotoxic T lymphocytes, which are the most important effectors of the cellular immune response.[7]

The findings from magnetic resonance imaging (MRI) in these case reports deserve consideration, since a decrease in the size of the lesions was interpreted as treatment efficacy. However, in some cases, the PML lesions were replaced with atrophy, a finding consistent with destruction of white matter by PML rather than with elimination of the lesions. Furthermore, the absence of contrast enhancement on MRI suggests that the immune checkpoint blockers may not have been potent enough to trigger the immune reconstitution inflammatory syndrome (IRIS). This may be partly a result of the timing of administration in the course of PML. For example, in another case report of a patient who had Hodgkin's lymphoma, an inflammatory form of PML developed within 24 hours after the first injection of nivolumab,[8] a presentation known as "unmasking IRIS."[9] The brain biopsy showed infiltration of CD4+ and CD8+ T cells within the lesion.

Enthusiasm with respect to PD-1 blockade is also tempered by a report of PML that occurred after 1 year of nivolumab treatment administered every 2 weeks for Hodgkin's lymphoma, as well as four unpublished cases of PML related to nivolumab that were reported in pharmacovigilance databases; one of the four patients had also received ipilimumab.[10] The cost and safety profile of these medications might also be considered before adoption, since immune-related adverse events may affect multiple organ systems.[11] Do pembrolizumab and nivolumab fit the bill for treatment of PML? The current reports are encouraging but suggest that the presence of JC virus–specific T cells in the blood is a prerequisite for their use. A controlled trial may be needed to determine whether immune checkpoint inhibitors are indeed able to keep JC virus in check in patients with PML.

Supplementary Material

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