Editorial Commentary

PD-1 inhibition: a novel approach to the treatment of progressive multifocal leukoencephalopathy

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Progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the brain due to an ubiquitous polyoma virus, JC virus, was first recognized in 1958 (1). PML was initially described in individuals with B cell malignancies, chronic lymphocytic leukemia and Hodgkins lymphoma, though it occurred with other predisposing illnesses as well. Through 1981, patients with hematological malignancies were the most frequently affected; however, the advent of the AIDS pandemic changed the epidemiology of PML. Before antiretroviral therapy was widely employed, PML was observed in 5% to 10% of HIV-infected individuals (2). The increased frequency of the disease in the setting of HIV increased interest in this formerly obscure disease. This interest was further piqued in 2005 following the recognition of an association of PML with natalizumab, a highly effective therapy for relapsing remitting multiple sclerosis. Currently, depending on the populations being studied, PML is most commonly observed with either hematological malignancy (3) or HIV infection (4). Regardless of the underlying disorder predisposing to PML, virtually all patients with the disorder have an immunological abnormality, most often, an impairment of cell-mediated immunity. In the absence of reversal of the underlying immunosuppression predisposing to PML, the disorder typically advances inexorably and is almost invariably fatal.

Irrespective of the population studied, the seroprevalence of JC virus is high with rates in adulthood approximating 70% (2). In light of the ubiquitous nature of the virus and the rarity of PML, even among immunosuppressed individuals, the barriers to the development of the disorder must be multiple and high. Currently, PML is believed to result as a stochastic event in which several steps must ensue. These include the following: (I) infection with JC virus; (II) establishment of latent or persistent JC virus infection in extra-neural tissue; (III) rearrangement of JC virus from an archetype strain to a neurotropic strain capable of productively infecting glial tissue; (IV) re-activation of the neurotropic JC virus strain from sites of viral latency; (V) viral entry into the brain; (VI) establishment of productive infection of oligodendrocytes; and, importantly, (VII) an ineffective immune system preventing immunosurveillance from eliminating or suppressing the infection. The importance of the immune response is highlighted by the virtually universal presence of an immune abnormality in patients with PML; the markedly improved survival rates for PML in affected individuals in whom the immunological abnormalities can be reversed, such as, the removal of natalizumab in natalizumab-associated PML or the introduction of antiretroviral therapy in AIDS-associated PML; and the occasional clinical expression of the disease within days to weeks of the introduction of an immunosuppressive drug in an individual with other predisposing causes, i.e., in a period of time too short for the series of events necessary for disease development.

Historically, survival with PML had been abysmal,

although survival rates improved dramatically in AIDS-associated PML with the introduction of antiretroviral therapy (5) and survival with natalizumab-associated PML approximates 75% following discontinuation of the offending monoclonal antibody. Despite those observations, in other contexts, PML survival remains poor and efforts to control this disorder have been disappointing. Strategies to treat PML with compounds that inhibit JC virus replication effectively *in vitro* have been disappointing. There have been only a handful of clinical trials conducted. The largest was a phase II trial of antiretroviral therapy versus antiretroviral therapy plus either intravenous or intrathecal cytosine arabinoside that enrolled 57 AIDS-associated PML patients which showed no benefit from the addition of cystosine arabinoside (6). Smaller phase I/II or phase II clinical trials that have investigated topotecan (7) and cidofovir (8) were also unsuccessful. Similarly, mefloquine which was demonstrated *in vitro* to have a high anti-JC viral activity (9) and penetrates the CNS blood brain barrier very well was found to be ineffective in reducing CSF JC viral load (10). All other measures to arrest PML have been predicated on anecdotal evidence including efforts to block viral entry or inhibit viral transport to the endoplasmic reticulum with mirtazapine, chlorpromazine, brefeldin, and retro-2cycl; inhibit viral DNA replication with ganciclovir or leflunomide; or enhance immunity with interleukins (IL2, IL5 or IL7) (11) or interferon alpha (12). Some of these therapies are associated with significant systemic toxicity and cannot be recommended in the absence of proof of efficacy.

The demonstration of a potential effect of programmed cell death protein 1 (PD-1) inhibition on JC viral replication in the CNS and possibly survival as revealed in this study of pembrolizumab administered as 2 mg per kilogram body weight every 4 to 6 weeks by Cortese and colleagues (13) recognizes a novel way of enhancing immunity as a therapeutic intervention for PML and, at first glance, appears very promising. In unpublished data cited in this study, the investigators report finding increased expression of PD-1 and programmed death ligand 1 (PD-L1) in PML lesions in brain tissue obtained at autopsy. They also report finding a higher percentage of PD-1 expression on CD4+ and CD8+ lymphocytes in the blood and CSF of PML patients was found than in healthy controls. The former confirms an earlier observation of other investigators of elevated PD-1 expression on CD4 and CD8 T lymphocytes in patients with PML (14). Based on these observations, they hypothesized that the expression of the PD-1-PD-L1 pathway may preclude clearance of the JC virus and that treatment with a PD-1 inhibitor might enhance the antiviral effect. In 5 of the 8 treated patients, they demonstrated a significant reduction of cerebrospinal fluid (CSF) JC viral load during treatment that was coupled with an increase in *in vitro* CD4+ and CD8+ anti-JC virus activity (13). Four of the 5 responders with a persistent reduction in JC viral load had clinical stabilization and no recurrence of PML 16 to 26 months after the last infusion suggesting a possible survival benefit with treatment (13). The three patients failing to demonstrate a meaningful reduction in CSF viral load also failed to mount an increase in *in vitro* anti-JC virus T cell activity despite having similar PD-1 suppression in their blood and CSF (13). This therapeutic approach is likely to be particularly valuable with certain underlying disorders that predispose to PML in which measures to reverse immunological dysfunction are either not possible or unlikely to be effective.

This study, of course, is very preliminary. It included a small number of patients with diverse PML predisposing illnesses (four with hematological malignancy; two with HIV infection; and two with idiopathic lymphopenia). The publication of these 8 cases was accompanied by two case reports in the same journal of a PD-1 inhibitor administration with PML. In one, a patient with PML complicating a diffuse large B-cell lymphoma demonstrated a reduction of CSF JC viral load to an undetectable level and at least a 17 months survival after pembrolizumab administration (15). In the other, PML occurring with primary immunodeficiency was treated with nivolumab and demonstrated a significant reduction in CSF JC viral load (16). However, caution is warranted as PML has been reported following nivolumab administration in at least one patient and review of pharmacovigilance databases reveals other cases (17). Furthermore, not only was pembrolizumab ineffective in 4 of the 8 patients treated by Cortese *et al.*, it has also been reported to be ineffective in treating PML in other patients despite a demonstrated decrease in PD-1+ T lymphocytes (18,19).

An alternative strategy to treat PML involves an enhancement of cell mediated immunity to JC virus by administering T cells from healthy donors that target BK virus. BK virus shares as much as a 75% genetic homology with JC virus (20) suggesting that these cells would be active against JC virus. In a study of 3 patients with PML, 2×10^5 cryopreserved, most closely human leukocyte antigen (HLA) matched T cells per kilogram targeting BK virus were administered with clinical and radiographic improvement

and CSF viral clearance noted in two (21). Additional studies are warranted to demonstrate the safety and efficacy of this approach to treating PML and the development of T cells that target JC virus rather than BK virus may prove even more effective.

While the administration of pembrolizumab in Cortese *et al.* series was unassociated with any major adverse event (recurrent psoriasis and a maculopapular rash were reported in one patient each), it can be associated with catastrophic neurological complications. PD-1 inhibitors have been associated with rapid disease progression and even death in individuals with multiple sclerosis (22), therefore, their use in PML that has complicated the use of an MS disease modifying drug would be contraindicated. In addition to natalizumab, other MS disease modifying therapies associated with PML, include fingolimod, dimethyl fumarate, alemtuzumab, but with markedly lower frequencies (23). This phenomenon of worsening multiple sclerosis has also been reported with monoclonal antibodies that are directed against another checkpoint inhibitor, CTLA-4 (24). Additionally, a wide variety of other neurological complications have been reported with checkpoint inhibitors including inflammatory myopathies, myasthenia gravis, demyelinating peripheral neuropathies, vasculitic neuropathies, aseptic meningitis, autoimmune encephalitis, and hypophysitis (25).

PML remains a rare, but devastating disease, for which effective treatments are lacking. A better understanding of the mechanisms that contribute to viral persistence and replication and the complex interaction between the immune system and viral regulation will almost certainly lead to a better understanding of how to effectively treat the disease. The absence of an animal model has not only hampered our ability to study the pathogenesis of the disorder but has also impeded the ability to test candidate therapies *in vivo*. This report of the apparent efficacy of pembrolizumab in a small number of patients with PML is a welcome step in the right direction and merits a larger well-designed clinical trial. Whether it should be adopted prior to such a study is an application of the art rather than the science of medicine. One may consider heeding the words of Claudius in Shakespeare's Hamlet (Act 4, Scene 3) when confronted with a rapidly advancing, fatal illness, "*Diseases desperate grown*, *by desperate appliance are relieved*, *or not at all*."

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Footnote

Conflicts of Interest: Dr. Joseph R. Berger has been a consultant for Amgen, Biogen, Celgene, Genentech/Roche, Merck/Serono, Millennium/Takeda, Novartis, and Shire. He serves on the scientific advisory boards of Excision-Bio and Inhibikase. He has received grant support from Biogen and Genentech/Roche.

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