Long-Term Effects of Immunotherapy and Stem Cell Transplants in MS Patients

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Multiple sclerosis (MS) is an autoimmune disorder in which the body's immune cells attack nerves in the brain and spinal cord. Nerve damage is mediated by inflammation and immune cell-mediated destruction of myelin, a protective protein surrounding neurons. As a result, nerve impulses are slowed or stopped, resulting in a multitude of symptoms including: impaired muscle and cognitive functions, loss of bowel and bladder control, difficulty seeing and fatigue. Generally, the symptoms of MS occur during acute episodes called relapses, which are separated by remission periods that are relatively free of disease symptoms. In progressive MS disease, neurologic functions continue to decline over time. Current treatments for MS are aimed at limiting the magnitude and frequency of attacks and improving quality of life, but no cures exist for patients. Immunosuppressants have been successfully used to minimize disease symptoms in relapsing patients, but are only partially capable of reducing the frequency of relapses and are not effective against progressive disease.

High-dose immunotherapy (HDIT) followed by autologous hematopoietic stem cell transplants (AHCT) has been successfully used to treat other autoimmune disorders, as well as disease in animal models of MS. To determine the efficacy of HDIT/AHCT for treatment of MS, researchers in the Clinical Research Division examined the ability of HDIT/AHCT to induce sustained remission from autoimmune events and to prevent further loss of neurological function in 26 patients with severe MS. Patients represented a heterogeneous group with severe progressive MS who had limited success with an array of prior therapies. HDIT was used to deplete autoreactive lymphocytes that contribute to MS pathogenesis, and consisted of a regimen of total body irradiation, high-doses of the cytotoxic chemotherapeutic agent cyclophosphamide and *in vivo* T-cell depletion. Patients were subsequently infused with lymphocyte-depleted autologous peripheral blood stem cells that were obtained prior to HDIT. Together, these treatments ablate autoimmune lymphocytes and permit regeneration of a self-tolerant immune system from T-cell-depleted stem cells.

Follow-up evaluations measured the patients' disability status, the extent of brain lesions, and the presence of oligoclonal immunoglobulin bands in the cerebral spinal fluid as a measure of

inflammation in the central nervous system. Nash and colleagues in the Clinical Research Division previously reported the initial patient evaluations, generally describing mild to moderate regimen-related toxicities, which were transient and reversible. Despite the severe stage of MS and extensive brain damage and loss of neurological function of patients prior to HDIT/AHCT, stabilization of disease was observed in the majority of patients. Furthermore, important modifications of the treatment protocol were also identified to increase the safety of HDIT/AHCT for patients.

In the current publication, Bowen *et al* report on the long-term evaluation of patients following HDIT/AHCT treatment. A significant number of patients remained stable up to six years post treatment, with few late side effects of immunotherapy. However, some patients demonstrated worsening neurological function, which was associated with an increased level of disability at initiation of the study. Additionally, many patients whose MS worsened did not show signs of increased CNS inflammation or brain lesions, suggesting that other disease mechanisms may be responsible for disease progression. Together these results indicate that HDIT/AHCT is a useful treatment option for some patients with MS, and that similar studies are warranted in patients with less severe MS. Randomized studies examining the clinical role of HDIT and AHCT in comparison with conventional MS treatments will also be important.

JD Bowen, GH Kraft, A Wunders, Q Guan, KR Maravilla, TA Gooley, PA McSweeney, SZ Pavletic, H Openshaw, R Storb, M Wener, BA McLaughlin, GR Henstorf, RA Nash. 2011. Autologous hematopoietic cell transplantation following high-dose immunosuppressive therapy for advanced multiple sclerosis: long-term results. *Bone Marrow Transplantation*. Epub ahead of print, doi: 10.1038/bmt.2011.208.

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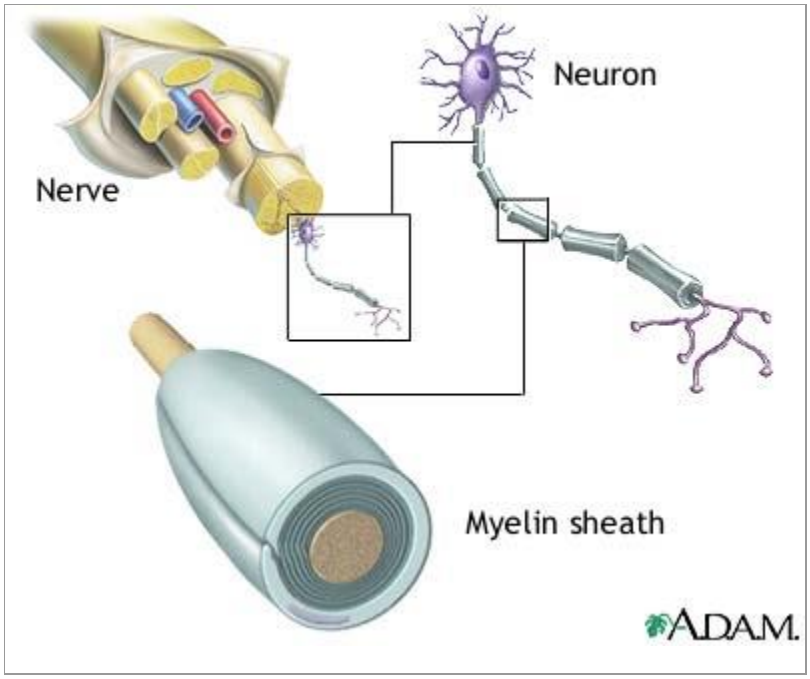

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