Failure of Autologous Hematopoietic Stem Cell Transplantation to Prevent Relapse of Neuromyelitis Optica

Here we describe a woman with relapsing neuromyelitis optica (NMO) who was seropositive for NMO-IgG and who experienced a relapse of myelitis 4 months after autologous hematopoietic stem cell transplantation (AHSCT) for a lymphoma that developed while receiving azathioprine therapy. Analysis of serum samples obtained at key points in her disease course using 3 different serological techniques (immunofluorescence, immunoprecipitation assay, and enzyme-linked immunosorbent assay) documented a marked increase in titer coinciding with the relapse.

Report of a Case. A 64-year-old woman who had a history of optic neuritis in 1989 presented with left-sided abdominal pain accompanied by dysesthesias and severe left leg weakness and spasticity in 2006. Magnetic resonance imaging revealed three T2-hyperintense lesions in the thoracic spinal cord 4 months after the first symptom, the longest spanning 2 vertebral segments. Cerebrospinal fluid analysis revealed a cell count, total protein, IgG index, and synthesis rate in the reference range but detected 9 cerebrospinal fluid–unique oligoclonal bands. Results of testing for NMO-IgG were positive (immunofluorescence titer, 480). Following a 5-day course of intravenous corticosteroids, her condition improved and she could ambulate with a walker. She was treated with 60 mg of prednisone every other day and azathioprine 150 mg daily. On October 2008, she presented with fatigue, fever, and night sweats. Her hemoglobin level was 7.3 g/dL. Adenopathy of the anterior mediastinum, epigastrum, retrocrural space, and retroperitoneum were discovered, and a bone marrow biopsy was consistent with Hodgkin lymphoma. She received six 4-week cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine, and reimagining revealed complete remission. Azathioprine use was discontinued. Serology for NMO-IgG revealed a 10-fold reduction by the immunoprecipitation assay compared with baseline and negative result by immunofluorescence at 1:120 serum dilution.

Figure. Timeline of clinical events and serological data. A, Clinical and neuromyelitis optica (NMO)--IgG titer evolution. Results of additional methods of titer evaluation for each time point are (Sep 2006) immunoprecipitation assay [IPA]=222 nmol/L, enzyme-linked immunosorbent assay [ELISA] > 160 U/mL; (Oct 2008) IPA=20.8 nmol/L, ELISA < 5 U/mL; (Aug 2009) IPA not tested, ELISA > 160 U/mL; (May 2010) IPA=262.8 nmol/L, ELISA > 160 U/mL; and (Dec 2010) IPA=19.9 nmol/L, ELISA < 5 U/mL. B, Sagittal T1-weighted image with gadolinium-enhanced T1 spinal cord magnetic resonance images (May 2010) showing abnormal enhancement from T3 through T8. IF, immunofluorescence; ON, optic neuritis; TM, transverse myelitis; qid, 4 times per day; qod, every other day; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AHSCT, autologous hematopoietic stem cell transplantation.
Comment. Neuromyelitis optica is an autoimmune disease of the central nervous system characterized by the disease-specific aquaporin-4 reactive autoantibodies that activate complement and lead to inflammatory demyelination and necrosis.

Use of AHSCT is being explored as a treatment for autoimmune diseases that are unresponsive to conventional treatments; its use permits the administration of potent immunosuppressive drugs in an effort to permanently eliminate autoactive immune cells and establish a new immune repertoire. No series of AHSCT for NMO have been published; however, recruitment is ongoing for a trial of AHSCT in NMO (www.clinicaltrials.gov; NCT00787722) in which 10 patients will be treated with high-dose cyclophosphamide and rabbit antithymocyte globulin/rituximab followed by AHSCT.

Because AHSCT is costly (generally ranging from $50 000 to $100 000, www.nbmtlink.org) and risk for morbidity and mortality are substantial, the expectations that it would prolong disease-free survival should be more rigorous than for less aggressive immunosuppression. Data on the efficacy of AHSCT for antibody-mediated autoimmune disease are scarce. In the evaluation of AHSCT success in 473 patients with severe autoimmune diseases, patients with idiopathic thrombocytopenic purpura had lower success rates (sustained response in 2 of 7 patients, or 29%) than other diseases that are not mediated by antibodies.2 De novo antibody-mediated autoimmune syndromes have been reported after AHSCT.3 In a study of pre- and post-AHSCT vaccination, immunological memory of a T-cell–dependent neoantigen was eradicated but humoral response persisted in 60% of juvenile patients with idiopathic arthritis or patients with systemic lupus erythematosus.3 Oligoclonal bands persisted in the cerebrospinal fluid of 5 of 6 inpatients with multiple sclerosis who were treated with AHSCT.6

This article raises concerns about the efficacy of AHSCT for NMO, and data from an ongoing clinical trial may determine whether some patients experience a benefit. In the reported case, it is uncertain whether inadequate reversion of immune tolerance or sustained autoimmunity to aquaporin 4 autoantigen was responsible for such treatment failure. This case further suggests that an association between NMO disease activity and titer of aquaporin 4 autoantibodies may exist, but routine testing for this purpose is not yet indicated.

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How Safe Could Intrathecal Transplantation of Mesenchymal Stem Cells Be Considered in Multiple Sclerosis?

We read with considerable interest the exploratory study by Karussis et al on the safety of intrathecally transplanted mesenchymal stem cells (MSCs) in patients with multiple sclerosis (MS) and those with amyotrophic lateral sclerosis (ALS). Nevertheless, the data presented in that study do not clearly support the positive conclusion drawn, at least in MS. More specifically, the scientific basis of the intrathecal route is limited because there is only 1 relevant study on the animal disease model. Additionally, there is, to our knowledge, no scientific evidence that the presence of MSCs within the central nervous system (CNS) is an absolute necessity for the effect these cells might have in autoimmune demyelination. Based on magnetic resonance imaging (MRI) findings, the presence of any significant unexpected pathology up to the 6-month follow-up may not be totally excluded because the unpredicted behavior of MSCs within the CNS at the microscopic level might potentially be harmful, though clinically silent or undetected by a 1.5-T MRI scanner. Moreover, it is questionable whether the transplanted MSCs migrated toward MS lesions as expected because no relevant MRI finding was evident according to the data.

Although, based on previous in vitro studies, the authors accept that there is a low risk of treatment-related malignant neoplasm induction, recent data indicate the spontaneous malignant transformation is biohazard in long-term ex vivo expansion of human MSCs. Finally, the immunomodulatory effects induced by the intravenously administered MSCs lack any evidence about T-helper 17 lymphocyte (Th17) response profiles in treated patients, thereby imposing further weakness on the concept of safety despite the profound reduction of other proinflammatory factors or the increase of regulatory T cells in patients who received transplants. In addition, recent preliminary data indicate that MSCs may induce Th17 responses concomitantly with Th1 response suppression. Such behavior of migrated MSCs might potentially exacerbate immune reactions within the CNS, in situ.

Within the emerging and promising field of regenerative medicine, the results and conclusions of clinical studies describing cell-based therapies should be interpreted with great caution to minimize any treatment-related harm to the already-unfortunate patients.

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Financial Disclosure: None reported.

In reply

Karacostas and colleagues express their concerns about safety issues arising from our trial with MSCs in MS and ALS. Our detailed responses to each question raised follow.

Concerning general safety issues, in our phase I/II study, our main goal was to investigate the feasibility and short-term safety of the treatment modality. We were able to rule out any short-term toxicity, as shown by the 6-month follow-up. Additionally, as mentioned in the manuscript, we followed up the patients for up to 3 years and were not confronted with any exceptional clinical change. We performed yearly MRI scans in all patients that did not reveal any unexpected pathology (up to at least 3 years) and continued to show stabilization and suppression of the disease (follow-up data not yet published). We definitely share the concerns regarding unknown long-term toxicities, especially because previous experience with other treatments of MS (natalizumab, liminode) has shown that small-scale trials are not sensitive enough to rule out all possible adverse effects. This is clearly underlined in our conclusions that “... larger studies are warranted to establish the long term safety and efficacy of this modality. ...”

Concerning the dangers of malignancy, there is indeed one study indicating a possible malignant transformation of MSCs in long-term cultures. However, this is the only one, of several studies, to show such a danger, and Røsland et al claim that the conditions of long-term in vitro cultures (for several months) may “provide stress-induced genomic instability, contributing to the malignant phenotype.” In our