LETTER TO THE EDITOR

Autologous HSCT for advanced MS: Is the glass half-empty or really half-full?

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Sir, On the basis of persisting demyelination and axonal degeneration in brains of patients with progressive multiple sclerosis (MS), Metz et al. (2007) concluded that ‘autologous hematopoietic stem cell transplantation fails to stop demyelination and neurodegeneration’. This was based on routine and immunohistochemical stains of brains from five patients who died at a median of 2 (range 0.5–18) months after high-dose immunosuppressive therapy (HDIT) and autologous hematopoietic stem cell transplantation (HSCT). Although this small series of autopsy cases contributed significant and interesting insights, the conclusion in the title would appear to be an overstatement of what is actually in evidence. In a ‘Scientific Commentary’ in response to Metz et al., Martin (2007) also noted limitations in the study, including the small size of the series and that four of the five patients died early after the intervention.

A general concern regarding the examination of biopsy or autopsy materials from patients to evaluate the effectiveness of therapeutic interventions has been that it provides only a single time point for each patient assessment. This is problematic in assessing efficacy of autologous HSCT for MS since it cannot be known what changes occurred in the MS lesions after treatment but before the autopsy, or what further changes could potentially have occurred with a longer interval between the study intervention and the autopsy. This approach could thus overlook an efficacious therapy.

Metz et al. observed that HDIT and autologous HSCT was associated with a marked suppression of peripheral immune cell infiltration in the brain lesions with very few T cells and no B or plasma cells in MS lesions even after 1.5 years, which was one of the important goals of this treatment. The non-lymphocyte associated ‘inflammatory activity’ they described in the brain lesions consisted of macrophages and microglia in MS lesions, but as noted by Martin in his commentary, what they observed may have been a response to tissue injury. In addition, it cannot be completely ruled out that the cause of death (infection-related in three of the five patients) may have played a role in the observed activation of microglia, a cell population that is known to be very sensitive to a variety of signals from tissue injury. In a conceptual model of MS in which an immune-mediated process results in brain injury and was active for a period of 7–24 years as in these patients, it could be hypothesized that once the ‘classic’ inflammatory process is effectively controlled by HDIT as observed in this report, demyelination and neuronal loss with secondary activation of macrophages and microglia due to neuronal damage that occurred pre-HDIT may continue for some period of time, but ultimately be self-limited. It is therefore interesting to note that the brain from the only patient who survived more than 6 months (to 1.5 years) after HDIT had markedly fewer amyloid precursor protein (APP) positive axons in lesions as compared to brains from patients who survived for shorter intervals or to the historical controls (Trapp et al., 1998; Kuhlmann et al., 2002). Finally for the cases examined, we would have hoped that a discussion of the clinical subtype or stage of the disease would have been included by Metz et al., as these co-authors have made important contributions to our understanding of the heterogeneity of MS. The clinical subtype or stage of MS...
may be relevant to the response one might expect after intensive immunosuppressive therapy. The five patients reported had advanced progressive MS with EDSS scores between 5.5 and 8.0 before HDIT. Even if axonal loss and demyelination may be ultimately self-limited after HDIT, patients with advanced progressive MS may not be the most suitable population to benefit from immune intervention, as suggested by previous clinical experiences. The recent study by Coles et al. (2006) documents the differential clinical responses between patients with relapsing-remitting and secondary progressive MS after treatment with alemtuzumab (Campath-1H) and lends support to this notion. To best evaluate the clinical potential of HDIT and autologous HSCT for MS, patients having active disease that is not yet progressive may in fact be a more appropriate population.

The clinical trial of HDIT and autologous HSCT (HALT MS) being conducted in the United States includes patients with less advanced MS (EDSS 3.0–5.5) and active disease relapsing on therapy. Since HDIT can markedly suppress the inflammatory activity in brain lesions, we are investigating if relatively early treatment may prevent the development of progressive MS and the associated axonal loss. Patients will be followed on study for 5 years after treatment. The general claims in the report by Metz et al. may incorrectly induce the readers to dismiss this question as if it had already been answered negatively. It should be emphasized that the most effective way to address the question regarding the effect of HDIT and autologous HSCT on axonal loss and demyelination is to do properly controlled clinical trials with the appropriate imaging studies and with a sufficient length of follow-up. Well-designed clinical trials of HDIT and autologous HSCT will contribute further insights into disease mechanisms and may provide another therapeutic tool in the growing armamentarium that physicians have available for treatment of severe MS.

References
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