Is haematopoietic stem cell transplantation a treatment option for severe MS or not?

Roland Martin

Institute for Neuroimmunology and Clinical Multiple Sclerosis Research (inims), Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Eppendorf, Falkenried 94, 20251 Hamburg, Germany

“Commentary to Brain article: Metz et al. “Autologous hematopoietic stem cell transplantation fails to stop demyelination and neurodegeneration in multiple sclerosis”

E-mail: roland.martin@zmnh.uni-hamburg.de

A number of treatments are now available to treat multiple sclerosis (MS) among them several beta interferons (IFN-β) and glatiramer acetate (GA) for relapsing–remitting MS (RR-MS), and mitoxantrone and natalizumab for aggressive forms of RR-MS and those patients who have failed the first line therapies IFN-β and GA. With mitoxantrone and natalizumab, higher efficacy comes at the price of more and more severe adverse events among them secondary leukaemias and compromise of cardiac function (mitoxantrone), and progressive multifocal leukoencephalopathy (PML)(natalizumab). Numerous other therapies that fall in the latter category are currently in development including alemtuzumab (Campath-1), fingolimode (FTY-720), cladribine and others. All these approaches share several characteristics. They all target the inflammatory phase of MS; with the exception of fingolimode, they all have to be injected; and their potential risks are higher than those of IFN-β and GA. Hence, their use needs to be weighed carefully, and patient involvement in treatment decisions is paramount.

Haematopoietic stem cell transplantation (HSCT) appears to represent yet a further escalation. Autologous HSCT encompasses mobilization and preservation of autologous haematopoietic stem cells (HSCs); subsequently, in most cases, myeloablative immunosuppression by a combination of chemotherapeutic drugs and often total body irradiation (TBI); and later the reinfusion of HSCs (Tyndall et al., 1999). Small treatment series with autologous HSCT during the last decade have shown remarkable suppression of inflammatory activity in most patients, but nevertheless—at least some progression of disease. In addition, transplant-related mortality has been between 5% and 8% for autologous HSCT performed before 2000 (Saccardi et al., 2006).

The data from these trials thus indicate that this procedure may be very efficient, but at the same time pose unacceptable risks. This risk/benefit ratio has been unacceptable for many neurologists, and therefore autologous HSCT has not as yet been tested in a pivotal controlled trial.

The rationale for HSCT is that myeloablative chemotherapy with or without TBI abrogates an aberrant immune system and all its cellular components, before reinfusion of HSCs and their subsequent differentiation into all haematopoietic lineages establishes a new and tolerant immune system (Muraro et al., 2003). The complete cessation of new inflammatory activity in the majority of patients has been demonstrated at least for one HSCT regimen (Mancardi et al., 2001) suggesting that the above rationale may indeed be correct. Furthermore, studies of the immune system post-HSCT demonstrate that the T cell repertoire is not only more complex, but also completely renewed when compared with the pre-transplant T cells (Muraro et al., 2005).

Metz and colleagues (2007) now present interesting data and raise new questions that challenge the mechanistic concept as to how HSCT might work. Their histopathological findings from five MS patients who died after HSCT show that there remains at least some smouldering inflammatory activity, mainly consisting of CD8+ lymphocytes and activated macrophages and microglia, and that active demyelination and axonal damage continue after the profound immunosuppression and autologous HSCT (Metz et al., 2007). This information seems to discourage the further exploration of HSCT as a treatment for aggressive forms of MS.

How does one interpret the findings of Metz et al. in the context of our current knowledge about the mechanisms and efficacy of available MS treatments? First, one has to
acknowledge that the case series is unusual, because four of the five patients died early after the intervention, i.e. within days and months post-HSCT. Therefore, we do not know how inflammation, demyelination and axonal damage might later have evolved. Furthermore, all but one patient received a conditioning regimen that contained busulphan, which has recently been identified as a major cause of transplant-related mortality in European HSCT patients (Saccardi et al., 2006). Hence, there is the possibility, discussed by Metz et al., that the low-grade inflammation is left over from pre-transplant disease activity. Microglial turnover in the CNS takes much longer than renewal of peripheral blood monocytes and macrophages and, therefore, this possibility cannot be excluded with certainty. Another interpretation is that demyelination and axonal damage, both observed by Metz et al., may continue despite a temporary interruption of inflammation, but inflammation may re-start later now in response to tissue damage rather than the driving force. The latter analysis is supported by the experience that even the most active immunomodulatory-suppressive approaches such as alemtuzumab do not stop disease progression despite the apparent complete block of inflammation (Coles et al., 2005).

The main conclusion, therefore, is that even the most profound anti-inflammatory treatments, which temporally and profoundly suppress immune function or even renew the immune repertoire, are not suited to treat MS at a stage when CNS damage is widespread and characterized by large areas of demyelination and axonal/neuronal dropout. HSCT should, therefore, not be performed in patients who have already advanced far into the progressive stages of MS, and this conclusion is supported by the clinical experience in HSCT trials (Saccardi et al., 2006). In contrast, if aggressive courses of MS can be identified early, which remains a major clinical challenge, HSCT offers the prospect to halt disease progression with a single treatment and establish a new and tolerant immune system. Current transplant-related mortality is ~1% and, in my view, acceptable in patients with severe and rapidly advancing disease. Only carefully performed controlled HSCT trials, which should incorporate sophisticated imaging measures to document the stop or continuation of all pathogenetic aspects of MS, as well as mechanistic studies of immune system and CNS function, will clarify these many questions. Efficient immunomodulatory therapies probably also will have to be combined with neuroprotective or even restorative approaches in the future. Cell-based therapies that target either the immune system or CNS are probably among these options. These strategies are considerably more complicated and present new challenges compared to administering an oral small molecule or a monoclonal antibody. However, we should not discard them prematurely, but rather approach them cautiously.

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**References**


