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Eva Havrdova

Aggressive multiple sclerosis – is there a role for stem cell transplantation?

Abstract Conventional drugs, including disease-modifying drugs, various cytostatic regimens and steroids, are unable to control disease activity in a small group of patients with "malignant" multiple sclerosis (MS). This group of patients could be offered aggressive therapies, such as high-dose immunosuppression followed by haematopoietic stem cell transplant (HSCT). Bone marrow or peripheral blood HSCT has been proposed for the treatment of autoimmune diseases because of its immunosuppressive and immunomodulatory effects, and recapitulation of lymphocyte ontogeny may stabilise or improve the course of MS in some patients.

There have been a few small studies conducted using high-dose immunoablation and HSCT. A recent clinical trial of 85 patients treated by HSCT revealed that more than 60 % of patients may benefit from this procedure. Due to the perceived risks associated with HSCT, only patients with malignant MS who no longer benefit from more conventional therapies were enrolled. HSCT is thus a justified and feasible treatment in certain patient groups, although transplant-related mortality must be reduced.

Key words multiple sclerosis · autologous haematopoietic stem cell transplantation · bone marrow transplantation · immunoablation · lymphocytes

E. Havrdova, MD, PhD (✉)
Department of Neurology
First School of Medicine, Charles University
Katerinska 30
12808 Praha 2, Czech Republic
Tel.: +420-224/965-546
Fax: +420-224/917-907
E-Mail: ehavr@LF1.cuni.cz

Rationale for HSCT in multiple sclerosis

Profound immunosuppression, to the extent of ablation of the immune system and its replacement with an allogeneic transplant or with immature haematopoietic progenitors, may be able to limit the destructive autoimmune process that occurs in multiple sclerosis (MS) by removing auto-aggressive lymphocytes and restoring immune tolerance to neuroantigens. In addition, recent observations suggest that haematopoietic precursors may have the potential to differentiate into neural and glial cells *in vivo* and promote lesion repair [19].

High-dose chemotherapy with autologous haematopoietic stem cell transplantation (HSCT) is standard for the treatment of selected haematological malignancies. Recently, HSCT has been used with varying degrees of success in the therapy of certain autoimmune diseases, such as systemic lupus erythematosus (SLE) and severe rheumatoid arthritis. For example, in patients with severe rheumatoid arthritis who are resistant to treatment with disease-modifying anti-rheumatic drugs, significant improvements in disease activity have been observed after HSCT, even to the point of remission [18]. Furthermore, autologous HSCT of SLE patients who have failed pulse intravenous cyclophosphamide therapy has produced drug-free clinical and serological remission for more than 4 years [4, 22].

Currently, there is no evidence from well-powered, robust clinical trials of the feasibility and possible beneficial effects of HSCT in patients with MS. Rather, anecdotal reports of patients with MS and concomitant malignant disease, such as leukaemia, have demonstrated some disease stability or improvement in MS after undergoing immunoablation with stem cell support for treatment of the malignant disease [16, 17].

Similar benefits of bone marrow transplantation (BMT) have been observed in animal studies that used experimental autoimmune encephalomyelitis (EAE) as a model for MS [8, 14]. In these studies, BMT led to the

generation of new haematopoietic stem cells that used new stimuli for developing lymphocyte populations, even though the genetic constitution contributing to the susceptibility of these animals to develop EAE remained unchanged. Furthermore, HSCT appeared to both prevent disease when administered before clinical onset and halt disease progression once the EAE had developed [2, 13].

Timing of HSCT

Usually the management of patients with MS is to initiate therapy with interferon beta (IFNβ) or glatiramer acetate (GA), and to use corticosteroids during attacks. (Mitoxantrone is given to individuals with rapidly progressive disease.) When patients develop severe neurological deficit, pulse therapy with intravenous steroids, with or without cytostatics (cyclophosphamide, mitoxantrone), is used. Although current therapies offer good efficacy in terms of reducing the inflammatory activity of the disease, they do not have a significant impact on substantial progression and on aggressive forms of MS once the inflammatory activity and relapses have subsided and the central nervous system (CNS) is degenerating. Treatment of secondary progressive MS (SPMS) with IFNβ and cytostatic agents, such as mitoxantrone, has been less successful in reducing magnetic resonance imaging (MRI) activity and relapse rates, although, mitoxantrone was the first drug approved for the treatment of SPMS in the United States [10]. Nevertheless, the potential for serious cumulative cardiotoxicity of mitoxantrone limits the duration of treatment. Thus, considering the potential adverse effects of mitoxantrone, and the fact that some patients do not appear to respond to any approved MS therapy – including those with primary progressive MS – alternative strategies must be investigated. Patients with rapid progression of disability, i. e. those that gain at least 1.0 point on the Expanded Disability Status Scale (EDSS) in the previous year, but without lower extremity paraplegia and with a preserved ability to walk at least several metres with an aid, may be candidates for HSCT.

As the success of HSCT in haematological diseases depends on early intervention, it is probable that the earlier stem cell therapy is initiated in MS, the better the prognosis. Moreover, studies suggest that axonal damage is an early event in MS lesions and normal-appearing white matter [11, 12, 21]. Treatment at an early stage, particularly in patients with as low an EDSS score as possible, should help prevent the massive axonal loss associated with later stages of MS and the accumulation of further deficits and disability.

Feasibility of HSCT in MS patients

A few studies have already demonstrated the feasibility of using autologous HSCT in MS patients who are frequently immunocompromised as a result of existing medications, including high-dose steroids and cytostatics [3, 6, 15]. In 1997, a Phase I/II pilot study of HSCT was published, which enrolled 15 patients with progressive MS and severe disablement (EDSS scores of 5–7.5) [6]. Durable neurological improvements were observed in the majority of patients within the 6-month follow-up. Mild, transient neurotoxicity occurred in six patients in the immediate post-transplant period only.

Recently, the same study group has supported these data further, with results from a trial of autologous HSCT in 85 patients with progressive MS, who were followed for 3–59 months (EDSS score of 4.5–8.5) [7]. Confirmed progression-free survival was 74 % at 3 years in patients with primary progressive MS, and slightly higher (78 %) in patients with SPMS or relapsing-remitting MS. In addition, the probability of disability progression was 20 % at 3 years. Neurological improvement of ≥ 1 point in the EDSS score was observed in 18 (21 %) patients. Moreover, post-transplant MRI showed activity at any time in only 8 % of evaluable cases. Thus, further study of HSCT in MS is both justified and feasible. However, significant mortality risk did exist. These data are now being utilised in the design of future trials to reduce this transplant-related mortality. Furthermore, due to the perceived risks associated with this intervention, the procedure should be undertaken only in patients with severe and rapidly progressing MS for which all conventional therapeutic approaches have failed to stop disease progression.

We are conducting a Czech study, started in February 1998, which aims to investigate the feasibility, safety and efficacy of arresting the progression of MS using an aggressive (high-dose) immunoablative conditioning procedure together with autologous HSCT. The cytotoxic agents used during the conditioning procedure (BCNU, etoposide, Arabinosylcytosine and melphalan) have been commonly used in autologous transplantation for malignant lymphomas, and are extremely myelo- and lymphotoxic, and relatively less toxic to extra-haematopoietic organs and tissues, with minimal neurotoxicity. During the procedure, stem cells are mobilised into the peripheral blood using cyclophosphamide plus haematopoietic growth factors. Approximately 10 days later, leukapheresis is conducted and repeated as necessary, in order to gather sufficient stem cells. Purged cells are frozen and conditioning commences 3–6 weeks later. Immunoablation is carried out as described in Table 1, then stem cells are re-infused. Clinical follow-up, scoring, analysis of lymphocyte subpopulations and other safety measures continue to be

Table 1 Conditioning regimen

BEAM (BCNU 300 mg/m^2, etoposide 800 mg/m^2, ARA-C 800 mg/m^2, melphalan 140 mg/m^2)
Or
BEAM (Days –6 to –2) + ATG (Fresenius) 4 mg/kg Days +1 and +2

BCNU 1-beta-D-arabinofuranosylcytosine; *ARA-C* Bischloroethylnitrosourea; *ATG* Antithymocyte globulin

undertaken every 3 months, and MRI is performed every 6–12 months.

Twenty-nine patients have been included in the study, and 13 patients have now been followed up for more than 36 months. More than 60 % of these patients remained stable as demonstrated by EDSS scores – one of them after initial worsening. This proportion of patients compares very favourably with confirmed treatment failure rates for IFNβ in SPMS of 35–60 % over 2–3 years of observation [5, 9, 20]. In addition, a meta-analysis of large comparative trials of progressive MS demonstrated that the treatment failure rate in placebo groups was about 45 % [23]. Thus, it appears that HSCT can stabilise progressive MS in a population of MS patients who are resistant to approved therapies and have such a poor prognosis.

Although it is widely accepted that lesion load does not correlate with disease stage and clinical disability, we were able to find a clear and statistically significant correlation between clinical worsening and lesion load accrual after HSCT. The speed of brain atrophy progression was also clearly higher in patients not responding to this type of therapy.

Although 70 % of patients worsened slightly following the mobilisation procedure, this was reversible and they improved when the procedure was complete. There were three cases with early toxicity events, including respiratory distress and neurological deterioration: one patient developed hepatitis C; one individual experienced ongoing disease activity, with enlarging hyper-intense MRI lesions, clinical deterioration and repeated infections (this patient died 30 months after HSCT); another patient developed Factor VIII inhibitor syndrome 1 year after HSCT.

A successful case history for HSCT therapy

One of the patients in our study was a 25-year-old female with an 11-year history of remitting MS, and with an EDSS score of 4.5 when she started treatment with IFNβ-1b. During this treatment, she experienced three relapses in 6 months, and her EDSS increased to 6.5. IFNβ-1b treatment was stopped and cyclophosphamide pulses were started without effect. Pulse steroid treatment was again needed for another relapse and intravenous immunoglobulin (IVIG) therapy was attempted. In the following 4 months she was only able to take four steps with bilateral support. The patient was offered immunoablation with HSCT because the course of her MS was deemed to be malignant and had not responded to any conventional treatments.

Six months after mobilization and immunoablation, she was able to walk 30 metres with two canes, and 3 years later was able to walk 1 km. She undergoes only temporary worsening of her status in association with infections, and her MRI results are stable. At least 5 years of an acceptable quality of life has been afforded to her by HSCT.

Effect of baseline disability

Another research group performing HSCT in Chicago (Burt et al.) has reported that treatment outcome largely depends upon baseline disability [1]. We can confirm this finding and consider that patients with an EDSS lower than those enrolled in our study, who should have a lower level of axonal loss, would benefit more from HSCT.

Conclusions

Despite the introduction of new immunomodulating and well-tolerated therapies for MS, there remain a small proportion of patients for whom these therapies are inadequate to control disease, in particular, those with an aggressive, malignant course of MS who are losing important CNS functions. Therefore, well-controlled trials of more intensive approaches to therapy are needed urgently. To date, a study of 85 patients treated with high-dose immunoablation and HSCT revealed that more than 60 % of treated patients may benefit from this procedure [7]. Therefore, ongoing research in this treatment modality is justified, and results of our recent study add to the feasibility of this approach. To maximise the therapeutic effect of HSCT, however, it will be necessary to use regimens that are better tolerated. In addition, careful selection of patients who are less disabled and who have less CNS damage will be necessary.

The acknowledgement that patients with a lower level of axonal loss may benefit most from such therapy requires further investigation, but does not eliminate the need for effective rehabilitation following the procedure. It remains unknown whether any type of maintenance treatment is beneficial or required as we cannot assume that the entire population of auto-aggressive lymphocytes are eliminated. Even if this were the case, it would be impossible to predict whether such cells would develop from the new stem cells over the short or long term.

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