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RESEARCH PAPER

Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience

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ABSTRACT

Background Autologous haematopoietic stem cell transplantation (HSCT) is a viable option for treatment of aggressive multiple sclerosis (MS). No randomised controlled trial has been performed, and thus, experiences from systematic and sustained follow-up of treated patients constitute important information about safety and efficacy. In this observational study, we describe the characteristics and outcome of the Swedish patients treated with HSCT for MS.

Methods Neurologists from the major hospitals in Sweden filled out a follow-up form with prospectively collected data. Fifty-two patients were identified in total; 48 were included in the study and evaluated for safety and side effects; 41 patients had at least 1 year of follow-up and were further analysed for clinical and radiological outcome. In this cohort, 34 patients (83%) had relapsing-remitting MS, and mean follow-up time was 47 months.

Results At 5 years, relapse-free survival was 87%; MRI event-free survival 85%; expanded disability status scale (EDSS) score progression-free survival 77%; and disease-free survival (no relapses, no new MRI lesions and no EDSS progression) 68%. Presence of gadolinium-enhancing lesions prior to HSCT was associated with a favourable outcome (disease-free survival 79% vs 46%, p=0.028). There was no mortality. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%).

Conclusions HSCT is a very effective treatment of inflammatory active MS and can be performed with a high degree of safety at experienced centres.

INTRODUCTION

Autologous haematopoietic stem cell transplantation (HSCT) has been used as treatment for multiple sclerosis (MS) since 1995.[1] Initially, this therapy was reserved for patients with treatment-resistant progressive forms of MS, but despite initial optimism, it soon became evident that the procedure was not able to stop deterioration in patients with progressive disease.[2] However, in the following years it became clear that HSCT could be a very effective treatment for relapsing-remitting MS (RRMS), and in particular highly aggressive RRMS.[3 4] It seems that long-term remission, and maybe even cure, can be achieved.[5–8]

The goal of this therapy is to achieve long-term remission through short-lasting ablation of the immune system. The mode of action is not yet fully understood, and several mechanisms probably contribute to the effect. We know that HSCT causes a profound renewal of the immune system and not just long-lasting immune suppression.[9] At least part of the effect is likely related to removal of autoreactive cells, but some of these cells probably escape the treatment and remain after HSCT.[10] Such autoreactive cells must be kept in control to maintain remission, which could be due to restoration of tolerance to self-antigens.[11]

HSCT was introduced in Sweden in 2004 at the Uppsala University Hospital as rescue therapy for aggressive MS. Following the first and encouraging experiences,[3] neurologists from other major Swedish hospitals consulted with Uppsala University Hospital when considering this treatment. Thereby, clinical criteria for the use of HSCT were proposed as follows: diagnosis of RRMS; aggressive disease with high relapse frequency; short duration of aggressive disease with documented potential for recovery during the previous 6 months; and failure of conventional treatment. Moreover, an informal but systematic common routine for prospective clinical and radiological follow-up was agreed upon.

So far, no randomised controlled trial of HSCT has been performed. A few case series, consisting mainly of patients with primary or secondary progressive disease, have been published.[1 2 5–7 12] Systematic follow-up data from patients with RRMS are still scarce;[3 4] such data are a valuable addition to our knowledge of safety and efficacy of this treatment. The purpose of this study was to describe the characteristics and outcome of the Swedish patients.

METHODS

Subjects

Neurologists from all the major hospitals in Sweden were contacted in order to identify MS patients that had been treated with HSCT for MS. Physicians were asked to obtain consent from the

patients and to fill out a follow-up form with prospectively collected data obtained at each neurologist–patient encounter. This form included demographical data, prior treatment, type of HSCT, expanded disability status scale score (EDSS)[13] before and after the procedure, MRI and cerebrospinal fluid (CSF) data, side effects and pregnancies.

In total, 52 patients were identified. After scrutiny, four of these had been treated for a concurrent autoimmune disease and/or had an uncertain diagnosis of MS. The remaining 48 patients were included in the study. The first patient was treated in May 2004; the last included patient was treated in April 2013. Patients were distributed in the following way: Uppsala, n=19; Stockholm, n=14; Gothenburg, n=4, Umeå, n=4; Örebro, n=3; Linköping, n=2; Lund, n=2.

Twenty-two patients were men and 26 women. Forty patients had RRMS; five had secondary progressive MS (SPMS); two had primary progressive MS; and one had progressive-relapsing MS. About half the patients did not meet one or more of the above-mentioned clinical criteria for HSCT as rescue therapy for aggressive RRMS; the major exception was the eight patients with progressive MS. These were transitional cases of SPMS or compassionate care for patients considered by their treating neurologist to have exhausted all other forms of therapy. The mean age at HSCT was 31 years (range 9–52). Mean disease duration prior to HSCT was 75 months (range 4–300); for RRMS patients mean duration was 66 months (range 4–192). The mean annualised relapse rate (ARR) in the year prior to HSCT was 4.1 (range 0–12); ARR for RRMS patients only was 4.8 (range 0–12). The median patient had tried two treatments prior to HSCT (range 0–4). Previous treatments were: interferon β (n=36), natalizumab (n=21), glatiramer acetate (n=18), mitoxantrone (n=15), intravenous immunoglobulins (n=4), fingolimod (n=2) and rituximab (n=2). Four patients had no previous treatment.

Procedure

Peripheral haematopoietic stem cells were mobilised with cyclophosphamide and filgrastim according to local routine. In typical cases, a single dose of 2 g/m^2 cyclophosphamide and filgrastim 5–10 μg/kg/day for 6–7 days were administrated. No ex vivo graft manipulation was performed. In most cases, patients were admitted for conditioning about 3 weeks after mobilisation. Two different protocols for the conditioning were used. A majority of patients (n=41) were treated with the BEAM/ATG protocol (BCNU 300 mg/m^2; etoposide 800 mg/m^2; cytosine-arabinoside 800 mg/m^2; melphalan 140 mg/m^2; ATG 7.5–10 mg/kg). Seven patients (RRMS, n=4; SPMS, n=2; primary progressive MS, n=1) were treated with a cyclophosphamide/ATG protocol (cyclophosphamide 200 mg/kg; ATG 10 mg/kg). Prophylaxis against fungal, viral and bacterial infection was administrated during neutropenia. Prophylaxis against varicella virus and *Pneumocystis carinii* continued for an additional 3 months. Patients were hospitalised for a mean of 24 days (range 10–38) during HSCT.

Follow-up

Prospective follow-up included EDSS scoring at 3 and 6 months after HSCT and then yearly; MRI investigation at baseline and then at 6 months after HSCT, followed by yearly investigations up to 3 years, thereafter every other year. Sixteen patients underwent repeated lumbar puncture (optional) before and after HSCT. Patients were asked to contact their treating physicians if they experienced new symptoms. If a relapse was suspected, an MRI investigation was made to confirm inflammatory activity. Patients were not treated with any disease-modulating drugs post-HSCT if they were stable.

Statistical analysis

Statistical analyses were done with GraphPad Prism V.5.0 (GraphPad Software, La Jolla, California, USA). The paired t test was used to establish statistical significance between different time points. A two-tailed p value of <0.05 was considered significant. Survival at different time points was estimated with Kaplan–Meier survival curves and analysis of the statistical significance of the difference between two survival curves was done with the log-rank test.

RESULTS

Seven patients had less than a year follow-up time. These were excluded from further analysis with exception for description of toxicity and side effects. The remaining 41 patients were analysed further (RRMS, n=34; progressive forms of MS, n=7). Their mean follow-up time was 47.4 months (range 12–108 months), and in total, 162 patient-years of follow-up time were analysed.

Relapses

Four patients experienced a relapse post-HSCT (6, 11, 14 and 31 months after HSCT). One of these patients went on to have another relapse, nearly 5 years after HSCT. This equates to a post-HSCT ARR of 0.03 or one relapse for every 33rd year of follow-up. All relapses were confirmed by demonstration of a new gadolinium-enhancing lesion on an acute MRI.

One of these relapses was treated with high-dose corticosteroids, the remaining were not treated. As a direct consequence of the relapses, disease modifying drug treatment with glatiramer acetate was started in three patients. In one of those, treatment was subsequently changed to intravenous immunoglobulin due to pregnancy. No other disease modifying drug treatment was used post-HSCT in this cohort.

EDSS

Progression of EDSS was defined as deterioration by at least 0.5 points sustained at subsequent follow-up visits. Eight patients progressed with this definition. The evolution of EDSS is summarised in table 1. The median EDSS when the decision for HSCT was made was 6 (range 1–8.5). The median EDSS at the latest follow-up was 4 (range 0–8). The median change in EDSS was −0.75 (range −7 through 1.5); if patients with progressive disease are excluded from the analysis, the median change was −1.5 (range −7 through 1.5). The median of the lowest EDSS in the year preceding HSCT was 3 (range 0–7.5; for patients with a disease duration <1 year, this score was by definition

Table 1 Evolution of EDSS

	Pre-HSCT		At HSCT	Post-HSCT	
	Lowest EDSS	Highest EDSS	EDSS	EDSS at 1 year	EDSS at 2 years
RRMS	2.5 (0–6.5)	6 (3.5–9)	5.5 (1.5–8.5)	3.25 (0–7)	3 (0–7)
PRMS	6.5 (5–7.5)	6.5 (6–8)	6.5 (6–8)	6.5 (6–8)	6.5 (6–7.5)

EDSS values are described as median (range).
The lowest and highest pre-HSCT EDSS are the lowest and highest EDSS scores recorded in the year preceding HSCT.
EDSS, expanded disability status scale; HSCT, haematopoietic stem cell transplantation; PRMS, progressive forms of multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

always 0). The median of the highest EDSS was 6 (range 3.5–9). The greater part of the EDSS improvement occurred in the first year after HSCT. Improvement occurring more than 2 years after HSCT was seen in only one patient (EDSS at 2 years 2.0; 3 years 1.5; and 6 years 1.0). The evolution of EDSS in patients with RRMS and progressive forms of MS are summarised in table 1.

MRI

At baseline, 16 patients had no gadolinium-enhancing (Gd+) lesions, 25 patients had at least one Gd+ lesion; 13 patients had more than 10 Gd+ lesions; and 6 patients more than 30 Gd+ lesions. Five patients had MRI activity after HSCT with new T2 lesions and/or new Gd+ lesions; four of these also had a clinical relapse (see above). In total, five new Gd+ lesions and eight new T2 lesions were detected, equating to one new T2 lesion for every 20th year of follow-up.

Analysis of the CSF

All patients who were examined prior to HSCT (n=26) had oligoclonal bands in the CSF. The mean value of the IgG index was 0.81 (±0.24). Sixteen patients were examined after HSCT, 11 (69%) retained oligoclonal bands in the CSF. The mean IgG index post-HSCT was significantly lower in comparison to the pre-HSCT value in those patients (0.85±0.25 vs 0.63±0.12, p=0.0007).

Survival and prognostic factors

At 5 years, relapse-free survival was 87%; MRI event-free survival was 85%; EDSS score progression-free survival was 77%; and disease-free survival (ie, no relapses, no new MRI lesions and no EDSS progression) was 68% (figure 1). Presence of Gd+ lesions prior to HSCT was associated with a favourable outcome (disease-free survival 79% vs 46%, p=0.028). Other factors, such as disease duration, relapsing-remitting disease course and EDSS were analysed, but no statistically significant differences could be demonstrated (figure 2). No difference arose between patients treated with the BEAM/ATG protocol (n=35) vis-a-vis patients treated with the cyclophosphamide/ATG protocol (n=6) (disease-free survival at 5 years 70% vs 56%, p=0.76). A full account of the differences in outcome between patients treated with the BEAM/ATG vis-a-vis cyclophosphamide/ATG protocol is available in the supplementary section (see online supplementary table S1).

Safety and side effects

Overall, no mortality was recorded and no patient required treatment in the intensive care unit. Almost all patients experienced acute toxicity during hospitalisation, with the well-known and expected side effects of alopecia, anaemia, thrombocytopenia and leukopoenia. Additionally, somewhat less than half the patients experienced fever with bacteraemia, while neutropenic fever with negative blood cultures was seen in about a third (table 2). One patient was diagnosed with invasive fungal infection and was successfully treated with fluconazole. After discharge from the ward, very few adverse events were recorded, the most common being reactivation of herpes viruses (table 2). No clinically relevant infection with reactivated cytomegalovirus or Epstein–Barr virus was diagnosed.

Late side effects consisted mainly of herpes zoster reactivation and thyroid disease. Eight patients (17%) experienced herpes zoster reactivation (4 during the first year; 3 during the second year; and 1 during the third year after HSCT) and four patients (8.3%) developed thyroid disease (two with hypothyreosis; one with hyperthyreosis; and one with both in succession). Additionally, one patient developed Crohn's disease; one patient developed alopecia areata; and one patient contracted epilepsy. No patient developed malignancy during the follow-up period.

Pregnancy

During the follow-up period, a total of eight pregnancies arose in four women. Five healthy infants were born (in one instance a pair of twins); two spontaneous abortions and one ectopic pregnancy occurred; one legal abortion was performed. Additionally, one man became father to a healthy child conceived by in vitro fertilisation with cryopreserved semen, and one woman became mother to a healthy infant after in vitro fertilisation with cryopreserved eggs after an otherwise normal pregnancy.

DISCUSSION

In this nation-wide survey, we have demonstrated that HSCT with a low or intermediate intensity protocol is a highly effective treatment of MS, and a majority of patients display no signs of disease activity at follow-up. Patients with inflammatory disease activity prior to treatment are more likely to respond to the procedure. Additionally, we have demonstrated that HSCT can be performed safely at experienced centres, with a low risk for serious complications.

Safety of the procedure has been a major concern. In 2006, it was reported that treatment-related mortality (TRM) in Europe was 5.3%.[12] In the same report it was also noted that treatment with busulphan inferred a greater risk of death. In a later report describing the outcome of 74 Italian patients treated with BEAM, TRM was 2.7%,[6] and in a smaller Czech study of 25 patients treated with BEAM, there were no fatalities.[5] Recently, no TRM was reported in a single-centre study encompassing 95 Russian patients treated with a reduced-intensity conditioning regimen based on BEAM.[14] In our study there was no TRM. This might be related to the Swedish practice, where HSCT is only performed at university hospitals with a wealth of experience from treatment of haematological diseases. Another important factor may be the low prevalence of multiresistant bacteria in Swedish hospitals.

The treatment response was most notable in the group of patients with on-going inflammatory activity at baseline. Post-HSCT, 79% of these patients had no new MRI lesions, no relapses and no EDSS progression. When present, new disease activity was predominantly seen during the first 2 years after HSCT. No patient who had been free from disease activity during the first 3 years following HSCT went on to have a clinical relapse or new MRI lesions. Similar evolution of progression-free survival in RRMS patients have been described[5] with few patients progressing beyond the time frame of 3 years.[6] From a prognostic perspective, our data suggest that freedom from disease during the first 3 years after HSCT infers an excellent prognosis.

The effect on prevention of formation of new T2 lesions was most remarkable, with a total of eight new T2 lesions detected after HSCT in the entire cohort. This is in stark contrast to the disease course prior to HSCT, when a majority of patients were inflammatory active, and the disease course in many cases could be described as malignant. This is also quite different from the natural history as described in the clinical trials of drugs, such as interferon β, when patients in the placebo arm had an increase of about six T2 lesions per year.[15]

The most used outcome measure in reports of the effects of HSCT has been progression-free survival, which was 77% at

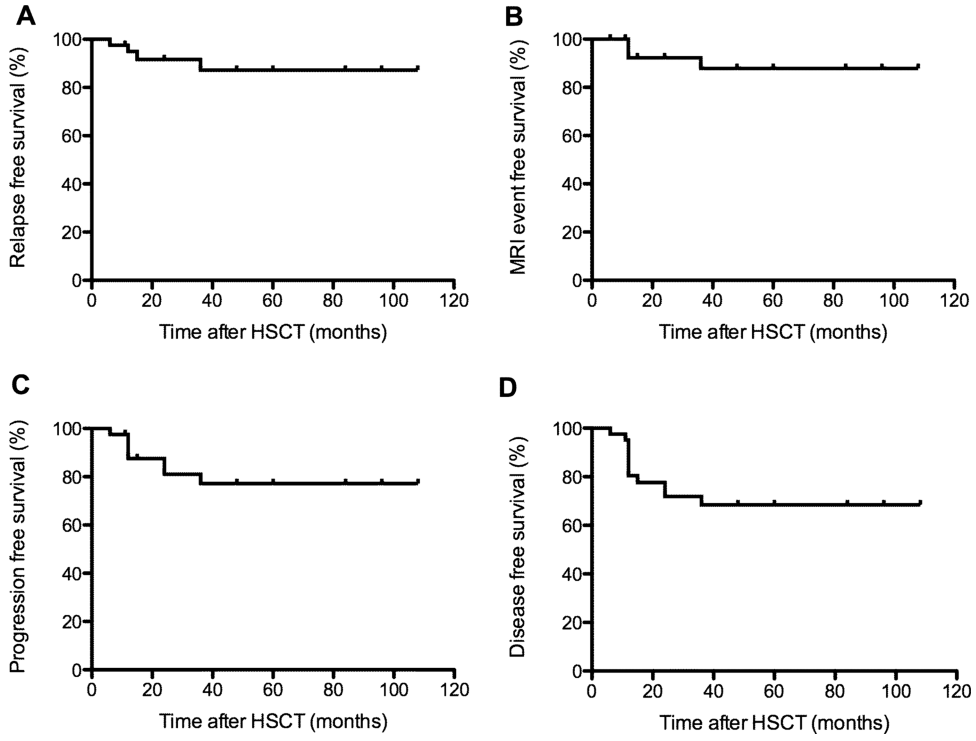

Figure 1 Kaplan–Meier survival curves of relapse-free survival, MRI event-free survival, progression-free survival and disease-free survival. Relapse-free survival, MRI event-free survival, progression-free survival and disease-free survival (no relapses, no new MRI lesions and no EDSS progression) after haematopoietic stem cell transplantation for all patients with follow-up time at least 1 year (n=41). EDSS, expanded disability status scale.

5 years. Previously, it has been reported in the range of 32–100% at 3–5 years,[4–6 14 16] and 25% at 15 years after HSCT.[7] The wide range of this measure is likely due to underlying differences in the treated cohorts (e.g, early inflammatory-active RRMS vs longstanding SPMS). Factors that have been associated with a better outcome of HSCT are presence of Gd+ lesions at baseline,[6 7] short disease duration[5 14] and diagnosis of RRMS.[5] In this study, we chose to use disease-free survival at 5 years as main outcome measure (i.e, freedom from all measurable forms of disease). We found a disease-free

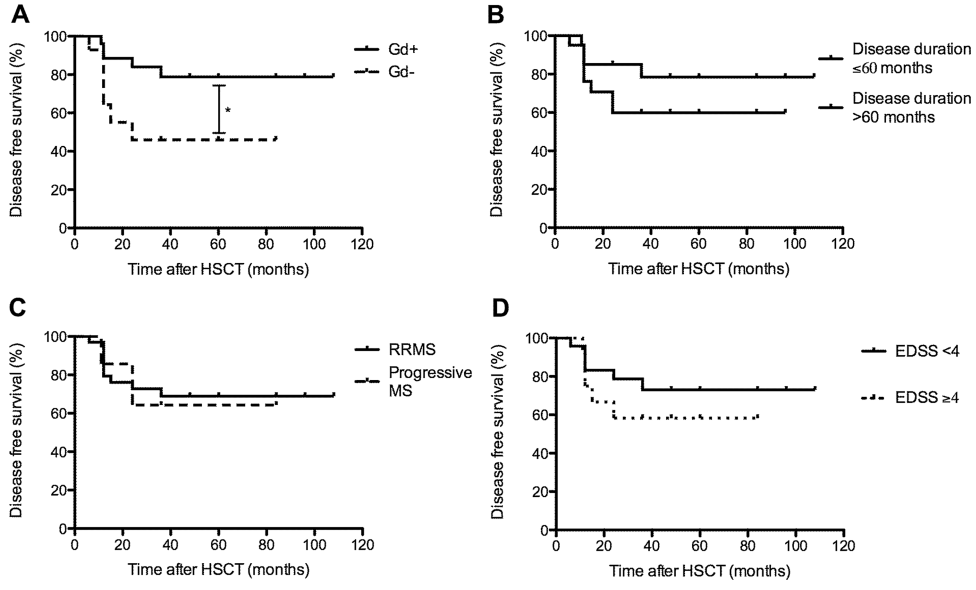

Figure 2 Prognostic factors to the outcome of HSCT. Gd+, presence of gadolinium-enhancing lesion(s); Gd-, absence of gadolinium enhancing lesions; RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status scale; HSCT, haematopoietic stem cell transplantation. (A) Presence of gadolinium-enhancing lesions was a prognostic factor for higher disease-free survival (no relapses, no new MRI lesions and no EDSS progression) at 5 years (79% vs 46%, p=0.028). (B-D) Disease duration, disease course and EDSS score could not be confirmed as statistically significant prognostic factors for disease-free survival.

Table 2 Events related to acute toxicity

	During hospitalisation		After discharge	
	n	Per cent	n	Per cent
Bacteraemia	22	46		
α-haemolytic streptococci	5	23		
Other streptococci	6	27		
Coagulase-negative staphylococci	4	18		
Neutropenic fever	17	35		
Typhlitis	5	10		
Mucositis	4	8.3		
Clostridium difficile infection	2	4.2	1	2.1
ATG reaction (serum sickness)	2	4.2		
Herpes simplex reactivation			2	4.2
Invasive candida albicans infection	1	2.1		
Deep vein thrombosis			1	2.1
Pyelonephritis			1	2.1
Norovirus infection			1	2.1
Varicella zoster reactivation			1	2.1

The table lists events related to acute toxicity (side affects appearing within 100 days after haematopoietic stem cell transplantation). In the table, the three most common bacteria present in blood cultures are listed. The percentages of these are proportions of bacteraemic patients.

survival of 66% at 5 years, similar to the 62% at 5 years that was reported previously in a smaller study.[4]

Presence of Gd+ lesions at baseline was favourable for the outcome of the procedure. There are at least three different possible explanations to this phenomenon. First, patients with Gd+ lesions are more likely to have an inflammatory disease (as opposed to a degenerative disease), which would be responsive to HSCT. Second, a more permissible blood-brain barrier could improve penetration of drugs into the central nervous system. Last, rapidly proliferating autoreactive cells are probably more susceptible to the procedure. If this is true, there may exist a window of opportunity for treatment when the patient is inflammatory active. No other prognostic factor could be determined with statistical significance.

It has been claimed that HSCT can reverse functional deficits. The median improvement of EDSS between the time point when the decision of HSCT was made and the latest follow-up was 0.75, and when patients with progressive forms of MS were excluded from the analysis the improvement was 1.5. This is slightly better than in the Italian study[6] where only 31% of RRMS patients improved >1 point in EDSS and on par with the results from Burt *et al*.[4] Some patients with very high EDSS levels improved markedly; in the extreme, improvement from the nadir of the disease with EDSS of 9.0, to 1.0 at the latest follow-up. In all likelihood, the lion's share of this improvement is due to remyelination and resolution of conduction block. In order to assess to which extent patients could improve from more longstanding functional deficits, likely of axonal origin, we also included an analysis of the lowest recorded EDSS in the year preceding HSCT. The average patient did not improve from this time point indicating that the degree of functional recovery from deficits present for more than 1 year is low. However, in nine cases (22%) such improvement was seen, which implies regenerative mechanisms, or could be an effect of neural reorganisation. During follow-up, EDSS scores approached the lowest recorded EDSS value, indicating that functional recovery is possible for almost all deficits acquired in the year preceding HSCT. The major part of the EDSS improvement took place during the first year after HSCT, with some additional improvement taking place during the second year, and virtually none after that. This suggests that when inflammatory activity has ceased, it takes about 2 years for the healing process to reach its end, similar to what can be seen in a non-inflammatory condition such as stroke.[17]

The retrospective analysis of data and the uncontrolled nature of this study is an obvious weakness. However, since these patients had an unusually aggressive disease and received an off-label treatment, they have been carefully monitored in a systematic and prospective way. Some reporter bias regarding EDSS and/or formation of new T2 lesions may still have existed. On the other hand, the near-abolition of inflammatory MS activity is convincing: a reduction of annualised relapse ratio from 4.1 to 0.03 and a frequency of new T2 lesions of 0.05 per year indicate a marked treatment effect, which is well within a large margin of error. Additionally, the results from this study are in line with other reports.

Taken together, an emerging corpus of evidence supports HSCT as a very effective treatment of inflammatory active MS, and that the procedure can be performed with a high degree of safety. Available data suggest that HSCT is superior to any other disease modifying therapy in terms of effect; further, that HSCT is on par with other advanced forms of immunotherapy, such as alemtuzumab, in terms of safety.[18] However, it is too early to recommend a more widespread use of HSCT, before more data from randomised controlled trials are available. Currently, there is at least one phase III trial addressing this issue (ClinicalTrials no. NCT00273364).

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Contributors ASa, BU, SL, J-EJ, CI, HH and KC performed the transplants and provided data on acute toxicity. JF initiated the survey and the follow-up routine. JF and JB worked out the data form. JF, EI, ASv, JL, MG, PN, MV, SF and CM performed follow-up and filled out the forms. JB made the data analysis and wrote the report. All authors critically read and revised the manuscript.

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Notes