# Clinical and MRI outcome after autologous hematopoietic stem cell transplantation in MS

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**Abstract—**The authors report the outcome of 14 patients with severe multiple sclerosis treated with autologous hematopoietic stem cell transplantation (AHSCT) after a median follow-up period of 3 years. The 3-year actuarial probability of progression-free survival was 85.7% and that of disease activity-free survival was 46.4%. On MRI, no T1-enhanced lesions were detected after AHSCT. The mean change in T2 lesion volume from baseline to the third year was −20.2% and that of the corpus callosum area was −12.7%; 50% of this reduction was seen during the first year.

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We assessed immune ablation with autologous hematopoietic stem cell transplantation (AHSCT) as potential treatment for patients with severe multiple sclerosis (MS).[1,2] Previous series have emphasized the tolerance of the procedure with limited information on the neurologic or MRI outcome beyond the first year after AHSCT.[3-6] We reported the short-term MRI evolution of the first five MS patients included in our AHSCT protocol[7] and the toxicity results of the entire series of 14 patients who were treated.[8] Here, we describe the clinical outcome and MRI evolution after a median follow-up period of 3 years.

**Methods.** Fifteen patients (13 women, 2 men; median age, 30 years; range, 22 to 45 years) were initially included in a prospective protocol to evaluate the safety of T-cell–depleted AHSCT. Eligibility criteria followed the recommendations of the Milan consensus conference.[2] Briefly, the criteria were 1) aged 18 to 60 years; 2) clinically definite secondary progressive MS (SPMS) or relapsing-remitting MS (RRMS) with a Kurtzke's Expanded Disability Status Scale (EDSS) score of 4.0 to 6.5; and 3) an increase in the EDSS by 1.0 point with an EDSS of ≤5.5 or 0.5 with an EDSS >5.5 over the previous year despite treatment with interferon or other immunotherapies that are stopped at least 1 month before the AHSCT. Six patients had RRMS with cumulative residual deficits on recovery, and nine patients had SPMS. The median number of relapses in the year before transplantation was three (range, one to seven) in the entire series and six (range, three to seven) in the RRMS group. The median EDSS at entry was 6.0 (range, 4.5 to 6.5). The median EDSS increase in the year before transplantation was 1.0 (range, 0.5 to 2.0) in the SPMS group and 1.5 (range, 1.0 to 4.5) in the RRMS group.

The transplantation procedure was previously described in detail.[7,8] Hematopoietic stem cells were obtained with cyclophosphamide (Cy) and granulocyte colony-stimulating factor. The grafts were depleted of T cells by $CD34^+$ immunomagnetic selection. Conditioning regimen included carmustine, Cy, and antithymocyte globulin (ATG). Patients were evaluated (neurologic examination, ambulation index [AI], EDSS, brain MRI) before AHSTC, at 1, 3, 6, 9, and 12 months after AHSCT, and then every 6 months (MRI done yearly after the first year). The MRI protocol was previously described in detail.[7]

The 3-year progression-free survival was defined as the probability to be alive without increase in the EDSS score (confirmed over 6 months) after AHSCT as compared with baseline measurement.[2,9] The 3-year disease activity-free survival was defined as the probability of being alive without progression of any type, which included no increase of the EDSS or AI at last assessment, no increase of the EDSS after initial improvement even if the worsening did not reach the baseline EDSS, and absence of objective relapses. The Kaplan–Meier estimator was used to assess progression-free and disease activity-free survival.

**Results.** Mobilization of hematopoietic stem cells from peripheral blood was unsuccessful in one RRMS patient. The tolerance to the AHSCT of the remaining 14 patients was previously reported.[8] Briefly, no patient died or had grade III/IV (severe) systemic complications as result of the procedure. Neurologic deterioration was observed in three patients. It was transient in two (one during mobili-

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***Table*** *Baseline and follow-up of clinical and MRI characteristics after autologous hematopoietic stem cell transplantation*

| Patient no. | Age, y/sex | MS type | Disease duration, y | Baseline EDSS | Last EDSS (month post AHSCT) | Relapses pre AHSCT | Relapses post AHSCT* | Baseline AI | Last AI* | MRI Gad+ pre | MRI Gad+ post | % change T2 lesion load compared with baseline | | | % change corpus callosum area compared with baseline | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | 1 y | 2 y | 3 y | 1 y | 2 y | 3 y |
| 1 | 30/F | SP | 8 | 6.0 | 6.0 (55) | 3 | 0 | 4 | 6 | + | − | −19.77 | −51.97 | −47.64 | −7.62 | −9.43 | −12.41 |
| 2 | 43/F | SP | 7 | 6.5 | 8.0 (54) | 2 | 0 | 6 | 8 | − | − | −26.62 | −31.89 | N.D. | −19.69 | −20.27 | N.D. |
| 3 | 24/F | RR | 9 | 5.0 | 5.0 (48) | 6 | 2† | 2 | 2 | + | − | −10.33 | −43.78 | −39.95 | −13.65 | −15.29 | −15.52 |
| 4 | 44/M | SP | 14 | 6.5 | 5.0 (46) | 2 | 1† | 4 | 2 | − | − | −5.94 | 2.86 | 3.28 | −11.06 | −10.78 | −7.99 |
| 5 | 27/F | RR | 8 | 6.5 | 6.5 (45) | 6 | 0 | 4 | 6 | + | − | −11.79 | −9.09 | −11.40 | −17.83 | −21.64 | −21.3 |
| 6 | 45/F | SP | 19 | 6.5 | 7.5 (39) | 3 | 0 | 6 | 8 | − | − | −11.66 | −24.31 | −22.69 | −13.89 | −12.8 | −12.16 |
| 7 | 23/F | RR | 6 | 6.5 | 6.5 (37) | 6 | 0 | 5 | 6 | − | − | 1.01 | 1.45 | −1.11 | −9.15 | −7.3 | −10.46 |
| 8 | 37/F | SP | 3 | 5.5 | 5.5 (36) | 1 | 0 | 3 | 3 | + | − | −26.79 | −23.02 | −21.64 | −8.21 | −10.24 | −9.11 |
| 9 | 31/F | SP | 10 | 6.0 | 5.0 (33) | 1 | 0 | 4 | 2 | − | − | −2.69 | −6.05 | | −2.2 | 0.31 | |
| 10 | 28/F | RR | 1 | 5.5 | 4.5 (30) | 6 | 4 | 2 | 2 | − | − | −5.03 | −3.96 | | −4.09 | −3.35 | |
| 11 | 28/F | SP | 9 | 6.5 | 6.5 (25) | 1 | 0 | 5 | 5 | − | − | −7.04 | −5.39 | | −1.15 | −0.94 | |
| 12 | 33/M | SP | 8 | 6.5 | 6.5 (22) | 3 | 3 | 5 | 5 | − | − | −23.97 | −23.05 | | −0.82 | −1.01 | |
| 13 | 37/F | SP | 10 | 5.5 | 5.5 (20) | 1 | 0 | 5 | 5 | − | − | 5.32 | | | −0.3 | | |
| 14 | 22/F | RR | 6 | 4.5 | 4.0 (19) | 7 | 0 | 2 | 2 | + | − | 1.77 | | | −8.65 | | |

AHSCT = autologous hematopoietic stem cell transplantation; MS = multiple sclerosis; SP = secondary progressive MS; RR = relapsing-remitting MS; EDSS = Expanded Disability Status Scale score; AI = ambulation index.

*See follow-up in the column of last EDSS.

†Subjective sensory symptoms without change in the neurological examination; N.D. = Not done at 3 years, but at 4 years the % change of the T2 lesion load compared with baseline was −36.2%, and the reduction of the corpus callosum area of −19.9%.

zation and another with high fever related to ATG administration) and persistent in the third patient (related to ATG-induced fever).[7] Four of the 12 female patients (all aged >37 years) had secondary amenorrhea.

After a median follow-up period of 36 months (range, 19 to 55 months), the EDSS remained stable in eight patients, improved in four (median, 1.0; range, 0.5 to 1.5), and worsened in two (1.0 and 1.5) (table). In one patient, the deterioration was related to the procedure. The 3-year actuarial probability of progression-free survival was 85.7 (95% CI, 60 to 96%) and that of disease activity-free survival was 46.4 (95% CI, 24 to 76%) (figure 1). An increase of one point in the AI was observed in 3 of 12 patients considered progression-free by the EDSS criteria (see table). In one patient, after an initial improvement that lasted for 12 months, the EDSS score progressed to baseline and then remained stable for 31 months.

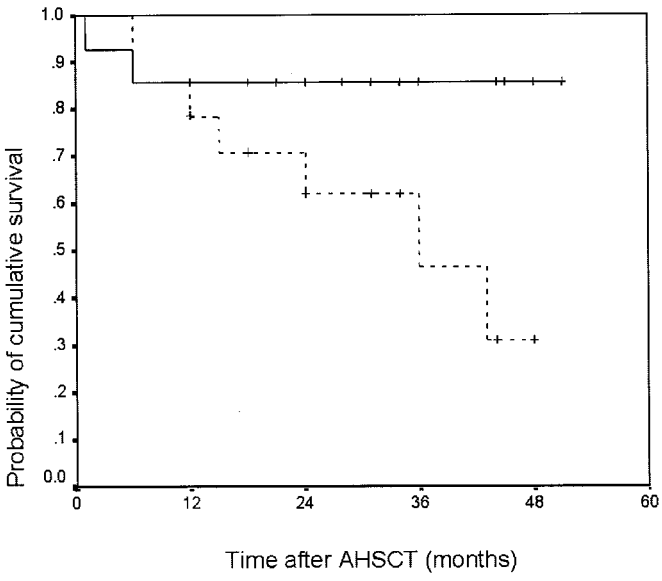


*Figure 1. Actuarial probability of progression-free survival (Expanded Disability Status Scale stable or better) (continuous line) and disease activity-free survival (see text for definition) after autologous hematopoietic stem cell transplantation in 14 patients with multiple sclerosis.*

Two patients had three episodes of transient subjective sensory symptoms that did not require treatment. The number of objective relapses decreased from 48 in the year before AHSCT to 7 (in two patients) during the follow-up period (see table). No patient received any additional immunotherapy during the entire follow-up period after the AHSCT.

Five patients had gadolinium-enhancing lesions on basal MRI. No T1-enhanced lesions were detected since the first month after AHSCT in any of the follow-up MRI studies. The mean percentage reduction of the T2 lesion volume at 3 years was 20.2% compared with baseline (figure 2); 50% of this reduction seen in the first year (see table).

A decrease in the corpus callosum area was observed throughout the study with a mean reduction of 12.71% at 3 years compared with baseline (see figure 2). The main reduction occurred during the first year. The decrease of the area of the corpus callosum was only 0.37% between the first- and second-year MRI (12 patients evaluated) and 0.20% between the second- and third-year MRI (7 patients) (see table).

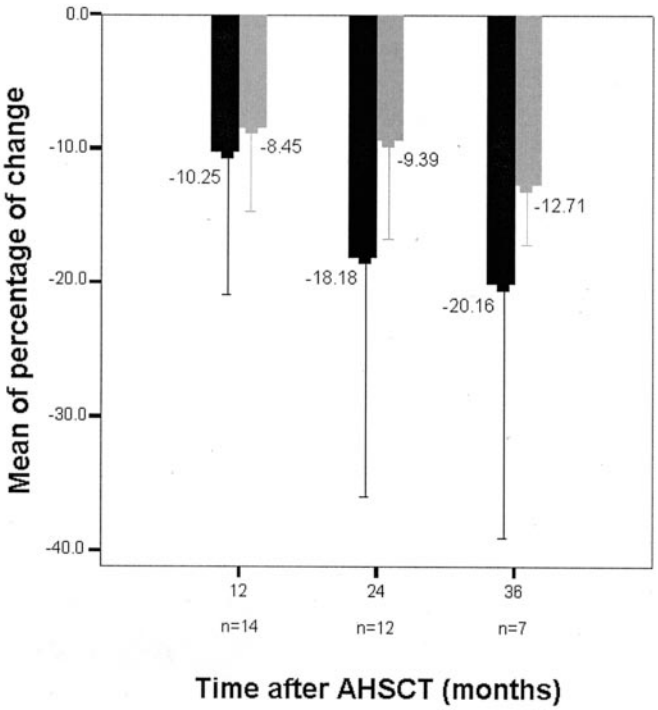


*Figure 2. Mean percentage change of the T2 lesion volume (black columns) and reduction of the corpus callosum area (gray columns) compared with baseline. Error bars represent the SD of the mean.*

**Discussion.** AHSCT remains an experimental treatment option for patients with severe forms of MS that should be considered only in the setting of approved protocols. Our 3-year results in this pilot trial showing an actuarial probability of progression-free survival of 85.7% with 46.4% of patients free of clinical disease activity support the view that AHSCT deserves further evaluation in the setting of multicenter controlled trials.

A main concern of AHSCT is the morbidity of the treatment. In a recent retrospective multicenter study of 85 MS patients who underwent AHSCT, 7 (8%) died and 27% had transient or, less frequent, long-lasting neurologic deterioration.[9] These figures are higher than those observed in our protocol and probably are explained by selection criteria (age >40 years and EDSS >6.5 probably predispose to higher morbidity) and use of more aggressive conditioning regimens.[9]

The probability of progression-free and disease activity-free survival at 3 years of our study should be taken with caution because of the small number of patients. A previous study with a similar follow-up period of AHSCT in 16 patients with progressive-relapsing MS (three patients) or SPMS showed a 3-year progression-free survival of 92%.[3] However, the 3-year disease activity-free survival was <20%.[3] The absence of a plateau in the disease activity-free survival curves suggests that AHSCT will not be a definitive cure of MS but may cause prolonged stabilization or perhaps change the aggressive course of the disease. Our results in the EDSS stabilization after AHSCT are supported with a dramatic decrease in the number of objective relapses that changed from 48 in the year before AHSCT to 7 (in two patients) after the procedure. Whether the same goal may be achieved with less-intensive immunosuppressor treatments is open to debate.

Unlike previous series of AHSCT in patients with MS, our study provided information on the long-term evolution of MRI measures of inflammation and brain atrophy. The procedure completely abolished gadolinium-enhancing lesions during the 3-year period, confirming the experience of a previous study with a shorter median follow-up period of 15 months.[6] Accordingly, we observed an important decrease in T2 lesion load. The mean decrease of 20.2% at 3 years was higher than that reported in trials of RRMS and SPMS patients treated with different types of beta interferon or glatiramer acetate.[10] It is important to note that the greatest reduction of T2 lesion load occurred during the first year after AHSCT, when we also observed an important decrease in the corpus callosum area. The trend toward an association between the reduction of the T2 lesion load and the increase of brain atrophy measures suggests that the resolution of edema and inflammation resulting from the AHSCT could explain part of this finding and masks any potential effect of the transplant in the rate of real degenerative changes. Alternatively, the atrophy of the corpus callosum could be a reflection of the damaging inflammatory events that were present before the transplant.


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