RESEARCH ARTICLE

Hematopoietic Stem Cell Transplantation in People With Active Secondary Progressive Multiple Sclerosis

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Abstract

Background and Objectives

Uncontrolled evidence suggests that autologous hematopoietic stem cell transplantation (AHSCT) can be effective in people with active secondary progressive multiple sclerosis (SPMS). In this study, we compared the effect of AHSCT with that of other anti-inflammatory disease-modifying therapies (DMTs) on long-term disability worsening in active SPMS.

Methods

We collected data from the Italian Bone Marrow Transplantation Study Group and the Italian Multiple Sclerosis Register. Patients were considered eligible if treatment had been started after the diagnosis of SPMS. Disability worsening was assessed by the cumulative proportion of patients with a 6-month confirmed disability progression (CDP) according to the Expanded Disability Status Scale (EDSS) score. Key secondary endpoints were the EDSS time trend after treatment start and the prevalence of disability improvement over time. Time to first CDP was assessed by means of proportional hazard Cox regression models. A linear mixed model with a time × treatment group interaction was used to assess the longitudinal EDSS time trends. Prevalence of improvement was estimated using a modified Kaplan-Meier estimator and compared between groups by bootstrapping the area under the curve.

Results

Seventy-nine AHSCT-treated patients and 1975 patients treated with other DMTs (beta interferons, azathioprine, glatiramer-acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab) were matched to reduce treatment selection bias using propensity score and overlap weighting approaches. Time to

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Italian BMT-MS Study Group coinvestigators are listed in the Appendix 2 at the end of the article.

Glossary

AHSCT = autologous hematopoietic stem cell transplantation; **ARR** = annualized relapse rate; **ATG** = antithymocyte globulin; **AUC** = area under the curve; **CDP** = confirmed disability progression; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IQR** = interquartile range; **MSMs** = marginal structural models; **OW** = overlap weighting; **PS** = propensity score; **SMDs** = standardized mean differences; **SPMS** = secondary progressive multiple sclerosis.

first CDP was significantly longer in transplanted patients (hazard ratio [HR] = 0.50; 95% CI = 0.31–0.81; $p = 0.005$), with 61.7% of transplanted patients free from CPD at 5 years. Accordingly, EDSS time trend over 10 years was higher in patients treated with other DMTs than in AHSCT-treated patients (+0.157 EDSS points per year compared with −0.013 EDSS points per year; interaction $p < 0.001$). Patients who underwent AHSCT were more likely to experience a sustained disability improvement: 34.7% of patients maintained an improvement (a lower EDSS than baseline) 3 years after transplant vs 4.6% of patients treated by other DMTs ($p < 0.001$).

Discussion

The use of AHSCT in people with active SPMS is associated with a slowing of disability progression and a higher likelihood of disability improvement compared with standard immunotherapy.

Classification of Evidence

This study provides Class III evidence that autologous hematopoietic stem cell transplants prolonged the time to CDP compared with other DMTs.

Secondary progressive multiple sclerosis (SPMS) is characterized by progressive accrual of neurologic disability independent of clinical relapses.[1] Although the exact mechanisms leading to disability progression in SPMS are not completely understood, recent evidence suggests a major role of compartmentalized inflammation within the CNS in driving neurodegeneration and eventually clinical progression. Inflammatory processes behind an intact blood-brain barrier involving adaptive and innate immunity have been indeed described in people with SPMS within the brain parenchyma,[2,3] the leptomeninges,[4] and the CSF.[5,6] Moreover, evidence for overt inflammatory disease activity may still be found in people with SPMS, who can experience relapses and the appearance of new active lesions on MRI,[1] which have been repeatedly associated with accelerated disability progression during SPMS.[7]

Although first randomized controlled clinical trials did not reveal the efficacy of disease-modifying therapies (DMTs) for disability progression in SPMS,[8,9] a recent randomized clinical trial established some benefits of siponimod[10] in reducing the risk of disability worsening compared with placebo. In line with this result, observational studies have suggested that the use of available anti-inflammatory DMTs in SPMS may be therapeutically beneficial,[11,12] especially in active SPMS.[11,13] Despite the lack of clear guidelines, anti-inflammatory DMTs are often prescribed in patients with SPMS. However, the overall risk reduction in disability worsening with available DMTs is only modest, and it is still unclear whether the effect of treatment persists over time.[14] In the EXPAND trial,[13] after 2 years of treatment with siponimod, the average postponement of disability was only 19 days per year, indicating a small benefit.[15]

Ablation of the immune system followed by autologous hematopoietic stem cell transplantation (AHSCT) has gained increasing evidence as a therapeutic strategy for refractory MS.[16,17] AHSCT eradicates autoreactive cell clones and induces sustained self-tolerance by resetting the abnormal immune system.[18] Although the ideal candidate of AHSCT is a young patient with aggressive relapsing-remitting MS, uncontrolled evidence suggests that AHSCT can slow down neurologic deterioration in active progressive MS,[19-21] but controversies exist.[22,23] The drugs used in AHSCT technology cross the almost intact blood-brain barrier of patients with SPMS and penetrate the CNS, with the potential to target compartmentalized inflammation.[24-26] Moreover, the myeloablative effects of AHSCT have the potential to target imprinted, pathogenic memory cells within the bone marrow niche, which are believed to drive chronic inflammation.[27] Given the absence of satisfactory treatment options for active SPMS, in the last 2 decades, AHSCT was used off-label for the treatment of 81 people with active SPMS in 14 Italian MS centers. In this study, we wanted to assess whether autologous hematopoietic stem cell transplants prolonged the time to confirmed disability progression (CDP) compared with other DMTs in SPMS.

We used the Italian Multiple Sclerosis Register[28] to collect data from patients with SPMS treated with standard immunotherapy and controlled for several clinical and demographic variables to mitigate treatment selection bias. We hypothesized that patients with active SPMS have better disability outcomes when treated with AHSCT than with other DMTs.

Methods

Study Design

All patients who underwent AHSCT in Italy from 1997 to 2019 after the diagnosis of SPMS[1] were considered eligible for this study. Patients were treated according to the European Group for Blood and Marrow Transplantation guidelines, following the decision of the treating physician and approval of the local Ethics Committee. Diagnosis of SPMS was made by the treating neurologist and was based on the evidence of CDP independent of clinical relapses lasting ≥6 months before AHSCT.

Control patients with SPMS never treated with AHSCT were collected from the Italian Multiple Sclerosis Register.[28] Patients with SPMS were considered eligible based on the following criteria: (1) if they had a baseline Expanded Disability Status Scale (EDSS) recording, (2) if they had at least 1 follow-up visit, and (3) if a DMT had been started after the diagnosis of SPMS.

Standard Protocol Approvals, Registrations, and Patient Consents

The Italian Multiple Sclerosis Register was approved by the Policlinico of Bari Ethics Committee (protocols 55587 and 0052885) and by the local ethics committees in all participating centers.

Transplant Technology

As detailed elsewhere,[21] peripheral hematopoietic stem cells were mobilized with cyclophosphamide plus filgrastim. Sixty-four patients were transplanted using the myeloablative conditioning regimen BEAM (BCNU, cytosine-arabinoside, etoposide, and melphalan) plus rabbit antithymocyte globulin (ATG). For 2 patients, fotemustine was used instead of BCNU. Eleven patients were transplanted using cyclophosphamide alone followed by ATG. Thiothepa + cyclophosphamide regimen was used in 3 patients. One patient was transplanted with a conditioning regimen made of bortezomib, cyclophosphamide, dexamethasone, and melphalan.

Study Endpoints

The primary objective was to compare the cumulative proportion of patients with a 6-month CDP in patients with active SPMS treated with AHSCT with that in those treated with other DMTs. CDP was defined as an increase of 1 point in the EDSS score (0.5 points if the baseline EDSS score was ≥5.5). Secondary endpoints were as follows:

1. To evaluate the EDSS score time course after baseline in the 2 treatment groups;
2. To compare the cumulative proportion of patients with a 6-month confirmed disability improvement (CDI), defined as a decrease of 1 point in the EDSS score (0.5 points if the baseline EDSS score was ≥5.5);
3. To compare the prevalence of disability improvement over time, defined as the proportion of patients who are in an improved status when compared with that at baseline over time.

Statistical Methods

Outcomes were compared between patients treated with AHSCT and patients treated with "other DMTs." The other DMT group comprises all patients satisfying the inclusion criteria and starting any DMT during their follow-up. Descriptive results were reported as mean with SD or median with interquartile range (IQR) or range. To mitigate treatment selection bias, we applied 2 different propensity score (PS) approaches. First, we matched individual patients on their propensity to receive AHSCT or one of the other DMTs. Patients were matched without replacement with a variable ratio up to 5:1 (other DMT:AHSCT) and using a nearest neighbor matching within a caliper of 0.25 SDs of the PS. Second, we applied an overlap weighting (OW) approach.[29] This method has the advantage over the n:1 PS matching method that no patients are excluded from the analysis, without modifying the target population.[29] The OW method assigns to each patient a weight proportional to the probability of that patient belonging to the opposite treatment group.[29] In our analysis, AHSCT-treated patients are therefore weighted by the probability to receive one of the other DMTs (1 PS), and patients treated with other DMTs are weighted by the probability of receiving AHSCT treatment (PS). OW leads to an exact balance on the mean of each baseline covariate included in the PS calculation. For both methods, individual PS were calculated using a multivariable logistic regression model including age at treatment start, sex, EDSS at treatment start, number of previous DMTs, annualized relapse rate (ARR) in the previous year, disease duration, and year of treatment start. Only main effects, without interactions, were included in the regression model. Because MRI data were missing for most of the patients in the Italian MS Register, they were not included in the primary PS calculation. Positivity assumption of PS was checked after its calculation. To assess the degree of imbalance of covariate distribution between the groups, Cohen standardized mean differences (SMDs) were calculated in the original group and after matching or weighting. An SMD <0.10 was considered an acceptable balance.

All regression models were run on the matched groups or weighted according to PS. Differences between treatment groups on time to CDP and CDI were assessed by the mean of proportional hazard Cox regression models. Results were reported as hazard ratio (HR) with the corresponding 95% CIs. A linear mixed model with random intercept and random slope was used to assess the longitudinal EDSS time trend after baseline. A time × treatment group interaction term was included into the model to test differences on EDSS time trend between the 2 treatment groups. Results were reported as annualized EDSS change with 95% CIs. Progression-free survival and cumulative probability of improvement were estimated by Kaplan-Meier approach and graphically displayed. The prevalence of CDI was estimated according to the recently reported methodology[30] and compared between groups by bootstrapping the area under the curve (AUC) with 500 replicates. The ratio between mean difference of AUCs on SD (z) was

calculated, and the p value was obtained by the normal distribution. Stata (v.16; StataCorp) was used for computation.

Sensitivity Analyses

The following sensitivity analyses were performed:

1. Unadjusted analysis (without PS) between patients treated with AHSCT and the other DMT group.
2. Inclusion of untreated patients in the other DMT group.
3. Application of marginal structural models (MSMs) to account for potential attrition bias derived by a different duration of on-treatment follow-up in the matched groups. MSMs are a method to control for the causal effect of a time-dependent exposure. In this case, MSMs were used to control for potential informative censoring during follow-up. We estimated at each 1-year time point the stabilized weights, from the inverse probability to be censored at fixed time points conditional on baseline variables. Then, we ran a weighted Cox regression analysis.
4. Inclusion of MRI activity in the PS calculation. Two analyses were performed: one with missing data imputed before the PS calculation using multiple imputation approach with a logistic regression model and 10 imputations. The second analysis used only the subset with complete MRI information.
5. Comparisons between (1) patients treated with AHSCT vs patients treated with interferon beta 1-b and (2) patients treated with AHSCT vs patients treated with mitoxantrone using a matching without replacement with a variable ratio up to 5:1 (DMT:AHSCT) with the same rules previously described. These 2 treatments were the only 2 DMTs approved in Italy for the treatment of SPMS during data collection.

Data Availability

Anonymized data are available on reasonable request from a qualified investigator.

Results

The SPMS group treated by AHSCT included 81 patients from 14 centers. Two patients did not have follow-up information and were excluded from the analysis. Data on 3915 patients with SPMS were extracted from the MS Italian Register. Of them, 851 were excluded because of missing follow-up EDSS data and 703 because their DMT start date was during relapsing-remitting MS. A total of 2,361 patients were included in the analysis; of them 1975 (83.7%) started a DMT, while 386 (16.3%) were never treated. DMT used by patients with SPMS were beta interferons (24%), azathioprine (13%), glatiramer acetate (13%), mitoxantrone (11%), fingolimod (9%), natalizumab (7%), methotrexate (6%), teriflunomide (6%), cyclophosphamide (6%), dimethyl

Table 1 Clinical and Demographic Characteristics in the Matched (Left Side) and in the Overlap Weighted (Right Side) Groups

	Matched group			Overlap weighted group		
Characteristic	**AHSCT (n = 69)**	**Other DMT (n = 217)**	**SMD AHSCT vs treated**	**AHSCT (n = 79)**	**Other DMT (n = 1975)**	**SMD AHSCT vs treated**
Age, mean (SD); median (range)	38.1 (7.7); 37.1 (24–58)	37.8 (7.2); 37.2 (22–58)	0.037	39 (7.8); 37.5 (24–58)	39 (7.8); 38.4 (19–76)	0.001
Sex (M/F), n (%)	24/45 (34.8/65.2)	86/131 (39.9/60.1)	0.10	28/51 (35.5/64.5)	719/1256 (36.4/63.6)	0.018
Baseline EDSS, mean (SD); median (IQR)	6.2 (0.9); 6.5 (6–7)	6.3 (0.8); 6.5 (6–7)	0.076	6.2 (0.9); 6 (6–6.5)	6.2 (0.9); 6.5 (6–7)	0.001
ARR previous y	1.08 (1.12)	0.90 (1.02)	0.17	1.01 (1.07)	1.01 (1.66)	0.001
Disease duration, mean (SD); median (IQR)	13.7 (6.5); 12.1 (10.1–16.5)	13.7 (6.1); 12.7 (9.3–17.8)	0.01	13.7 (6.8); 12.1 (10.1–17.3)	13.7 (6.6); 12.9 (9.3–18)	0.001
No. of previous treatments, mean (SD); median (IQR)	2.4 (1.2); 2 (1–3)	2.3 (1.4); 2 (1–3)	0.024	2.2 (1.1); 2 (1–3)	2.2 (1.4); 2 (1–3)	0.001
Year of treatment start, median (IQR)	2007 (2002–2014)	2007 (2004–2012)	0.019	2007 (2003–2014)	2008 (2004–2012)	0.001
Year of SP conversion, median (IQR)	2004 (1999–2013); [n = 53]	2004 (2001–2009)	0.011	2004 (1999–2013) [n = 57]	2005 (2001–2010)	0.008
Years from SP conversion, mean (SD); median (IQR)	3.53 (3.01); 2.53 (1.49–4.75) [n = 53]	2.72 (3.20); 1.76 (0.59–3.79)	0.26	3.61 (2.99); 2.56 (1.69–4.81) [n = 57]	2.91 (3.22); 1.95 (0.58–4.09)	0.22
Follow-up (y); median (IQR); range	6.8 (3.2–11.8); 0.1–20.1	3.1 (1.7–6.4); 0.1–18.4	—	5.6 (2.2–11.1); 0.1–20.1	3.9 (1.7–6.4); 0.1–30.9	—

Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IQR = interquartile range; Other DMTs = beta interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab; SMD = standardized mean difference; SP = secondary progressive.

fumarate (4%), and alemtuzumab (1%). A slightly higher frequency of EDSS visits for year was observed in the Italian MS Register (mean 2.76 [SD 1.98]) compared with the AHSCT group (mean 1.95 [SD: 2.30]). Table 1 reports the clinical and demographic characteristics of the 2 treatment groups after PS matching and OW approach, with SMD between the 2 groups. The mean follow-up of the matched group was 5.2 years, with a median of 3.6 years (IQR:1.8–7.6 years). Seven (8.9%) transplanted patients started a DMT after a median of 2.2 years (range 1–17; mean = 6 years, SD = 6 years) from AHSCT.

AHSCT-Treated vs Other DMT-Treated Patients

Time to CDP

The time to CDP was significantly longer in AHSCT-treated patients when compared with the matched other DMT group (HR = 0.50; 95% CI: 0.31–0.81; $p = 0.005$, Figure 1A). After 3 years, the proportion of patients free from CDP was 58.1% (95% CI: 50.3–64.9) in the other DMT group and 71.9% (95% CI: 58.5–81.5) in the AHSCT group; after 5 years it was, 46.3% (95% CI: 37.4–54.5) in the other DMT group and 61.7% (95% CI: 47.5–73.1) in the AHSCT group. Similar results were observed when the OW procedure was applied to the whole group (Figure 1B).

Yearly EDSS Change

Figure 2A reports the estimated slopes of the EDSS change in the 2 treatment groups: the mean EDSS change over 10 years in the AHSCT group was estimated as −0.013 EDSS points per year (95% CI: −0.087 to 0.061 EDSS points per year), while in the other DMT group, the mean EDSS change was +0.157 EDSS points per year (95% CI: 0.117–0.196 EDSS points per year, p for time by treatment group interaction <0.001). Similar results were observed by the OW analysis, and the estimated slopes of EDSS change are shown in Figure 2B. The estimated yearly EDSS change was −0.017 (95% CI: −0.099 to 0.065) in the AHSCT group and +0.18 (95% CI: 0.15–0.21) in the other DMT group (p for time × treatment group interaction <0.001).

ARR

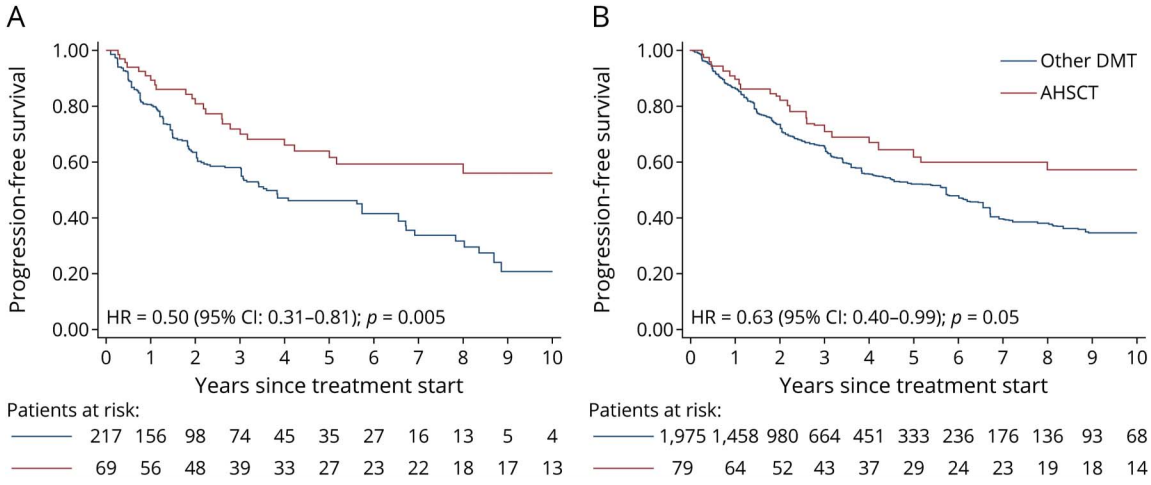
After matching, the ARR in the first 2 years of follow-up was 0.024 (95% CI: 0–0.051) in the AHSCT group and 0.32 (95% CI: 0.24–0.39) in the other DMT group (RR = 0.075; 95% CI: 0.023–0.24; $p < 0.001$). Over the entire follow-up, the ARR was 0.020 (95% CI: 0.006–0.034) and 0.45 (95% CI: 0.36–0.55), respectively (RR = 0.044; 95% CI: 0.021–0.091; p <0.001).

Similar results were observed in the OW analysis, with an ARR in the first 2 years of follow-up of 0.025 (95% CI: 0.0002–0.050) in AHSCT-treated patients and of 0.38 (95% CI: 0.30–0.46) among patients in the other DMT group (RR = 0.067; 95% CI: 0.024–0.184; p <0.001). The ARR over the entire follow-up was 0.020 (95% CI: 0.003–0.037) and 0.43 (95% CI: 0.35–0.51), respectively, with a significant difference between the 2 groups (RR = 0.046; 95% CI: 0.019–0.110; p <0.001).

EDSS Improvement

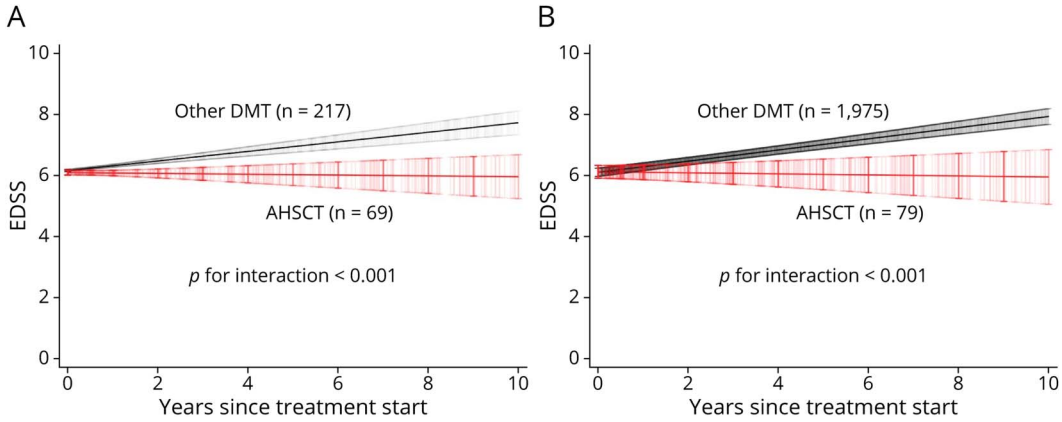
Figure 3A shows the Kaplan-Meier curves for time to CDI. In the matched groups, the improvement rate was significantly higher in AHSCT-treated patients when compared with the other DMT group (HR = 4.21; 95% CI: 2.42–7.33; $p < 0.001$). After 1 year, the cumulative proportion of patients who had at least an improvement event was 30.2% (95% CI: 20.6–42.8) in the AHSCT group and 3.4% (95% CI: 1.6–7.0)

Figure 1 Time to Confirmed Disability Progression in Patients With SPMS Treated With AHSCT and Matched Patients Treated With Other Anti-inflammatory DMTs



Kaplan-Meier Curve for Time to First Confirmed Progression for (A) Propensity Score–Matched Treatment Groups and (B) the Overlap Weighting–Matched Groups. Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; DMTs = disease-modifying therapies (Beta interferons, azathioprine, Glatiramer Acetate, Mitoxantrone, Fingolimod, Natalizumab, Methotrexate, Teriflunomide, Cyclophosphamide, Dimethyl Fumarate, and Alemtuzumab); EDSS = Expanded Disability Status Scale; HR = hazard ratio; SPMS = secondary progressive multiple sclerosis.

Figure 2 Evolution of Neurologic Disability in Patients With SPMS Treated With AHSCT and Matched Patients Treated With Other Anti-inflammatory DMTs



Annualized EDSS Change Together With 95% CIs 1–10 years after Treatment Start for (A) Propensity Score–Matched Treatment Groups and (B) the Overlap Weighting–Matched Groups. Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; DMTs = disease-modifying therapies (Beta Interferons, azathioprine, Glatiramer Acetate, Mitoxantrone, Fingolimod, Natalizumab, Methotrexate, Teriflunomide, Cyclophosphamide, Dimethyl Fumarate, and Alemtuzumab); EDSS = Expanded Disability Status Scale; SPMS = secondary progressive multiple sclerosis.

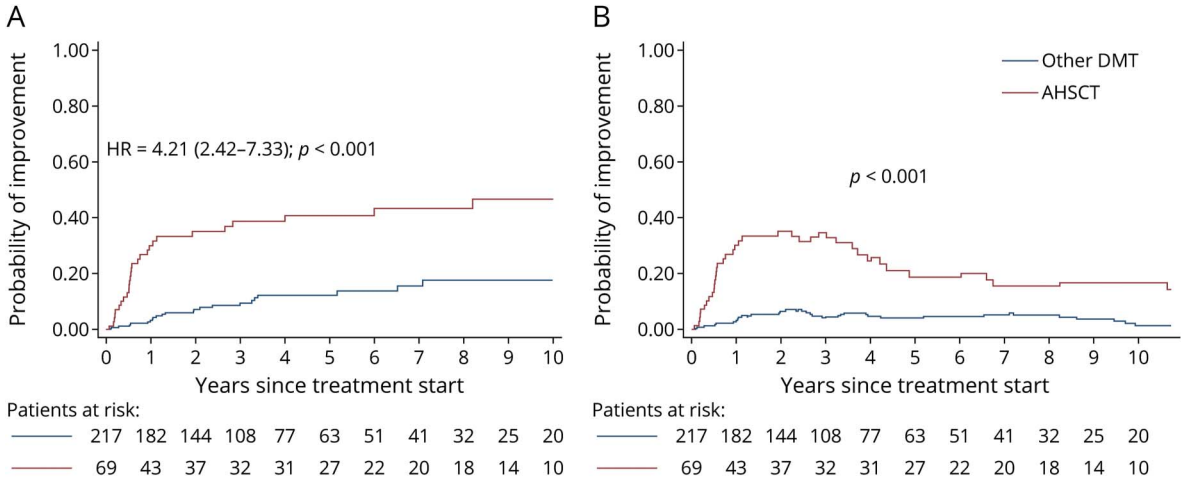
in the other DMT group; after 3 years, it was 38.8% (95% CI: 28.0–51.9) in the AHSCT group and 7.8% (95% CI: 4.2–13.3) in the other DMT group. AHSCT-treated patients also showed a higher prevalence of improvement (Figure 3B) over time ($p < 0.001$) when compared with the matched control group. The proportion of patients who reached and maintained an improvement status after 3 years was 34.7% (95% CI: 23.2–46.3) in the AHSCT group, while it was 4.6% (95% CI: 1.7–8.6) in the other DMT group; after 5 years, 18.7% (95% CI: 7.9–29.8) of AHSCT-treated patients maintained the improvement when compared with that at baseline vs 4.1% (95% CI: 1.3–8.3) of patients treated with other DMTs.

Sensitivity Analyses

Unadjusted Comparison of the AHSCT and Other DMT Groups

In unadjusted analyses without PS matching, the time to CDP was significantly longer in AHSCT-treated patients when compared with the "other DMT" group (HR = 0.49 [95% CI: 0.33–0.72], $p < 0.001$), while time to CDI was significantly lower (HR = 6.35 [95% CI: 4.37–9.22], $p < 0.001$). The mean

Figure 3 Time to Confirmed Disability Improvement and Prevalence of Disability Improvement in Patients With SPMS Treated With AHSCT and Propensity Score–Matched Patients Treated With Other Anti-inflammatory DMTs



(A) Kaplan-Meier Curve for Time to First Confirmed Disability Improvement. (B) Prevalence of Confirmed Disability Improvement 1–10 years after Treatment Start.Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; DMT = disease-modifying therapies (beta interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab); EDSS = Expanded Disability Status Scale; SPMS = secondary progressive multiple sclerosis.

Table 2 Demographic and Clinical Characteristics of Propensity Score–Matched AHSCT and Control Group After the Inclusion of Untreated Patients

Characteristics	AHSCT (n = 72)	Control (n = 228)	SMD
Age, mean (SD)	38.5 (7.7)	39.5 (7.6)	0.12
Sex (M/F), n(%)	26/46 (35.6/64.4)	83/145 (36.4/63.6)	0.016
Baseline EDSS, mean (SD); median (IQR)	6.2 (0.9); 6.5 (6–6.5)	6.2 (0.9); 6 (6–6.5)	0.08
ARR previous y	1.05 (1.04)	0.76 (0.93)	0.29
Disease duration, mean (SD); median (IQR)	13.5 (6.7); 11.8 (10.1–16.5)	13.4 (6.2); 12.9 (8.9–17.1)	0.022
No. of previous treatments, median (IQR); range	2 (1–3); 0-5	2 (1–3); 0-6	0.19
Year of treatment start, median (IQR)	2007 (2003–2014)	2008 (2004–2013)	0.027
Year of SP conversion, mean; median (IQR)	2004 (1999–2013) [n = 54]	2006 (2001–2011)	0.061
Years from SP conversion, mean (SD); median (IQR)	3.40 (3.01); 2.45 (1.35–4.50) [n = 54]	2.60 (3.00); 1.60 (0.50–3.60)	0.26

Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IQR = interquartile range; Other DMTs = beta interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab; SMD = standardized mean differences; SP = Secondary Progressive.

EDSS change over 10 years in the AHSCT group (n = 79) was estimated as +0.021 EDSS points per year (95% CI: −0.027, 0.068) vs +0.15 (95% CI: 0.14–0.16) in the other DMT group (n = 1975) (p for time by treatment group interaction < 0.001).

Inclusion of Untreated Patients

Untreated patients were added to the group of patients treated with other DMTs. The untreated group was made up of older patients with similar disease duration and EDSS and lower ARR in the previous year when compared with other DMT–treated patients. A total of 72 AHSCT-treated patients were matched to 228 patients in the control group (26 untreated [11.4%] and 202 treated [88.6%]). Characteristics of matched patients are reported in Table 2. Results were similar to those reported in the main analysis (eFigure 1, links.lww.com/WNL/C535): time to CDP was significantly longer in AHSCT-treated patients (HR = 0.48; 95% CI: 0.30–0.78; p = 0.003). Accordingly, the EDSS increased in the control group (yearly change +0.125; 95% CI: 0.099–0.151 EDSS points) while it was substantially stable in the AHSCT group (yearly change +0.017 EDSS points; 95% CI: −0.032 to 0.066) with a significant difference between the 2 groups (p < 0.001).

Marginal Structural Model

Results of the analysis run by applying MSM to the matched group (69 AHSCT vs 217 other DMT) confirmed those reported in the main analysis. The time to CPD was significantly longer in AHSCT-treated patients when compared

Table 3 Demographic and Clinical Characteristics of Matched AHSCT-Treated and Other DMT–Treated Patients Accounting for Baseline MRI Activity

Characteristics	AHSCT (n = 79)	Treated With Other DMTs (n = 135)	SMD
Age, mean (SD)	38.1 (7.7)	38.3 (7.5)	0.032
Sex (M/F), n(%)	27/52 (33.8/66.2)	50/85 (36.9/63.1)	0.066
Baseline EDSS, mean (SD); median (IQR)	6.3 (0.9); 6.5 (6–7)	6.4 (0.9); 6.5 (6–7)	0.18
ARR previous y	1.13 (1.21)	1.06 (1.06)	0.066
Disease duration, mean (SD); median (IQR)	13.4 (6.6); 11.8 (8.5–16.5)	13.6 (5.1); 12.9 (8.9–17.1)	0.032
No. of previous treatments, median (IQR); range	2 (1–3); 0-5	2 (1–3); 0-6	0.011
Year of treatment start, median (IQR)	2006 (2003–2014)	2008 (2004–2013)	0.15
Year of SP conversion, median (IQR)	2004 (2000–2013) [n = 57]	2005 (2001–2011)	0.12
Years from SP conversion, mean (SD); median (IQR)	3.50 (2.94); 2.53 (1.49–4.75) [n = 57]	2.65 (2.84); 1.57 (0.59–4.05)	0.30

Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; ARR = annualized relapse rate; DMTs = disease-modifying therapies; EDSS = Expanded Disability Status Scale; IQR = interquartile range; Other DMTs = beta interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab; SMD = standardized mean difference; SP = secondary progressive.

Table 4 Summary of the Most Relevant Study Outcomes in Primary and Main Sensitivity Analyses

Outcome	Matching	Overlap weighting
AHSCT vs other DMT		
Time to CDP	HR = 0.50; 95% CI: 0.31–0.81; $p = 0.005$	HR = 0.63; 95% CI: 0.40–0.99; $p = 0.05$
Yearly EDSS change	p Value time × group <0.001	p Value time × group <0.001
ARR	RR = 0.044; 95% CI: 0.021–0.091; $p < 0.001$	RR = 0.046; 95% CI: 0.019–0.110; $p < 0.001$
Cumulative incidence of EDSS improvement	HR = 4.21; 95% CI: 2.42–7.33; $p < 0.001$	HR = 3.95; 95% CI: 1.81–8.65; $p = 0.001$
Prevalence of EDSS improvement	p Value <0.001	—
AHSCT vs other DMT (baseline MRI activity in the propensity calculation)		
Time to CDP	HR = 0.58; 95% CI: 0.35–0.96; $p = 0.033$	—
Yearly EDSS change	p Value time × group <0.001	—
AHSCT vs untreated/patients treated with other DMTs		
Time to CDP	HR = 0.48; 95% CI: 0.30–0.78; $p = 0.003$	—
Yearly EDSS change	p Value time × group <0.001	—

Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; ARR = annualized relapse rate; CDP = confirmed disability progression; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HR = hazard ratio; Other DMTs = beta interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab.

with that in the other DMT group (HR = 0.58; 95% CI: 0.35, 0.96; $p = 0.032$).

Inclusion of MRI Activity in the PS Model

Data on MRI activity were available for 73/79 (92.4%) patients in the AHSCT group and for 812/1975 (41.1%) patients in the other DMT group. The AHSCT group had a higher frequency (51/73; 70%) of MRI active scans (defined as scans with at least 1 gadolinium-enhancing lesion) than the other DMT group (156/812; 19.2%). After multiple imputation of missing values, 79 AHSCT-treated patients were matched to 135 patients in the other DMT group. The 2 groups were well balanced (Table 3). Results on the primary outcome were similar to those reported in the main analysis: time to CDP was significantly delayed in AHSCT-treated patients compared with that in patients in the other DMT group (HR = 0.58; 95% CI: 0.35–0.96; $p = 0.033$). The EDSS increased in the control group (yearly change +0.145; 95% CI: 0.115–0.175 EDSS points) while it was substantially stable in the AHSCT group (yearly change +0.015 EDSS points; 95% CI: −0.034 to 0.064), with a significant difference between the 2 groups ($p < 0.001$). In the complete case analysis, 71 patients in the AHSCT group were matched to 100 patients in the other DMT group, and similar results were observed (EDSS points yearly change +0.127; 95% CI: 0.091–0.164 in the other DMT group vs 0.015; 95% CI: −0.038 to 0.068 in the AHSCT group; $p = 0.001$).

AHSCT vs Interferon Beta-1b and Mitoxantrone

A total of 56 AHSCT-treated patients were matched with 63 interferon beta-1b–treated patients (eTable 1, links.lww.com/WNL/C536). Results were similar to those reported for the analysis on other DMTs. In fact, we observed an EDSS point yearly change of +0.126 (95% CI: 0.078–0.174) in the interferon beta group and of 0.047 (95% CI: −0.011 to 0.106) in the AHSCT group, with a significant difference between the 2 groups ($p = 0.040$).

A total of 74 AHSCT-treated patients were matched with 138 mitoxantrone-treated patients (eTable 1, links.lww.com/WNL/C536). An EDSS point yearly change of +0.129 (95% CI: 0.103–0.155) was found in the mitoxantrone group vs 0.023 (95% CI: −0.025 to 0.072) in the AHSCT group ($p < 0.001$). A summary of the most relevant study outcomes of the principal analysis and the main sensitivity analyses is reported in Table 4.

This study provides Class III evidence that autologous hematopoietic stem cell transplants prolonged the time to CDP compared with other DMTs.

Discussion

To date, no prospective clinical trial has been performed to evaluate the efficacy of AHSCT in active SPMS. In this study, we showed that the use of AHSCT for the treatment of active SPMS is associated with better disability outcomes than other DMTs. Despite treatment with most of the available anti-inflammatory DMTs (i.e., beta interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab), our SPMS control group exhibited a mean disability accumulation of 0.16 EDSS points per year, with rates of CDP in line with those

reported by other independent groups of patients with SPMS.[12,31] Conversely, AHSCT-treated individuals showed a stable EDSS time course over time (−0.013 EDSS points per year). This result translates into a significantly delayed time to first CDP in AHSCT-treated patients compared with matched controls, with a percentage of patients without CPD at 5 years of 61.7%.

Taken together, our findings confirm and extend the results of previous uncontrolled studies, which suggested that AHSCT has the potential to slow down neurologic progression in patients with active SPMS.[19-21,32] AHSCT has demonstrated a striking effect in abolishing clinical relapses and MRI signs of inflammatory activity,[21,33-35] which have been repeatedly associated with worse outcomes during the course of SPMS.[7,11] Accordingly, it has been demonstrated that AHSCT is able to reduce long-term CSF markers of ongoing CNS inflammation and axonal damage.[36] The profound anti-inflammatory effect of AHSCT has been confirmed by pathologic studies of MS lesions of patients with SPMS, in which a dramatic reduction of T-cell and B-cell infiltrates has been described.[24,37] Although residual demyelination and neurodegeneration have been reported after AHSCT,[24,37] it seems that AHSCT is able to reduce the compartmentalized inflammation behind the blood-brain barrier, slowing down disability worsening in patients with SPMS. In line with this hypothesis, several independent studies have demonstrated that AHSCT is able to reduce neurofilament light chain levels,[38] slow down cognitive decline,[39] and normalize long-term rates of cerebral gray matter and white matter atrophies,[40] core pathologic features of disability progression during SPMS.

We have previously reported that superimposed relapses[21] and inflammatory activity at baseline MRI[19] are favorable predictors of a better outcome after AHSCT treatment in patients with SPMS. Similar results have been reported in other groups of patients with SPMS[11] and primary progressive MS,[41,42] in which the effect of immunotherapy in reducing disability worsening was more pronounced in patients with active progressive MS.

Relapsing-remitting MS and SPMS form a continuum, with the boundary between them being somewhat indistinct.[43] Progression independent from relapsing activity may indeed accumulate over time in relapsing-remitting MS[44] and evidence for overt inflammatory disease activity may still be found in people with SPMS, underscoring the challenge in distinguishing the 2 disease phenotypes. This is particularly true for people affected by aggressive MS, who experience frequent and severe relapses and high radiologic disease activity,[45] which are strong risk factors for accelerated conversion to SPMS. Although in our study, transplanted patients were relatively young and their disease course was characterized by the presence of inflammatory disease activity, they all had experienced continuous disability progression for ≥6 months during AHSCT and had a baseline EDSS score ≥4, which has been proposed as the minimum level of disability for a diagnosis of SPMS to be made according to the Lorscheider criteria.[46] Accordingly, the mean disease duration of our AHSCT group was almost 14 years, which is consistent with time to SPMS conversion in the MS population.[47,48] Therefore, although our results could not be applicable to people with late SPMS without signs of inflammatory activity, they indicate that AHSCT is effective in reducing disability worsening in patients with active SPMS. These results, altogether with previous studies,[11,13] reinforce the notion that ongoing inflammation during progressive MS represents a treatable target and requires adequate immunotherapy. Finally, whether AHSCT could be of some benefit in patients with relapsing-remitting MS experiencing progression independent of relapse activity during treatment with high-efficacy therapies, which is an increasingly encountered clinical scenario, needs to be explored in future studies.

Because disability improvement in a progressive disease can be a transient condition with little clinical impact, analyzing the incidence of CDI has limited value in assessing the effect of a treatment in restoring neurologic functions. The prevalence of improvement, indicating the proportion of patients with improvement at each time point, is more informative in this context because it reflects more meaningful changes in neurologic disability. In this study, we showed that patients who underwent AHSCT were more likely to experience a sustained disability improvement. Our data indicate that 18.7% of patients with SPMS treated with AHSCT maintained an improvement (a lower EDSS than baseline) 5 years after transplant, compared with 4.1% of patients treated by other DMTs. Although the mechanisms underlying CNS repair are not completely understood, one of the biggest challenges for recovery seems to be the presence of a chronic inflamed microenvironment impairing remyelination and neuronal plasticity,[49] which could be potentially targeted by the CNS-penetrant chemotherapy used during AHSCT.

Safety is a major concern when considering AHSCT as a treatment strategy for patients with MS and represents the major limit to its widespread use. A meta-analysis[50] and a multicenter international cohort study[20] found that patients with SPMS have an increased transplant mortality rate compared with younger patients affected by relapsing-remitting MS. Safety results of our group of AHSCT-treated patients has already been detailed elsewhere[21]: one patient with SPMS died after intracranial hemorrhage 56 days after AHSCT, resulting in a transplant mortality rate of 1.3%.

To overcome the intrinsic limitations of observational studies, in this study, we controlled for multiple demographic and clinical variables to mitigate treatment selection bias. The superiority of AHSCT on disability outcomes was confirmed using the PS matching and the OW approach. As sensitivity analysis, we also included untreated patients with SPMS and confirmed the protective effect of AHSCT on disability worsening and time to CDP. Similar results were found after the application of MSMs to account for potential attrition bias derived by a different duration of on-treatment follow-up in the matched groups. A sensitivity analysis after the inclusion of

measures of MRI activity in the PS calculation confirmed the results of the main analysis. The superiority of AHSCT was also confirmed when considering separately as a control group, patients treated with interferon beta-1b and mitoxantrone, which were the only 2 DMTs approved for the treatment of SPMS in Italy during data collection of this study. However, it should be noted that the 2 groups of patients were recruited separately and thus likely have inherent biases, which can be only partially corrected during propensity weighting.

Notably, our SPMS control group did not include patients treated with siponimod, cladribine, ocrelizumab, or rituximab. In the EXPAND study,[10] siponimod treatment was associated with a delayed time to CDP than placebo, with CDP rate of 23% over 3 years. Similar results have been published after treatment with rituximab in SPMS,[12] with CDP rates of 25% and 50% over 3 and 10 years, respectively. A recent MSBase study[13] did not find any difference in disability outcome in patients with SPMS treated with available high-efficacy (natalizumab, alemtuzumab, mitoxantrone, ocrelizumab, rituximab, cladribine, and fingolimod) and low-efficacy (interferon beta, glatiramer acetate, and teriflunomide) DMT, suggesting that the expected effect of B-cell depleting agents on disability worsening should be in line from that we observed in our control other DMT group. It should be noted, however, that in the MSBase study,[13] only a minority of patients were treated with B-cell depleting agents, and definite conclusions on the relative efficacy of AHSCT vs highly active therapies in SPMS cannot be drawn. Ongoing prospective randomized clinical trials comparing AHSCT and the best available therapy in relapsing-remitting MS and active SPMS (as the BEAT-MS study) will provide important evidence in this setting.

Our data indicate that AHSCT is superior to a subset of low-efficacy and high-efficacy DMTs in slowing down disability worsening in patients with active SPMS. The intense CNS-penetrant chemotherapy of AHSCT could have the advantage to target the compartmentalized inflammation behind the almost intact blood-brain barrier in patients with SPMS, reducing disability progression. It is important to note that because our study population was composed of relatively young patients with clinical activity during SPMS, the results of this study could not be applicable to patients with SPMS without signs of inflammatory disease activity. On the other hand, our results reinforce the notion that ongoing inflammation during progressive MS requires adequate immunotherapy.

In this study, we showed that some transplanted patients experienced sustained disability improvement. The possibility to improve disability and maintain improvement is a crucial need for patients with a progressive disease, and it is hardly obtained with standard anti-inflammatory drugs.

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Continued

Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 1 *(continued)*

Name	Location	Contribution
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Riccardo Saccardi, MD	Department of Cellular Therapies and Transfusion Medicine, Careggi University Hospital, Florence, Italy	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
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Appendix 2 *(continued)*

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