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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 (DMT) 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-months 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 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: 79 AHSCT-treated patients and 1975 patients treated with other DMT (beta-interferons, azathioprine, glatiramer-acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab) were matched to reduce treatment selection bias using propensity-score and overlap weighting approaches. Time to first CDP was significantly longer in transplanted patients (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 DMT than in AHSCT-treated patients (+0.157 EDSS points per year compared to -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 versus 4.6% of patients treated by other DMT ($p<0.001$).

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 to standard immunotherapy.

Classification of Evidence: This study provides Class III evidence that autologous hematopoietic stem cell transplants prolonged the time to confirmed disability progression compared to other disease modifying therapies.

Introduction

Secondary progressive multiple sclerosis (SPMS) is characterized by progressive accrual of neurological 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 cerebrospinal fluid[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 (DMT) 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 to placebo. In line with this result, observational studies have suggested that the use of available anti-inflammatory DMT in SPMS may be therapeutically beneficial[11,12], especially in active SPMS[11,13]. Despite the lack of clear guidelines, anti-inflammatory DMT are often prescribed in patients with SPMS. However, the overall risk reduction in disability worsening with available DMT is only modest and it is still unclear whether the effect of treatment persists over time[14]. In the EXPAND trial[13], after two 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 neurological 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 SPMS patients 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 thought to drive chronic inflammation[27]. Given the absence of satisfactory treatment options for active SPMS, in the last two 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 compared to other disease modifying therapies 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 demographics variables to mitigate treatment selection bias. We hypothesized that patients with active SPMS have better disability outcomes when treated with AHSCT than with other DMT.

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 (EBMT) 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 confirmed disability progression independent of clinical relapses lasting ≥6 months prior to AHSCT.

Control patients with SPMS never treated with AHSCT were collected from the Italian Multiple Sclerosis Register[28]. Patients with SPMS were considered eligible: i) if they had a baseline Expanded-Disability-Status-Scale (EDSS) recording, ii) at least one follow-up visit and iii) 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 anti-thymocyte globulin (ATG). For two patients, fotemustine was used instead of BCNU. Eleven patients were transplanted using cyclophosphamide alone followed by ATG. Thiothepa+cyclophosphamide regimen was used in three 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-months confirmed disability progression (CDP) in patients with active SPMS treated with AHSCT versus those treated with other DMT. 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:

- To evaluate the EDSS score time course after baseline in the two treatment groups
- To compare the cumulative proportion of patients with a 6-months 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)
- To compare the prevalence of disability improvement over time, defined as the proportion of patients who are in an improved status as compared to baseline over time.

Statistical methods

Outcomes were compared between patients treated with AHSCT and patients treated with "other DMT". The "other DMT" group comprises all the patients satisfying the inclusion criteria and starting any DMT during their follow up. Descriptive results were reported as mean with standard deviation (SD) or median with interquartile range (IQR) or range. To mitigate treatment selection bias, we applied two different propensity score (PS) approaches. First, we matched individual patients on their propensity to receive AHSCT or one of the other DMT. 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 DMT (1-PS) and patients treated with other DMT 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 DMT, ARR in the previous year, disease duration and year of treatment start. Only main effects, without interactions, were included in the regression model. Since 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's standardized mean differences (SMD) were calculated in the original cohort and after matching or weighting. A SMD <0.10 was considered an acceptable balance.

All regression models were run on the matched cohorts or weighted according to PS. Differences between treatment groups on time to CDP and CDI were assessed by mean of proportional hazard Cox regression models. Results were reported as hazard-ratio (HR) with the corresponding 95% confidence intervals (CI). 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 two treatment groups. Results were reported as annualized EDSS change with 95%CI. 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 standard deviation (z) was calculated and the p-value was obtained by the normal distribution. Stata (v.16; StataCorp) was used for the computation.

Sensitivity analyses

The following sensitivity analyses were performed:

i) Unadjusted analysis (without propensity score) between patients treated with AHSCT *vs* "Other DMT" group.

ii) Inclusion of untreated patients in the "other DMT" group.

iii) Application of marginal structural models (MSM) to account for potential attrition bias derived by a different duration of on-treatment follow-up in the matched groups. MSM are a method to control for the causal effect of a time-dependent exposure. In this case MSM 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 timepoints conditional on baseline variables. Then we run a weighted Cox regression analysis.

iv) Inclusion of magnetic resonance imaging (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 ten imputations. The second analysis used only the subset with complete MRI information.

v) Comparisons between i) patients treated with AHSCT *vs* patients treated with Interferon beta 1-b and ii) 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 two treatments were the only two DMT approved in Italy for treatment of SPMS at the time of data collection.

Data availability

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

Results

The SPMS cohort 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 SPMS patients were extracted from the MS Italian Register. Of these, 851 were excluded because of missing follow up EDSS data and 703 since their DMT start date was during relapsing-remitting MS. A total of 2361 patients were included in the analysis; of them 1975 (83.7%) started a DMT while 386 (16.3%) were never treated. DMT used by SPMS patients were beta-interferons (24%), azathioprine (13%), glatiramer acetate (13%), mitoxantrone (11%), fingolimod (9%), natalizumab (7%), methotrexate (6%), teriflunomide (6%), cyclophosphamide (6%), dimethyl fumarate (4%), 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 to the AHSCT group [mean 1.95 (SD: 2.30)]. **Table 1** reports the clinical and demographic characteristics of the two treatment groups after propensity score matching and after OW weighting approach, with SMD between the two groups. The mean follow-up of the matched cohort 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, standard deviation = 6 years) from AHSCT.

AHSCT *vs* "Other DMT" patients

Time to CDP

The time to CDP was significantly longer in AHSCT patients as compared to 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 cohort (**Figure 1B**).

Yearly EDSS change

Figure 2A reports the estimated slopes of the EDSS change in the two treatment groups: the mean EDSS change over 10 years in the AHSCT cohort was estimated as -0.013 EDSS points per year (95%CI:-0.087, 0.061 EDSS points per year) while in the "other DMT" cohort the mean EDSS change was +0.157 EDSS points per year; 95%CI: 0.117, 0.196 EDSS points per year) and the difference was statistically significant (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 showed in **Figure 2B**. The estimated yearly EDSS change was -0.017 (95%CI: -0.099, 0.065) in the AHSCT

cohort and +0.18 (95%CI: 0.15, 0.21) in the "other DMT" cohort (p for time*treatment group interaction < 0.001).

Annualized relapse rate

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; <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 patients and of 0.38 (95% CI: 0.30-0.46) among "other DMT" patients (RR=0.067; 95%CI: 0.024-0.184; <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 two groups (RR=0.046; 95%CI: 0.019-0.110; <0.001).

EDSS Improvement

Figure 3A shows the Kaplan-Meier curves for time to CDI. In the matched cohorts the improvement rate was significantly higher in AHSCT patients as 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 AHSCT patients and 3.4% (95%CI: 1.6, 7.0) in the "other DMT" group; after 3 years it was 38.8% (95%CI: 28.0,51.9) in AHSCT patients and 7.8% (95%CI: 4.2,13.3) in the "other DMT" group. AHSCT patients also showed a higher prevalence of improvement (**Figure 3B**) over time (p < 0.001) as 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 patients

maintained the improvement as compared to baseline *vs* 4.1% (95%CI: 1.3,8.3) of patients treated with other DMT.

Sensitivity analyses

Unadjusted comparison of AHSCT *vs* "Other DMT" group

In unadjusted analyses without propensity score matching, the time to CDP was significantly longer in AHSCT patients as compared to 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 EDSS change over 10 years in the AHSCT cohort (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" cohort (n=1975) (p for time by treatment group interaction<0.001).

Inclusion of untreated patients

Untreated patients were added to the cohort of patients treated with other DMT. The untreated group was made up of older patients with similar disease duration and EDSS and lower ARR in the previous year as compared with "other DMT" treated subjects. A total of 72 AHSCT 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**): time to CDP was significantly longer in AHSCT 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: -0.032,0.066) with a significant difference between the two groups (p < 0.001).

Marginal structural model

Results of the analysis run by applying MSM to the matched cohort (69 AHSCT *vs* 217 other DMT) confirmed those reported in the main analysis. The time to CPD was significantly longer in AHSCT patients as compared to the "other DMT" group (HR= 0.58; 95%CI: 0.35, 0.96; p=0.032).

Inclusion of MRI activity in the propensity score model

Data on MRI activity were available for 73/79 (92.4%) patients in the AHSCT group and for 812/1975 (41.1%) in the "other DMT" group. 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 patients were matched to 135 patients in the "other DMT" group. The two 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 patients compared to 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: -0.034,0.064) with a significant difference between the two groups ($p < 0.001$). In the complete cases analysis, 71 AHSCT were matched to 100 "other DMT" and similar results were observed (EDSS points yearly change +0.127; 95%CI: 0.091,0.164 in "other DMT" group *vs* 0.015; 95%CI: -0.038, 0.068 in AHSCT; p = 0.001).

AHSCT *vs* Interferon beta-1b and Mitoxantrone

A total of 56 AHSCT patients were matched with 63 Interferon beta-1b patients (**eTable 1)**. Results were similar to those reported for the analysis on "other DMT". In fact, we observed an EDSS points yearly change of +0.126 (95%CI: 0.078,0.174) in Interferon beta group and of 0.047 (95%CI: -0.011, 0.106) in AHSCT with a significant difference between the two groups (p=0.040).

A total of 74 AHSCT patients were matched with 138 Mitoxantrone patients (**eTable 1**). An EDSS points yearly change of +0.129 (95%CI: 0.103,0.155) was found in Mitoxantrone group *versus* 0.023 (95%CI: -0.025, 0.072) in AHSCT ($p<0.001$).

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 confirmed disability progression compared to other disease modifying therapies.

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 DMT. Despite treatment with most of the available anti-inflammatory DMT (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 cohorts of SPMS patients[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 patients compared to 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 neurological 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 pathological studies of MS lesions of patients with SPMS, in which a dramatic reduction of T and B cells 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 grey matter and white matter atrophy[40], core pathological 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 in patients with SPMS. Similar results have been reported in other cohorts 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 multiple sclerosis 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

two disease phenotypes. This is particularly true for people affected by aggressive MS, who experience frequent and severe relapses and high radiological 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 at the time of 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 cohort 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.

Since 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 neurological functions. The prevalence of improvement, indicating the proportion of patients who are improved at each time point, is more informative in this context as it reflects more meaningful changes in neurological 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 SPMS patients maintained an improvement (a lower EDSS than baseline) 5 years after transplant, compared to the 4.1% of patients treated by other DMT. 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 multi-center international cohort study[20] found that patients with SPMS have an increased transplant-mortality-rate compared to younger patients affected by relapsing-remitting MS. Safety results of our cohort 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 the present work we controlled for multiple demographic and clinical variables to mitigate treatment selection bias. The superiority of AHSCT on disability outcomes was confirmed using the propensity score matching and the overlap weighting 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 marginal structural models 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 propensity score 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 two DMT approved for the treatment of SPMS in Italy at the time of data collection of this study. However, it should be noted that the two cohorts 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 following 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, fingolimod) and low-efficacy (interferons beta, glatiramer acetate, teriflunomide) DMT, suggesting that the expected effect of B cells-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 cells-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 *vs* the best available therapy in relapsing-remitting- and active SP- MS (as the BEAT-MS study) will provide important evidence in this setting.

Conclusions

Our data indicate that AHSCT is superior to a subset of low- and high-efficacy DMT 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, since our study population was composed of relatively young patients with clinical activity during SPMS, the results of this study could not be applicable to SPMS patients

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 in disability and maintain improvement is a crucial need for patients with a progressive disease, and it is hardly obtained with standard anti-inflammatory drugs.

Appendix 2. Coinvestigators

Name	Location	Role	Contribution
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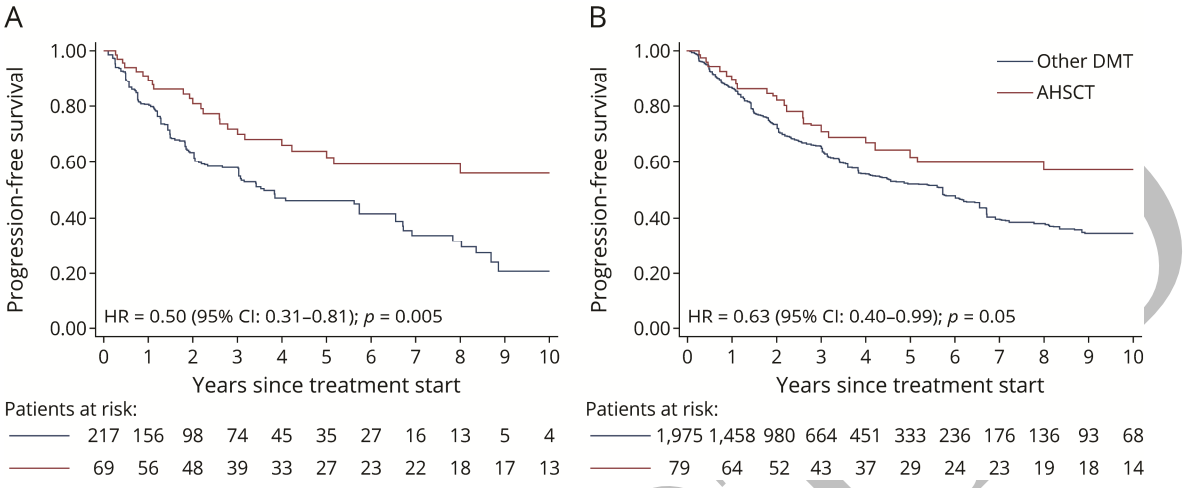
Figure Legends

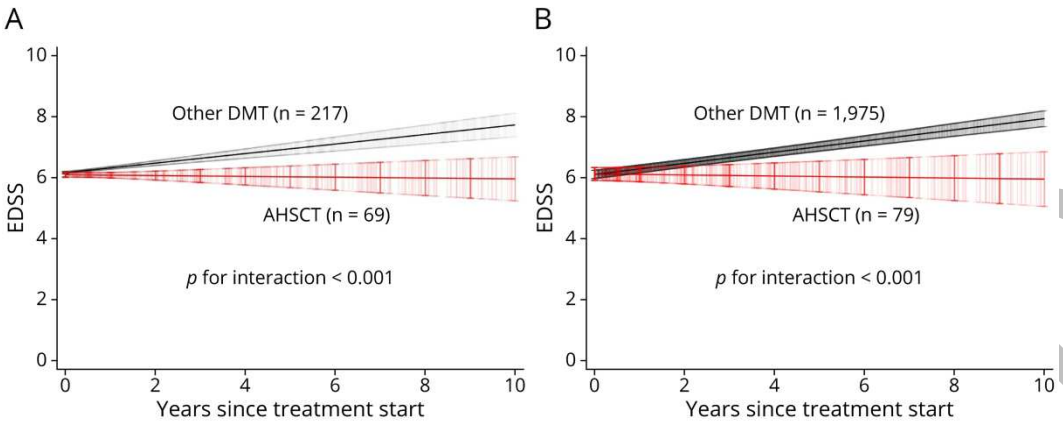
Figure 1. Time To Confirmed Disability Progression In Patients With SPMS Treated With AHSCT And Matched Patients Treated With Other Anti-Inflammatory DMT.



Kaplan-Meier curve for time to first confirmed progression for **A)** propensity score matched treatment groups and **B)** the overlap weighting matched groups.

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; DMT=Disease-Modifying-Therapies (beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab); EDSS= Expanded-Disability-Status-Scale; HR=Hazard Ratio; CI=Confidence Interval.

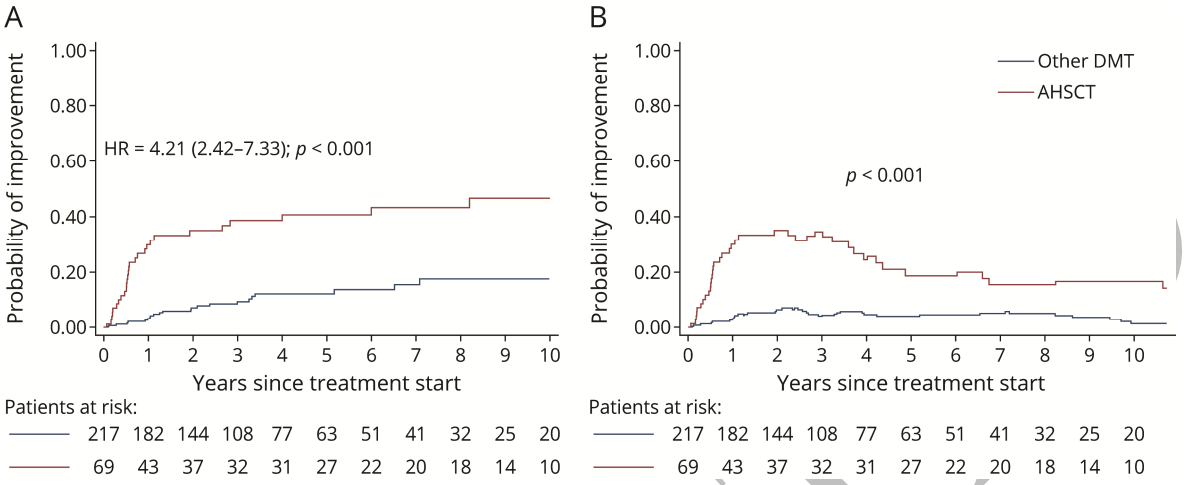
Figure 2. Evolution Of Neurological Disability In Patients With SPMS Treated With AHSCT And Matched Patients Treated With Other Anti-Inflammatory DMT.



Annualized EDSS change together with 95% confidence intervals 1 to 10 years after treatment start for **A)** propensity score matched treatment groups and **B)** the overlap weighting matched groups.

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; DMT=Disease-Modifying-Therapies (beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab); EDSS= Expanded-Disability-Status-Scale;

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 DMT.



A) Kaplan-Meier curve for time to first confirmed disability improvement. **B)** Prevalence of confirmed disability improvement 1 to 10 years after treatment start.

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; DMT=Disease-Modifying-Therapies (beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab); EDSS= Expanded-Disability-Status-Scale.

Table 1 – Clinical and demographic characteristics in the matched (left side) and in the overlap weighted (right side) groups

Characteristic	Matched cohort			Overlap weighted cohort		
	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 year	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
N. 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	3.53 (3.01);	2.72 (3.20);	0.26	3.61 (2.99);	2.91 (3.22); 1.95	0.22

conversion, mean (SD); median (IQR)	2.53 (1.49-4.75) [n=53]	1.76 (0.59-3.79)		2.56 (1.69-4.81) [n=57]	(0.58-4.09)	
Follow-up (years); 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	-

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; Other DMT=beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab; SMD= Standardized Mean Differences; SD=Standard Deviation; M=Male; F=Female; EDSS= Expanded-Disability-Status-Scale; IQR=Interquartile Range; ARR=Annualized Relapse Rate; SP=Secondary Progressive.

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 year	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
N. 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

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; Other DMT=beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab; SMD= Standardized Mean Differences; SD=Standard Deviation; M=Male; F=Female; EDSS= Expanded-Disability-Status-Scale; IQR=Interquartile Range; ARR=Annualized Relapse Rate; SP=Secondary Progressive.

Table 3 – Demographic and clinical characteristics of matched AHSCT and other DMT patients accounting for baseline MRI activity

Characteristics	AHSCT (n=79)	Treated (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 year	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
N. 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

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; Other DMT=beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab; SMD= Standardized Mean Differences; SD=Standard Deviation; M=Male; F=Female; EDSS= Expanded-Disability-Status-Scale; IQR=Interquartile Range; ARR=Annualized Relapse Rate; 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/Other DMT patients		
Time to CDP	HR=0.48; 95% CI: 0.30-0.78; p=0.003	-
Yearly EDSS change	p-value time*group < 0.001	-

AHSCT= Autologous Hematopoietic Stem Cell Transplantation; Other DMT=beta-interferons, azathioprine, glatiramer acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, alemtuzumab; HR= Hazard Ratio; EDSS= Expanded-Disability-Status-Scale; CDP= Confirmed Disability Progression.

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