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

Autologous Hematopoietic Stem Cell Transplantation Reduces Disability Progression In Patients With Secondary Progressive Multiple Sclerosis: Results From The Italian Multiple Sclerosis Register

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Introduction

Secondary progressive multiple sclerosis (SPMS) is characterized by progressive accrual of neurological disability independent of clinical relapses(1). Compartmentalized inflammation within the brain parenchyma(2–4) the leptomeninges(5) and the cerebrospinal fluid(6) represents a key driver of disability worsening in SPMS. Persistent inflammation within the CNS, in terms of clinical relapses or MRI activity, has been repeatedly associated with accelerated disability progression (7,8). Although first randomized controlled clinical trials did not reveal the efficacy of disease-modifying therapies (DMT) for disability progression during SPMS(9,10), a recent randomized clinical trial established some benefits of siponimod(11,12) in reducing the risk of disability worsening compared to placebo. In line with this result, observational studies have suggested that the use of available DMT in SPMS may be therapeutically beneficial(13,14), especially in active SPMS(13). 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.

Ablation of the immune system followed by autologous hematopoietic stem cell transplantation (AHSCT) has been gain increasing evidence as a therapeutic strategy for refractory MS(15–17). 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 MS patient with aggressive relapsing-remitting MS, uncontrolled evidence suggests that AHSCT is able to prevent long-term neurological deterioration even in progressive MS(19–21). The drugs used in AHSCT technology cross the blood-brain-barrier and penetrate into the CNS, with the potential to target compartmentalized inflammation. Given the absence of satisfactory treatment options for SPMS, in the last two decades AHSCT was used off-label for the treatment of 81 patients with aggressive SPMS in 14 Italian MS centers.

137 The aim of this cohort study was to compare the effect of AHSCT on disability worsening in patients
138 with SPMS with that of other DMTs in SPMS patients from the Italian Multiple Sclerosis Register.
139
140 Methods
141 *Study Design*
142 All patients with SPMS(1), treated with AHSCT at 14 Italian MS Centers from 1997 to 2019 were
143 considered eligible for this study. Patients were treated according to the European Group for Blood
144 and Marrow Transplantation (EBMT) guidelines, following the decision of the treating physician and
145 approval of the local Ethics Committee. Although no formal guideline was used for patient selection,
146 patients had aggressive disease course, characterized by the occurrence of relapses, MRI
147 inflammatory activity or accrual of accelerated neurological disability despite active treatment.
148 Detailed information on conditioning regimen and transplant care is reported in the Supplementary
149 Materials.
150 Control patients with SPMS never treated with AHSCT were collected from the Italian MS
151 Register(22). Patients were considered eligible: a) if they had a baseline EDSS recording, b) at least
152 one follow-up visit and c) if a DMT had been started after the diagnosis of SPMS. Untreated patients
153 were included in a sensitivity analysis.
154
155 *Study endpoints*
156 The primary objective was to compare disability worsening as assessed by the EDSS score time course
157 after baseline in patients with SPMS treated with AHSCT versus those treated with other DMT.
158 Secondary endpoints were the cumulative proportion of patients with a 6-months confirmed
159 disability progression (CDP), defined as an increase of 1 point in the EDSS score (0.5 points if the

160 baseline EDSS score was ≥5.5), the cumulative proportion of patients with a 6-months confirmed
161 disability improvement (CDI), defined as a decrease of 1 point in the EDSS score (0.5 points if the
162 baseline EDSS score was ≥5.5) and the prevalence of disability improvement over time, defined as
163 the proportion of patients who are in an improved status as compared to baseline over time.
164
165 *Statistical methods*
166 Outcomes were compared between patients treated with AHSCT and patients treated with "other
167 DMT". The "other DMT" group comprises all the patients satisfying the inclusion criteria and starting
168 any DMT during their follow up. Untreated patients were excluded from the analysis and included in
169 a sensitivity analysis. Descriptive results were reported as mean with standard deviation (SD) or
170 median with interquartile range (IQR) or range.
171 We applied two different propensity score (PS) approaches to mitigate the differences of baseline
172 characteristics between the treatment groups. First, we matched individual patients on their
173 propensity to receive AHSCT or one of the other DMT. Patients were matched without replacement
174 with a variable ratio up to 5:1 (other DMT : AHSCT) and using a nearest neighbor matching within a
175 caliper of 0.25 SDs of the PS. Second, we applied an overlap weighting (OW) approach(23). This
176 method has the advantage over the n:1 PS matching method that no patients are excluded from the
177 analysis, without modifying the target population(23). The OW method assigns to each patient a
178 weight proportional to the probability of that patient belonging to the opposite treatment group(23).
179 In our analysis, AHSCT treated patients are therefore weighted by the probability to receive one of
180 the other DMT (1-PS) and patients treated with other DMT are weighted by the probability of
181 receiving AHSCT treatment (PS). OW leads to an exact balance on the mean of each baseline covariate
182 included in the PS calculation.

183 For both methods, individual PS were calculated using a multivariable logistics regression model
184 including age at treatment start, gender, EDSS at treatment start, number of previous DMT, ARR in
185 the previous year, disease duration and year of treatment start. Only main effects, without
186 interactions, were included in the regression model. Since MRI data were missing for most of the
187 patients, they were not included in the primary PS calculation. A sensitivity analysis was run by
188 adjusting for a PS including MRI variables. Positivity assumption of PS was checked after its
189 calculation.
190 To assess the degree of unbalance of covariate distribution between the groups, Cohen's
191 standardized mean differences (SMD) were calculated in the original cohort and after matching or
192 weighting. A SMD < 0.10 was considered an acceptable balance.
193 All regression models were run on the matched cohorts or weighted according to PS. A linear mixed
194 model with random intercept and random slope was used to assess the longitudinal EDSS time trend
195 after baseline. A time*treatment group interaction term was included into the model to test
196 differences on EDSS time trend between the two treatment groups. Results were reported as
197 annualized EDSS change with 95% Confidence Intervals (CI). Differences between treatment groups
198 on time to CDP and CDI were assessed by mean of proportional hazard Cox regression models. Results
199 were reported as hazard-ratio (HR) with the corresponding 95% CI. Progression-free survival and
200 cumulative probability of improvement were estimated by Kaplan-Meier approach and graphically
201 displayed. The prevalence of CDI was estimated according to the recently reported methodology(24)
202 and compared between groups by bootstrapping the area under the curve (AUC). Stata (v.16;
203 StataCorp) was used for the computation.
204
205 *Sensitivity analyses*

206 The following sensitivity analyses were performed:

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

208 ii) Application of marginal structural models (MSM) to account for potential attrition bias
209 derived by a different duration of on-treatment follow-up in the matched groups. We
210 estimated at each 1-year time point the stabilized weights, from the inverse probability to be
211 censored at fixed timepoints conditional on baseline variables. Then we run a weighted Cox
212 regression analysis.

213 iii) Inclusion of magnetic resonance imaging (MRI) activity in the PS calculation. Two analyses
214 were performed: one with missing data imputed before the PS calculation using multiple
215 imputation approach with a logistic regression model and ten imputations. The second
216 analysis used only the subset with complete MRI information.

217 iv) Comparisons between a) patients treated with AHSCT vs patients treated with Interferon beta
218 1-b and b) patients treated with AHSCT vs patients treated with Mitoxantrone using a
219 matching without replacement with a variable ratio up to 5:1 (DMT : AHSCT) with the same
220 rules previously described. These two treatments were the only two approved in Italy for
221 treatment of SPMS.

222

223 Results

224 **Figure 1S** reports the flowchart for SPMS patients' selection and inclusion. The SPMS cohort treated
225 by AHSCT included 81 patients from 14 centers. Two patients did not have follow-up information and
226 were excluded from the analysis. Data on 8465 SPMS patients were extracted from the Italian
227 Registry. Of these, 4550 were excluded due to the lack of a baseline EDSS assessments, 851 because
228 of missing follow up EDSS data and 703 since their DMT start date was during RRMS. A total of 2361

229 patients were included in the analysis; of them 1975 (83.7%) started a DMT ("other DMT" group)
230 while 386 (16.3%) were never treated. **Table 1S** reports the demographic and clinical characteristics
231 of the three groups (AHSCT, other DMT, untreated). Patients in the "other DMT" group were older
232 and with a longer disease duration, a lower baseline EDSS and a lower ARR in the previous year as
233 compared to AHSCT patients. DMT used by SPMS patients were mainly Interferons (38%),
234 Azathioprine and Glatiramer acetate (both around 20%). The untreated group was made up of older
235 patients with similar disease duration and EDSS and lower ARR in the previous year as compared with
236 "other DMT" treated subjects. **Table 1** reports the same characteristics for the matched and the OW
237 weighted cohorts, showing that both matching and OW weighting consistently reduced the SMD
238 between the two groups. The mean follow-up of the matched cohort was 5.2 years, with a median
239 of 3.6 years (IQR:1.8-7.6 years).
240
241 *AHSCT vs "Other DMT" patients*
242 *Yearly EDSS change*
243 **Figure 1** reports the estimated slopes of the EDSS change in the two treatment groups: the mean
244 EDSS change over 10 years in the AHSCT cohort was estimated as -0.013 EDSS points per year (95%
245 CI:-0.087, 0.061 EDSS points per year) while in the "other DMT" cohort the mean EDSS change was
246 +0.157 EDSS points per year; 95% CI: 0.117, 0.196 EDSS points per year) and the difference was
247 statistically significant (p for time by treatment group interaction<0.001). Similar results were
248 observed by the OW analysis and the estimated slopes of EDSS change are showed in the
249 Supplementary **Figure 2S**. The estimated yearly EDSS change was -0.017 (95% CI: -0.099, 0.065) in
250 the AHSCT cohort and +0.18 (95% CI: 0.15, 0.21) in the "other DMT" cohort (p for time by treatment
251 group interaction < 0.001).

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 2**) . 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 3S**).

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 showed also 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 just 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 are still improved as compared to baseline vs 4.1% (95% CI: 1.3,8.3) of patients treated with other DMTs.

Sensitivity analyses

Inclusion of untreated patients

Untreated patients were added to the cohort of patients treated with other DMT. 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 2S.**

Figure 4S shows the results of the analysis on EDSS change. Results were similar to those reported in the main analysis: 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 HSCT group (yearly change +0.017 EDSS points; 95% CI: -0.032,0.066) with a significant difference between the two groups ($p < 0.001$). Results on time to EDSS progression were very close to those reported in the main analysis (**Figure 5S**).

Marginal structural model

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

Magnetic resonance (MRI) activity in the propensity score

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%; **Table 1S**). After multiple imputation of missing values, 79 HSCT patients were matched to 135 patients in the "other DMT" group. The two groups were well balanced (**Table 3S**). Results on the primary outcome were similar to those reported in the main analysis: 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 HSCT 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 HSCT

296 were matched to 100 “other DMT” and similar results were observed (EDSS points yearly change
297 +0.127; 95% CI: 0.091,0.164 in “other DMT” group vs 0.015; 95% CI: -0.038, 0.068 in HSCT; p = 0.001).
298 *HSCT vs Interferon beta-1b*
299 A total of 56 HSCT patients were matched with 63 Interferon beta-1b patients (**Table 4S**). Results
300 were similar to those reported for the analysis on “other DMTs”. In fact we observed an EDSS points
301 yearly change of +0.126; 95% CI: 0.078,0.174 in Interferon beta group and of 0.047; 95% CI: -0.011,
302 0.106 in HSCT with a significant difference between the two groups (p=0.040).
303 *HSCT vs Mitoxantrone*
304 A total of 74 HSCT patients were matched with 138 Mitoxantrone patients (**Table 4S**). Also for this
305 comparison on the primary outcome, results were similar to those reported previously. An EDSS
306 points yearly change of +0.129; 95% CI: 0.103,0.155 in Mitoxantrone group and of 0.023; 95% CI: -
307 0.025, 0.072 in HSCT with a significant difference between the two groups (p<0.001).
308
309 Discussion
310 To date, no prospective clinical trial has been performed to evaluate the efficacy of AHSCT in SPMS.
311 In this study, we showed that the use of AHSCT for the treatment of SPMS was associated with better
312 disability outcomes than other DMT. Despite treatment with active DMT, our SPMS control group
313 exhibited a mean disability accumulation of 0.16 EDSS points per year, with rates of CDP in line with
314 those reported by other independent cohorts(14,25). Conversely, treatment with AHSCT induced an
315 average improvement of EDSS over time (-0.013 EDSS points per year). This result translates into a
316 significant delayed time to first CDP in AHSCT patients compared to matched controls, with a
317 percentage of patients without CPD at 5 years of 61.7%.

318 Taken together, our findings confirm and extend the results of previous uncontrolled studies which
319 suggested that AHSCT has the potential to slow down neurological progression in patients with
320 SPMS(19–21,26). AHSCT has demonstrated a striking effect in abolishing clinical relapses and MRI
321 signs of inflammatory activity(19,27–32), which have been associated with worse outcomes during
322 the course of SPMS(7,13). Accordingly, it has been demonstrated that AHSCT is able to reduce CSF
323 markers of ongoing CNS inflammation and axonal damage(33). The profound anti-inflammatory
324 effect of AHSCT has been confirmed by pathological studies of MS lesions of patients with
325 SPMS(34,35), in which a dramatic decrease in T and B cells infiltrates has been described up to 7
326 years(35). Although residual demyelination and neurodegeneration have been reported after AHSCT
327 (34,35), it is arguable that the almost complete resolution of compartmentalized inflammation
328 behind the blood–brain barrier obtained with AHSCT has the potential to slow down disability
329 worsening in patients with SPMS, as suggested by the positive results of anti-inflammatory B-cell
330 targeted therapies in progressive MS(36,37). In line with this hypothesis, it has been demonstrated
331 that anti-inflammatory DMT could also reduce axonal damage in patients with SPMS(38–41),
332 potentially preventing disability accumulation.
333
334 We have previously reported that superimposed relapses(19) and inflammatory activity at baseline
335 MRI(20) are favorable predictors of a better outcome after AHSCT in patients with SPMS. Similar
336 results have been reported in other cohorts of patients with SPMS(13), in which the effect of
337 immunotherapy in reducing disability progression was significant only in patients with active SPMS.
338 Therefore, it is still unknown whether immunotherapy, including AHSCT, can be effective in patients
339 with SPMS without evidence of inflammatory activity. On the other hand, the results of this study

support the notion that the presence of inflammation during SPMS represents a treatable target and requires adequate treatment.

A very intriguing result was 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. 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 .

Notably, our SPMS control group did not include patients treated with siponimod or rituximab. In the EXPAND study(11), 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(14), with CDP rates of 25% and 50% over 3 and 10 years, respectively. Baseline characteristics of these studies were quite balanced, with evidence of MRI inflammatory activity and relapses in the year before treatment start in about 20% of patients. Although our cohort was composed by younger patients with a higher baseline ARR, it is noteworthy that the rate of CDP at 10 years was significantly lower in patients treated with AHSCT than in patients treated with rituximab.

Limitations

The main limitation of the present study relies on its observational nature. Since our AHSCT study cohort was composed mainly by patients with aggressive, active SPMS and did not represent a

363 standard population of patients with SPMS, we controlled for multiple demographic and clinical
364 variables to mitigate treatment selection bias. The superiority of AHSCT on disability outcomes was
365 confirmed using both the propensity score matching and the overlap weighting (in which no patients
366 are excluded from the analysis, without modifying the target population). As sensitivity analysis, we
367 also included untreated patients with SPMS and confirmed the protective effect of AHSCT on
368 disability worsening and time to CDP. The same results were obtained after the inclusion of measures
369 of MRI activity in the propensity score calculation and from the application of marginal structural
370 models to account for potential attrition bias derived by a different duration of on-treatment follow-
371 up in the matched groups. The superiority of AHSCT was also confirmed when considering as a control
372 group patients treated with interferon beta 1b and mitoxantrone, which were the only two DMTs
373 approved for the treatment of SPMS at the time of data collection of this study. Finally, although the
374 EDSS raters were not blinded to the treatment and this could have introduced some bias, the long-
375 term follow-up has partially mitigated this measurement bias.
376
377 Conclusions
378 AHSCT induced a marked slowing of disability progression in patients with active SPMS as compared
379 to other DMT. Prospective randomized clinical trials are needed to confirm the efficacy of AHSCT in
380 patients with active SPMS.
381
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FIGURE 1

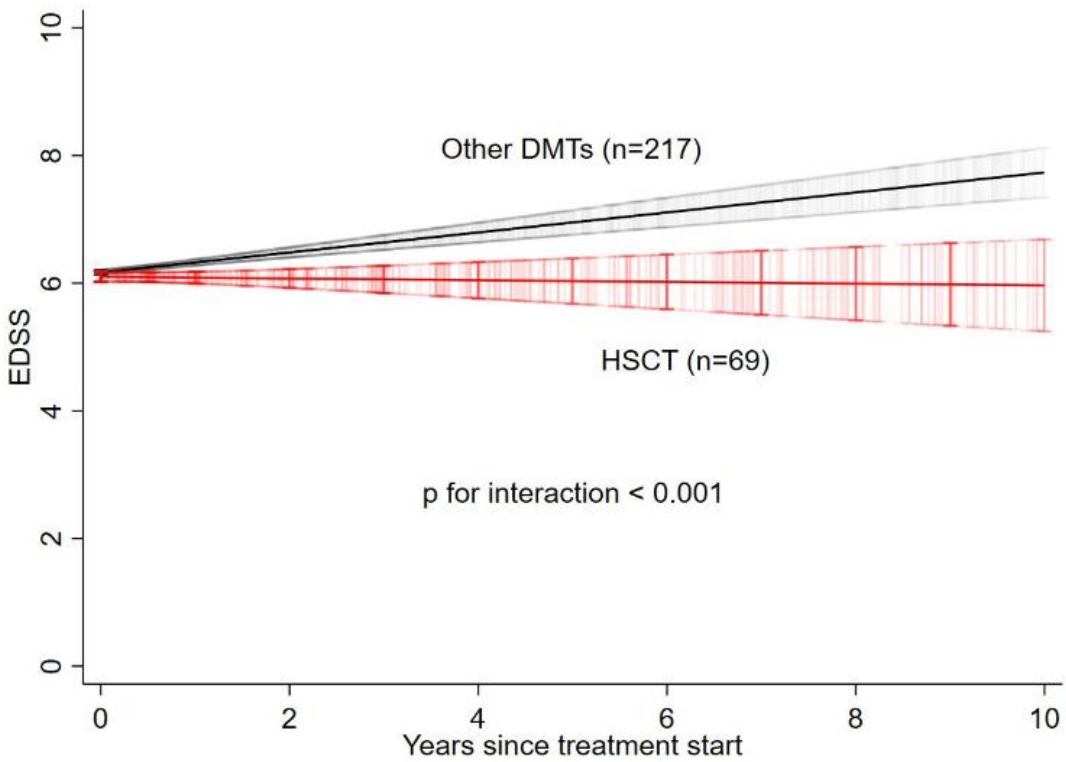

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Table 1 – Clinical and demographic characteristics in the matched (left side) and in the overlap weighted (right side) gro

Characteristic	Matched cohort			Overlap weighted cohort		
	AHSCT (n=69)	Treated (n=217)	SMD AHSCT vs Treated	HSCT (n=79)	Treated (n=1975)	SMI Tre
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)	0.0
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)	0.0
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)	0.0
ARR previous year	1.08 (1.12)	0.90 (1.02)	0.17	1.01 (1.07)	1.01 (1.66)	0.0
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)	0.0
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)	0.0
Year of treatment start,	2007.7 (6.4); 2007 (2002-2014)	2007.6 (5.3); 2007 (2004-2012)	0.019	2007.7 (6.2); 2007 (2003-2014)	2007.7 (5.4); 2008 (2004- 2012)	0.0

mean (SD); median (IQR)						
Year of SP conversion, mean (SD); median (IQR)	2005 (7.9); 2004 (1999-2013); [n=53]	2005 (5.8); 2004 (2001-2009)	0.011	2005 (7.9); 2004 (1999-2013) [n=57]	2005 (6.1); 2005 (2001-2010)	0.0
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	-

Table 1S – Demographic and clinical characteristics of the three treatment groups.

Characteristics	HSCT (n=81)	Treated (n=1975)	Untreated (n=386)	SMD HSCT vs Treated	SM Un
Age, mean (SD); median (range)	37.8 (7.8); 36.8 (24-58)	46.7 (9.6); 46.3 (19-76)	50.2(11.1); 50 (20-85)	1.02	1.2
Sex (M/F), n(%)	28/53 (34.6/65.4)	758/1217 (38.4/61.6)	125/261 (32.4/67.6)	0.096	0.0
Baseline EDSS, median (IQR); range	6.5 (6-6.5); 4-8.5	5.5 (4.5-6); 0-9	5.5(4-6.5); 0-9	0.86	0.8
ARR previous year	1.19 (1.27)	0.47 (0.77)	0.29 (0.61)	0.68	0.9
Disease duration, mean (SD); median (IQR)	13.3 (6.6); 11.8 (8.5-16.3)	15.5 (8.7); 14.3 (9.2-20.8)	16.6(10.1); 14.7(9.1-22.9)	0.29	0.4
N. of previous treatments, median (IQR); range	2 (1-3); 0-6	1 (0-1); 0-6	0 (0-1); 0-4	1.37	1.7
Year of treatment start, mean; median (IQR); range	2007.6; 2006 (2003-2013); 1997-2019	2007.5; 2008 (2003-2012); 1990-2018	-	0.012	-
Year of SP conversion, mean; median (IQR); range	2005; 2004 (2000-2013); 1986-2018 [n=57]	2004; 2004 (2000-2009); 1978-2017	2002.4; 2003(1997-2009); 1977-2018	0.14	0.3
Treatments, n(%)*					
Interferon beta (IFN)	-	761 (38.5)	-		
Glatiramer acetate (GA)	-	424 (21.5)	-		
Fingolimod (FTY)	-	299 (15.1)	-		
Natalizumab (NTZ)	-	228 (11.5)	-		
Mitoxantrone (MIT)	-	360 (18.2)	-		
Azathioprine (AZA)	-	431 (21.8)	-		
Other	-	690 (34.9)	-		
N. of treatments received during follow-up					
1		1132 (57.3)			
2		555 (28.1)			
3		259 (13.1)			
4		29 (1.5)			
Time spent in treatment during follow-up (%)		95.7 (13.4); 100 (1.6-100)			

Table 2S – Demographic and clinical characteristics of matched HSCT and Control group (treated and untreated) patients

Characteristics	HSCT (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, mean; median (IQR)	2007.5; 2007 (2003-2014)	2007.6; 2008 (2004-2013)	0.027
Year of SP conversion, mean; median (IQR)	2005; 2004 (1999-2013) [n=54]	2005; 2006 (2001-2011)	0.061

Table 3S – Demographic and clinical characteristics of matched HSCT and other DMTs patients

Characteristics	HSCT (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, mean; median (IQR)	2007.6; 2006 (2003-2014)	2008.4; 2008 (2004-2013)	0.15
Year of SP conversion, mean; median (IQR)	2005; 2004 (2000-2013) [n=57]	2006; 2005 (2001-2011)	0.12

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Table 4S – Demographic and clinical characteristics of matched HSCT and Interferon beta-1b (left side) or Mitoxantrone

Characteristics	HSCT (n=56)	Interferon beta-1b (n=63)	SMD		HSCT (n=74)	Mitoxan (n=138)
Age, mean (SD)	39.6 (7.6)	39.5 (6.6)	0.016		38.4 (7.6)	38.8 (6.4
Sex (M/F), n(%)	23/33 (41/59)	29/34 (46/54)	0.10		27/47 (36.5/63.5)	35/103 (
Baseline EDSS, mean (SD); median (IQR)	6.2 (0.9); 6.5 (6-6.5)	6.3 (0.7); 6.5 (6-7)	0.11		6.3 (0.9); 6.5 (6-7)	6.4 (0.9)
ARR previous year	0.76 (0.79)	0.60 (0.73)	0.20		1.05 (1.07)	0.97 (1.1
Disease duration, mean (SD); median (IQR)	13.9 (6.9); 12.3 (10.4-17.5)	14.6 (6.9); 14.4 (9.7-18.9)	0.086		13.5 (6.8); 11.9 (8.5-17.3)	13.3 (5.5 (8.7-16.1
N. of previous treatments, median (IQR); range	2 (1-3); 0-4	2 (2-3); 0-5	0.059		2 (1-3); 0-6	2 (2-3); (
Year of treatment start, mean; median (IQR)	2007; 2006 (2002-2013)	2005; 2005 (2000- 2007)	0.33		2007; 2006 (2002-2012)	2006; 20 2008)
Year of SP conversion, mean; median (IQR)	2004; 2004 (1998-2010) [n=42]	2000; 2000 (1998-2002)	0.62		2004; 2004 (1999-2011)	2003; 20 2005)

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