Preliminary Communication

Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With Relapsing-Remitting Multiple Sclerosis

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IMPORTANCE No current therapy for relapsing-remitting multiple sclerosis (MS) results in significant reversal of disability.

OBJECTIVE To determine the association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability and other clinical outcomes in patients with MS.

DESIGN, SETTING, AND PARTICIPANTS Case series of patients with relapsing-remitting MS (n = 123) or secondary-progressive MS (n = 28) (mean age, 36 years; range, 18-60 years; 85 women) treated at a single US institution between 2003 and 2014 and followed up for 5 years. Final follow-up was completed in June 2014.

INTERVENTIONS Treatment with cyclophosphamide and alemtuzumab (22 patients) or cyclophosphamide and thymoglobulin (129 patients) followed by infusion of unmanipulated peripheral blood stem cells.

MAIN OUTCOMES AND MEASURES Primary end point was reversal or progression of disability measured by change in the Expanded Disability Status Scale (EDSS) score of 1.0 or greater (score range, 0-10). Secondary outcomes included changes in the Neurologic Rating Scale (NRS) score of 10 or greater (score range, 0-100), Multiple Sclerosis Functional Composite (MSFC) score, quality-of-life Short Form 36 questionnaire scores, and T2 lesion volume on brain magnetic resonance imaging scan.

RESULTS Outcome analysis was available for 145 patients with a median follow-up of 2 years and a mean of 2.5 years. Scores from the EDSS improved significantly from a pretransplant median of 4.0 to 3.0 (interquartile range [IQR], 1.5 to 4.0; n = 82) at 2 years and to 2.5 (IQR, 1.9 to 4.5; n = 36) at 4 years ($P < .001$ at each assessment). There was significant improvement in disability (decrease in EDSS score of ≥1.0) in 41 patients (50%; 95% CI, 39% to 61%) at 2 years and in 23 patients (64%; 95% CI, 46% to 79%) at 4 years. Four-year relapse-free survival was 80% and progression-free survival was 87%. The NRS scores improved significantly from a pretransplant median of 74 to 88.0 (IQR, 77.3 to 93.0; n = 78) at 2 years and to 87.5 (IQR, 75.0 to 93.8; n = 34) at 4 years ($P < .001$ at each assessment). The median MSFC scores were 0.38 (IQR, −0.01 to 0.64) at 2 years ($P < .001$) and 0.45 (0.04 to 0.60) at 4 years ($P = .02$). Total quality-of-life scores improved from a mean of 46 (95% CI, 43 to 49) pretransplant to 64 (95% CI, 61 to 68) at a median follow-up of 2 years posttransplant (n = 132) ($P < .001$). There was a decrease in T2 lesion volume from a pretransplant median of 8.57 cm^3 (IQR, 2.78 to 22.08 cm^3) to 5.74 cm^3 (IQR, 1.88 to 14.45 cm^3) ($P < .001$) at the last posttransplant assessment (mean follow-up, 27 months; n = 128).

CONCLUSIONS AND RELEVANCE Among patients with relapsing-remitting MS, nonmyeloablative hematopoietic stem cell transplantation was associated with improvement in neurological disability and other clinical outcomes. These preliminary findings from this uncontrolled study require confirmation in randomized trials.

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Multiple sclerosis (MS) is thought to be an immune-mediated disorder of the central nervous system that in most patients begins as an inflammatory relapsing-remitting disease.[1] Despite standard therapies, the majority of patients eventually enter a secondary-progressive phase for which no therapy has demonstrated efficacy. Fifty percent of patients are unable to continue employment by 10 years from diagnosis, require assistance to ambulate by 15 years, or are unable to walk by 25 years.[2] Despite an annual cost of approximately US $47 000 per patient[3,4] to treat MS, no therapy approved by the US Food and Drug Administration (FDA) has been demonstrated to significantly reverse neurological disability or improve quality of life.[5-11]

Autologous hematopoietic stem cell transplantation (HSCT) is a form of immune suppression but unlike standard immune-based drugs, it is designed to reset rather than suppress the immune system.[12-14] In a previous study, a nonmyeloablative regimen for patients with relapsing-remitting MS was associated with improvement in neurological disability and quality of life in 21 patients.[15] This report includes all patients from a single institution treated with a nonmyeloablative regimen with at least 6 months of follow-up, including the 21 patients previously reported.[15]

Methods

Patients

All patients who underwent HSCT for MS at Northwestern University (Chicago, Illinois) between July 2003 and February 2014 are included in this report. All patients signed informed consent and were treated and followed up identically per a study protocol approved by the Northwestern University institutional review board. Similar institutional review board approval was obtained for the reporting of patients treated off the study protocol. Race/ethnicity was recorded by the transplant team during the initial history and physical of each patient.

Patients who were treated according to the study protocol underwent transplant and met all the following criteria: (1) had relapsing-remitting MS defined as acute relapses followed by partial or complete recovery and stable clinical manifestations between relapses, (2) fulfilled revised McDonald Diagnostic Criteria for MS,[16] (3) treatment was unsuccessful with at least 1 FDA-approved drug, (4) had an Extended Disability Status Scale (EDSS) score from 2.0 to 6.0, (5) were aged 18 to 55 years, and (6) during the preceding year, had either at least 2 relapses treated with a corticosteroid or 1 relapse treated with a corticosteroid and additional gadolinium-enhanced lesions on magnetic resonance imaging (MRI) scan at a separate time.

In addition, there were also patients treated off the study protocol on a compassionate basis for secondary-progressive MS, which was defined as a gradual progression of disability with or without superimposed relapses, or received HSCT for other reasons, including (1) brainstem, visual, or cognitive impairment with high risk of further paraplegic, quadriplegic, visional, or cognitive impairment, (2) EDSS score greater than 6.0, (3) treatment was unsuccessful with currently available FDA-approved drugs, (4) coexisting autoimmune or neurological disease, (5) allergy to gadolinium, (6) older than 55 years, and (7) tumefactive MS (tumor-like MRI appearance).

Most immune-modulation or suppression medications were stopped at the time of mobilization (collection of stem cells), except for natalizumab and fingolimod, which were discontinued 6 and 3 months, respectively, before transplant. After HSCT, patients did not receive immune-based therapies until clinical relapse or when new lesions were detected on an MRI scan.

Stem Cell Collection and Transplant Regimen

Peripheral blood stem cells were collected 10 days after patients received 2 g/m^2 of cyclophosphamide (administered intravenously) and 5 to 10 μg/kg of filgrastim (administered subcutaneously) daily beginning 5 days after receiving cyclophosphamide. The conditioning (immunoablative) regimen consisted of 50 mg/kg/d of cyclophosphamide (administered intravenously) 5 to 2 days before stem cell infusion (day 0) plus either 20 mg of alemtuzumab given 2 days before stem cell infusion (22 patients) or 0.5 mg/kg of thymoglobulin (administered intravenously) 5 days before stem cell infusion, 1.0 mg/kg 4 days before, and 1.5 mg/kg on 3 days, 2 days, and 1 day before stem cell infusion (129 patients).

In addition, 1000 mg of methylprednisolone was infused 30 minutes prior to each antithymocyte globulin infusion. On the day of stem cell infusion, oral prednisone was initiated with a dose of 60 mg/d given for 3 days, 40 mg/d for 2 days, 20 mg/d for 2 days, and 10 mg/d for 2 days. If fever developed, 250 mg of methylprednisolone was administered intravenously.

Supportive Care Guidelines

Blood products were irradiated and leukocytes were depleted. Filgrastim (5-10 μg/kg/d) was started on day 5 and continued until engraftment. Hyperhydration (150 mL/h of normal saline), diuretics, and intravenous mesna were continued until 24 hours after the last dose of cyclophosphamide. A Foley catheter was placed in patients with a history of urinary retention. Intravenous cefepime or piperacillin-tazobactam was started on the day of stem cell infusion and intravenous vancomycin was added for a febrile episode.

Oral daily acyclovir was started at hospital admission and continued for 1 year, oral fluconazole was started 2 days after HSCT and continued for 6 months, and oral trimethoprim-sulfamethoxazole (3 times/wk) was started after platelet engraftment and continued for 6 months. Cytomegalovirus was monitored for 90 days and treated preemptively by switching from acyclovir to oral valganciclovir (900 mg twice/d) until a negative result was reached on quantitative polymerase chain reaction.

Study End Points

The primary end point was disability defined by the EDSS score (range, 0-10 in 0.5 increments). A decrease of 1.0 or greater is considered significant improvement and an increase of 1.0 or greater is considered significant progres-

sion (eTable in the Supplement).[17-19] Other prespecified and prospectively collected end points included safety, relapse-free survival (no acute relapses), progression-free survival, disease activity–free survival (no acute relapses, no progression, and no gadolinium-enhanced or new T2 lesions on MRI scan), Neurologic Rating Scale (NRS) score,[20] Multiple Sclerosis Functional Composite (MSFC) score, Short Form 36 (SF-36) quality-of-life score, new gadolinium-enhanced lesions on MRI scan, and total T2-weighted lesion volume on brain MRI scan. The NRS scores range from 0 to 100[19]; a decrease of 10 or greater is considered significant progression and an increase of 10 or greater is considered significant improvement (eTable in the Supplement).[19-21] The MSFC measures leg function with the Timed 25-Foot Walk, arm coordination with the 9-Hole Peg Test, and cognitive function with the Paced Auditory Serial Addition Test 3, and reports an integrated score from individual *z* scores (eTable in the Supplement).[18] The SF-36 comprises 8 scales of functional health and well-being and perception of change in health on a scale of 0 to 100 with scores averaged to give a physical, mental, and total health score.

Magnetic resonance imaging was obtained on a Siemens 1.5-Tesla scanner, which was used both before and after HSCT. Postcontrast T1-weighted imaging was delayed until 5 minutes after intravenous infusion of gadolinium (single dose of 0.1 mmol/kg). Patient positioning inside the scanner was standardized according to the University of Texas, Houston, MRI Analysis Center imaging acquisition manual. The T2 lesion volume, which correlates with clinical disease severity, was determined using the semiautomated contouring technique with Image J software (National Institutes of Health; http://rsbweb.nih.gov/ij/docs/faqs.html). The same observer (X.H.) marked all lesions, and an experienced reader (S.F.) blinded to MRI chronological order randomly reviewed MRI scans for accuracy.

Outcome parameters (MRI scan results and scores on the EDSS, NRS, MSFC, and SF-36) were measured at baseline, 6 months, 1 year, and then annually for 5 years. Thyroid function tests were performed if the patient was symptomatic. Between scheduled assessments, patients and their physicians were instructed to contact the study team to arrange unscheduled visits if any new symptoms were present.

Statistical Analysis

Two-tailed paired *t* tests (Microsoft Excel 2007) were used for comparison of prespecified primary and secondary outcome measures before and after HSCT. In post hoc analyses, a repeated-measures, mixed-effects model (SAS version 9.4; SAS Institute Inc) was used to calculate the least-squares means and SDs for change in EDSS score, adjusted for disease duration (>10 years or <10 years), type of MS (secondary-progressive vs relapsing-remitting), and presence of fever during transplant. Trends across time were examined by entering time into the model.

Differences between groups were assessed with the log-rank test. If significant effects were found at the 5% level, they were fit in a multivariate Cox regression model. SAS PROC MIXED was used to build repeated-measures, mixed-effects

Table 1. Baseline Demographics and Multiple Sclerosis (MS) Disease Characteristics (N = 145)[a]

	No. (%) of Patients
Sex	
Men	60 (41.4)
Women	85 (58.6)
Race/ethnicity	
White	124 (85.5)
Black	9 (6.2)
Asian	7 (4.8)
Hispanic	5 (3.4)
Type of MS	
Relapsing-remitting	118 (81.4)
Secondary-progressive	27 (18.6)
Age group, y	
18-25	11 (7.6)
26-35	55 (37.9)
36-45	56 (38.6)
46-60	23 (15.8)
Prior use of FDA-approved immune-modulation or suppression therapy	
Corticosteroids	143 (98.6)[b]
Glatiramer acetate	87 (60.0)
Interferon beta-1a (Avenox)	71 (49.0)
Interferon beta-1b	47 (32.4)
Interferon beta-1a (Rebif)	59 (40.7)
Natalizumab	39 (26.9)
Fingolimod	12 (8.3)
Cyclophosphamide	10 (6.9)
Plasmapheresis	10 (6.9)
Angioplasty stenting for chronic cerebrospinal venous insufficiency	1 (1.0)
Other[c]	31 (21.4)
No. of different immune-modulation or suppression treatments used before HSCT	
2-3	86 (59.3)
4-5	52 (35.9)
≥6	7 (4.8)
No. of relapses during year before study	
0	31 (21.4)
1	32 (22.1)
2	57 (39.3)
>2	25 (17.2)
Baseline disability score[d]	
<4	66 (45.5)
4-6	61 (42.1)
>6	18 (12.4)
No. of gadolinium-enhanced lesions on baseline MRI scan	
0	61 (42.1)
1-2	40 (27.6)
3-4	16 (11.0)
>4	28 (19.3)

Abbreviations: FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; MRI, magnetic resonance imaging.

[a] The sample size is not 151 because 6 patients were not included in outcome analysis (see Results section). Percentages may not equal 100% due to rounding.

[b] One patient refused corticosteroids and one patient's physician did not treat relapses with corticosteroids.

[c] There were 9 patients who had received intravenous immunoglobulin; 6 had received mitoxantrone; 3 patients for each of the following medications: dimethyl fumarate, azathioprine, mycophenolate mofetil, daclizumab, methotrexate; and 1 had received cladribine.

[d] Assessed with the Expanded Disability Status Scale (score range: 0-10; a higher score indicates higher level of disability).

Table 2. Association of Hematopoietic Stem Cell Transplantation (HSCT) and Change in Expanded Disability Status Scale (EDSS) Scores

		After HSCT					
EDSS Score[a]	Before HSCT	6 mo	1 y	2 y	3 y	4 y	5 y
No. of patients	145	123	112	82	64	36	27
Median (IQR)	4.0 (3.0-5.5)	3.0 (2.0-4.0)	3.0 (2.0-4.5)	3.0 (1.5-4.0)	2.5 (1.5-5.0)	2.5 (1.9-4.5)	2.5 (1.5-4.5)
Mean (SD)	4.1 (1.5)	3.3 (1.7)	3.1 (1.7)	3.0 (1.8)	3.1 (2.0)	3.1 (1.9)	3.1 (2.0)
95% CI	3.96-4.44	2.99-3.60	2.76-3.44	2.6-3.4	2.6-3.6	2.46-3.74	2.31-3.90
P value[b]		<.001	<.001	<.001	<.001	<.001	.009
Type of change in score, No. (%) [95% CI]							
Decrease of ≥1.0 point (improvement)		54 (44) [35-53]	57 (51) [41-61]	41 (50) [39-61]	32 (50) [37-63]	23 (64) [46-79]	14 (52) [32-71]
Increase or decrease of ≤0.5 point		61 (50) [40-59]	44 (39) [30-49]	32 (39) [28-50]	25 (39) [27-52]	10 (28) [14-45]	9 (33) [17-54]
Increase of ≥1.0 point (progression)		8 (6.5) [3-12]	19 (9.8) [5-20]	9 (11.0) [5-21]	7 (11.0) [2-22]	3 (8.3) [4-34]	4 (14.8) [5-20]

Abbreviation: IQR, interquartile range.

[a] Range of scores is 0 to 10 in 0.5 increments.

[b] Comparison group is before HSCT.

models. A compete case analysis was used in all models. Post hoc power calculation indicated that within-patient differences of 1.0 and 0.33 on the EDSS could be deemed significant at the 2-sided 5% level with 100% power given the sample size of 145 patients. *P* values were obtained from type 3 analysis of variance[22] results obtained from the mixed-effects models to examine if there was a difference across time in the outcome measures.

Kaplan-Meier analysis was used to estimate relapse-free, progression-free, and disease activity-free survival. The MSFC and *z* scores were calculated in accordance with the Administrative and Scoring Manual.[23] Secondary outcomes were exploratory and not analyzed for association or interaction with disease duration, type, age, or fever during treatment, and were not adjusted for multiple comparisons.

Results

Of 151 patients who received HSCT during the study period, 123 had relapsing-remitting MS and 28 had secondary-progressive MS. A total of 55 patients were treated on the study protocol. Ninety-six patients were treated off the study protocol on a compassionate basis for any of the following reasons: (1) had secondary-progressive MS (n = 28); (2) denied insurance for being entered into the trial (n = 18); (3) had brainstem, visual, or cognitive impairment with high risk of further paraplegic, quadriplegic, visional, or cognitive impairment (n = 15); (4) had an EDSS score of greater than 6.0 (n = 15); (5) experienced treatment failure with available FDA-approved drugs (n = 12); (6) had a coexisting autoimmune or neurological disease (n = 4); (7) had an allergy to gadolinium (n = 2); (8) were older than 55 years (n = 1); or (9) had tumefactive MS (n = 1).

Of these 151 patients, 6 patients were not included in outcome analysis because 1 had nonreproducible neurological findings, 1 patient was lost to follow-up 1 year after HSCT, and 4 patients have not returned for complete assessment. The median age was 37 years (mean, 36 years; range, 18-60 years). The median duration of disease from time of diagnosis was 61 months (mean, 80 months; range, 9-264 months). Prior use of immune-modulation or suppression medications, the number of clinical relapses during the year prior to treatment, EDSS score at enrollment, and the number of gadolinium-enhanced lesions on baseline MRI scan appear in **Table 1**.

Engraftment and Toxicity

The median day of engraftment (white blood cell count >1.0 × 10^9/L) was day 10 (95% CI, 9.36-9.70) and the median day of hospital discharge was day 10 (95% CI, 10.21-10.75). The median number of platelet transfusions was 2.60 (95% CI, 2.21-2.99) and red blood cell transfusions was 2.00 (95% CI, 1.86-2.52). Twelve patients had positive rectal cultures for vancomycin-resistant enterococcus at the time of admission, and 2 patients had positive nasal cultures for methicillin-resistant *Staphylococcus aureus* at admission. Only 1 patient had a positive blood culture identified as coagulase-negative staphylococcus. Four patients had diarrhea that tested positive for *Clostridium difficile*.

Patients were followed up for a median of 2 years (mean, 2.5 years; range, 6 months-5 years) and the final follow-up date was June 2014. There were no treatment-related deaths and no early or late infectious cases of fungal, *Pneumocystis jirovecii*, cytomegalovirus, Epstein-Barr virus, or JC virus. Four patients developed late reactivation of dermatomal zoster, which was treated with oral acyclovir. Immune-mediated thrombocytopenia (ITP) developed in 3 of 22 (14%; 95% CI, 3%-35%) patients treated with alemtuzumab compared with 4 of 129 (3.1%; 95% CI, 0.9%-7.8%) patients treated with antithymocyte globulin (*P* = .07). Drug-free remission of ITP occurred in all cases after transient treatment with corticosteroids and intravenous immunoglobulin or rituximab.

Hypothyroidism was present in 9 patients (6.2%; 95% CI, 2.9%-11.4%) before receiving HSCT. After transplant, 7 additional patients developed hypothyroidism or hyperthyroidism. For patients with normal thyroid function before HSCT, thyroid dysfunction developed posttransplant in 2 of 20 treated with alemtuzumab (9%; 95% CI, 1%-32%) and 5 of 122 treated with antithymocyte globulin (4.0%; 95% CI, 1.3%-9.3%) (P = .26). The incidence rate of posttransplant immune dysfunction (ITP, hypothyroidism, or hyperthyroidism) was 22.7% (95% CI, 7.8%-45.4%) in 5 of 22 patients receiving alemtuzumab compared with 6.9% (95% CI, 3.2%-12.7%) in 9 of 129 patients receiving antithymocyte globulin (P = .03).

During hospitalization for HSCT, 1 patient was incidentally found to have a preexisting localized adrenal carcinoma. No posttransplant cancers occurred in patients treated with cyclophosphamide and antithymocyte globulin. Two patients treated with cyclophosphamide and alemtuzumab developed cancer; one had breast in situ ductal carcinoma 3 years posttransplant and the other (who had also received mitoxantrone) developed lymphoma 5 years posttransplant.

Primary End Point

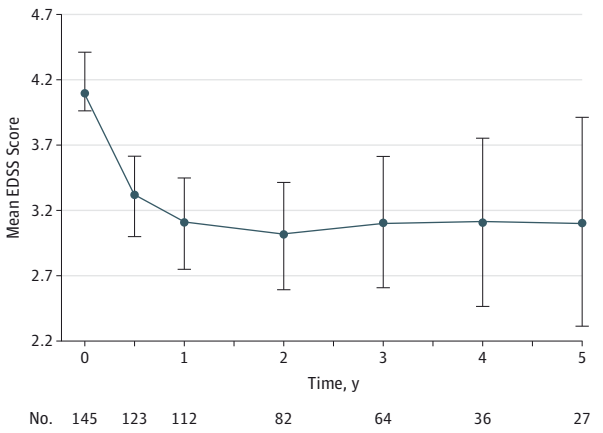
Transplant was associated with significant improvement in the EDSS score (**Table 2**). The EDSS score improved significantly for the entire group (P < .001 at all time intervals except 5 years, which was P = .009) from a pretransplant median score of 4.0 to 3.0 at 6 months, 1 year, and 2 years and to 2.5 at 3, 4, and 5 years (Table 2 and **Figure 1**). A general decrease in EDSS score over time posttransplant was observed (P < .001). The proportion of patients with a 1.0 or greater change in EDSS score was 51% (95% CI, 41%-61%) in 57 of 112 patients with an indication of improvement at 1 year and 10% (95% CI, 5%-20%) in 19 of 112 patients with an indication of progression; 50% (95% CI, 39%-61%) in 41 of 82 for improvement at 2 years and 11% (95% CI, 5%-21%) in 9 of 82 for progression; 50% (95% CI, 37%-63%) in 32 of 64 for improvement at 3 years and 11% (95% CI, 2%-22%) in 7 of 64 for progression; 64% (95% CI, 46%-79%) in 23 of 36 for improvement at 4 years and 8% (95% CI, 4%-34%) in 3 of 36 for progression; and 52% (95% CI, 32%-71%) in 14 of 27 for improvement at 5 years and 15% (95% CI, 5%-20%) in 4 of 27 for progression.

Secondary End Points

Treatment-related mortality was 0% and overall survival was 99.3%. The 1 death that occurred 30 months after HSCT was related to hypertensive cardiovascular disease. The Kaplan-Meier estimated relapse-free survival was 89% (95% CI, 81%-94%) at 2 years and 80% (95% CI, 69%-88%) at 4 years; progression-free survival was 92% (95% CI, 85%-96%) and 87% (95% CI, 78%-93%), respectively; and disease activity-free survival was 80% (95% CI, 70%-86%) and 68% (95% CI, 56%-77%) (**Figure 2**).

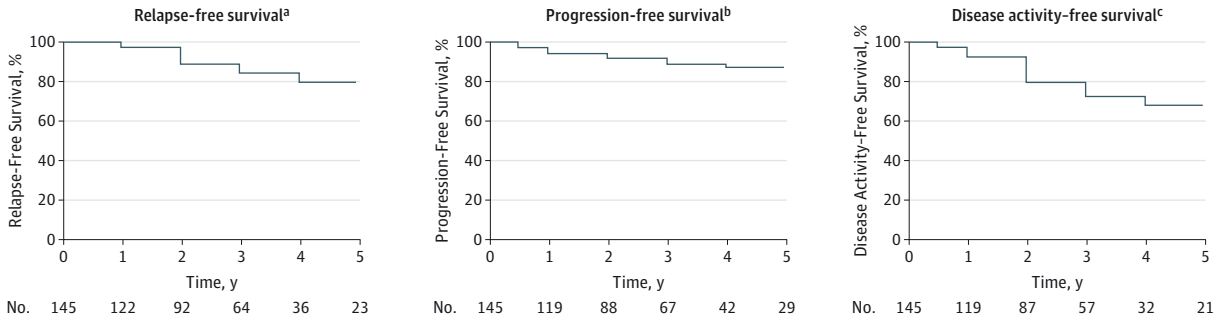
Receipt of HSCT was associated with significant improvement in the NRS and MSFC component scores (**Table 3**). The NRS impairment score improved significantly from a pretransplant median of 74 to 83 at 6 months, 85 at 1 year, 88 at 2 years, 90.5 at 3 years, 87.5 at 4 years, and 85 at 5 years. A general increase in NRS score (P < .001) over time

Figure 1. Neurological Disability Before and After Hematopoietic Stem Cell Transplantation Measured by the Expanded Disability Status Scale (EDSS)



Time zero is prior to transplant. Error bars represent 95% confidence intervals.

Figure 2. Survival Status After Hematopoietic Stem Cell Transplantation



Time zero is prior to transplant. Data are up to but not including 5 years of follow-up.

[a] No acute relapses.

[b] No increase in Expanded Disability Status Scale score.

[c] No acute relapses, no progression, no new gadolinium-enhanced or T2 lesions detected with magnetic resonance imaging.

Table 3. Neurologic Rating Scale (NRS), Multiple Sclerosis Functional Composite (MSFC), and Short Form 36 Component Scores

	Before HSCT	After HSCT					
		6 mo	1 y	2 y	3 y	4 y	5 y
NRS Score							
No. of patients	143	119	111	78	56	34	25
Median (IQR)	74 (61 to 82)	83.0 (73.5 to 92.0)	85.0 (73.5 to 93.0)	88.0 (77.3 to 93.0)	90.5 (77.5 to 95.3)	87.5 (75.0 to 93.8)	85 (72 to 93)
Mean (SD)	71 (14)	80.8 (14.1)	82.3 (13.1)	84.1 (12.7)	85.4 (12.6)	82.7 (14.4)	81.9 (13.1)
95% CI	68.99 to 73.61	78.13 to 83.27	79.72 to 84.68	82.31 to 87.08	81.89 to 88.71	77.68 to 87.72	76.49 to 87.31
P value[a]		<.001	<.001	<.001	<.001	<.001	<.001
MSFC Score[b]							
No. of patients		102	91	67	50	30	20
Median (IQR)[b]		0.19 (−0.10 to 0.56)	0.30 (−0.09 to 0.59)	0.38 (−0.01 to 0.64)	0.39 (0.22 to 0.62)	0.45 (0.04 to 0.60)	0.60 (0.36 to 0.71)
Mean (SD)		0.19 (0.43)	0.19 (0.51)	0.27 (0.44)	0.19 (0.63)	0.24 (0.55)	0.41 (0.48)
95% CI		0.11 to 0.27	0.08 to 0.30	0.16 to 0.38	0.01 to 0.37	0.03 to 0.45	0.18 to 0.63
P value[a]		<.001	.001	<.001	.04	.02	.001
Timed 25-Foot Walk							
No. of patients	138	110	106	80	61	36	24
Median (IQR), sec	6.22 (4.65 to 8.34)	5.47 (4.50 to 8.00)	5.57 (4.20 to 8.30)	5.09 (4.10 to 7.54)	4.70 (3.89 to 8.88)	5.25 (4.05 to 7.77)	4.35 (3.85 to 7.31)
Mean (SD), sec	7.66 (5.43)	6.86 (4.25)	6.93 (4.16)	6.71 (4.33)	7.89 (7.11)	6.97 (4.98)	5.60 (2.74)
95% CI	6.75 to 8.57	6.06 to 7.66	6.13 to 7.73	5.75 to 7.67	6.07 to 9.71	5.29 to 8.65	4.43 to 6.76
P value[a]		.06	.04	.02	.46	.84	.003
z Score, mean (median)[c]		−0.15 (−0.40)	−0.13 (−0.39)	−0.18 (−0.47)	0.04 (−0.54)	−0.13 (−0.44)	−0.38 (−0.61)
9-Hole Peg Test[d]							
No. of patients	138	113	102	77	57	36	25
Median (IQR), sec	24.68 (20.79 to 29.82)	23.70 (20.35 to 27.90)	22.73 (19.45 to 29.12)	23.13 (19.83 to 28.17)	22.39 (19.41 to 27.35)	23.21 (20.69 to 28.31)	23.49 (20.32 to 28.25)
Mean (SD), sec	28.87 (15.66)	26.89 (13.87)	26.95 (14.08)	26.52 (14.17)	26.92 (9.72)	26.92 (10.26)	26.09 (11.98)
95% CI	26.23 to 31.51	24.3 to 29.48	24.18 to 29.72	23.30 to 29.74	24.34 to 29.50	23.45 to 30.39	21.14 to 31.04
P value[a]		.006	.001	.002	.07	.31	.41
z Score, mean (median)[b]		0.11 (0.12)	0.13 (0.15)	0.13 (0.13)	0.13 (0.16)	0.10 (0.13)	0.12 (0.12)
PASAT-3 score							
No. of patients	132	109	98	70	54	30	22
Median (IQR)	71.69 (56.69 to 83.73)	78.00 (59.00 to 91.70)	81.50 (58.08 to 93.23)	84.15 (63.75 to 93.23)	83.00 (68.98 to 95.00)	83.15 (68.50 to 89.50)	90.00 (79.25 to 92.98)
Mean (SD)	68.96 (19.99)	74.13 (19.61)	74.97 (22.11)	78.17 (19.70)	78.51 (20.08)	77.77 (18.61)	80.90 (21.48)
95% CI	65.52 to 72.40	70.41 to 77.85	70.54 to 79.40	73.47 to 82.87	73.03 to 83.99	70.81 to 84.71	71.43 to 90.47
P value[a]		<.001	<.001	<.001	<.001	<.001	<.001
z Score, mean (median)[b]		0.26 (0.45)	0.30 (0.63)	0.46 (0.76)	0.48 (0.70)	0.44 (0.71)	0.60 (1.05)
Short Form 36							
Mental score							
No. of patients	132	99	93	72	42	25	14
Median (IQR)	49.00 (33.08 to 65.78)	70.00 (55.22 to 82.50)	68.40 (52.98 to 84.00)	70.06 (57.31 to 82.45)	69.85 (50.25 to 83.68)	76.00 (60.10 to 85.33)	60.00 (42.78-87.70)
Mean (SD)	49.00 (20.77)	65.00 (26.65)	66.00 (23.95)	65.73 (25.21)	64.61 (25.37)	72.00 (17.79)	51.00 (25.62)
95% CI	45.42 to 52.58	59.68 to 70.32	61.07 to 70.93	59.81 to 71.65	56.70 to 72.52	64.66 to 79.34	38.1-73.9
P value[a]		<.001	<.001	<.001	.03	.002	.59

(continued)

Table 3. Neurologic Rating Scale (NRS), Multiple Sclerosis Functional Composite (MSFC), and Short Form 36 Component Scores (continued)

	Before HSCT	After HSCT					
		6 mo	1 y	2 y	3 y	4 y	5 y
Physical score							
No. of patients	132	99	93	72	42	25	14
Median (IQR)	40.00 (25.30 to 49.55)	60.00 (43.10 to 75.30)	58.40 (39.00 to 76.50)	64.40 (42.35 to 79.70)	66.60 (41.95 to 83.55)	75.00 (47.40 to 85.40)	71.00 (37.75-78.60)
Mean (SD)	40.00 (17.42)	56.00 (26.89)	59.00 (25.32)	59.11 (27.37)	61.24 (24.77)	67.00 (22.55)	50.00 (26.11)
95% CI	37.00 to 43.00	50.64 to 61.36	53.78 to 64.21	52.68 to 65.54	53.52 to 68.96	57.69 to 76.31	34.08-63.93
P value[a]		<.001	<.001	<.001	<.001	.001	.04
Total score							
No. of patients	132	99	93	72	42	25	14
Median (IQR)	45.00 (32.00 to 59.65)	66.00 (50.44 to 80.59)	67.50 (48.94 to 79.91)	69.76 (52.19 to 82.07)	60.94 (47.19 to 85.42)	79.00 (53.25 to 88.69)	66.00 (36.99-82.84)
Mean (SD)	46.00 (18.50)	61.00 (26.85)	64.00 (24.32)	64.12 (26.38)	64.64 (24.06)	71.00 (19.33)	50.00 (25.13)
95% CI	42.81 to 49.19	55.64 to 66.36	58.99 to 69.01	57.92 to 70.32	57.14 to 72.14	63.02 to 78.98	36.62-65.38
P value[a]		<.001	<.001	<.001	.001	.002	.17

Abbreviations: IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; PASAT-3, Paced Auditory Serial Addition Test 3.

[a] Comparison group is before HSCT.

[b] Positive scores indicate improvement.

[c] Negative scores indicate improvement.

[d] The score is a performance average using the right and left hands.

posttransplant was observed. The median Timed 25-Foot Walk improved from 6.22 seconds pretransplant to 5.47 seconds at 6 months posttranspant, 5.57 seconds at 1 year, 5.09 seconds at 2 years, 4.70 seconds at 3 years, 5.25 seconds at 4 years, and 4.35 seconds at 5 years.

The median timed 9-Hole Peg Test average for both the right and left hands improved from 24.68 seconds pretransplant to 23.70 seconds at 6 months posttransplant, 22.73 seconds at 1 year, 23.13 seconds at 2 years, 22.39 seconds at 3 years, 23.21 seconds at 4 years, and 23.49 seconds at 5 years. The median percentage correct score for the Paced Auditory Serial Addition Test 3 improved from 71.69% pretransplant to 78% at 6 months posttransplant, 81.5% at 1 year, 84.15% at 2 years, 83% at 3 years, 83.15% at 4 years, and 90% at 5 years.

The number of gadolinium-enhanced lesions on brain MRI scan decreased significantly ($P < .001$) at all posttransplant time points. The mean number of gadolinium-enhanced lesions was 3.22 at 3 to 6 months before HSCT, 2.57 within 3 months of HSCT, 0.01 at 6 months, 0.13 at 1 year, 0.07 at 2 years, 0.24 at 3 years, 0.67 at 4 years, and 0.08 at 5 years posttransplant. Brain T2 lesion volume decreased significantly between the pretransplant MRI scan and the most recent posttransplant MRI scan (eFigure 1 in the Supplement). With a mean follow-up of 27 months available for 128 patients with complete pretransplant and posttransplant MRI scans, the median T2 lesion volume decreased by 33% from a median of 8.57 cm^3 (interquartile range [IQR], 2.78-22.08 cm^3; mean [SD], 15.69 [18.09] cm^3; 95% CI, 12.53-18.54 cm^3) to a median of 5.74 cm^3 (IQR, 1.88-14.45 cm^3; mean [SD], 10.92-12.60 cm^3; 95% CI, 8.72-13.12 cm^3) ($P < .001$).

There were 132 patients who had complete sets of SF-36 questionnaires and their pretransplantation evaluation and most recent posttransplantation evaluation were compared (median follow-up of 2 years). Physical health improved from a median score of 40 (IQR, 25.3-49.5; mean [SD], 40 [17]; 95% CI, 37-43) to 55 (IQR, 40.0-78.9; mean [SD], 58 [22]; 95% CI, 54-62) ($P < .001$). Mental health improved from a median score of 49 (IQR, 33.1-65.8; mean [SD], 49 [21]; 95% CI, 46-53) to 69 (IQR, 50.8-83.6; mean [SD], 66 [22]; 95% CI, 63-70) ($P < .001$). Total SF-36 score improved from a median of 45 (IQR, 32.0-59.7; mean [SD], 46 [18]; 95% CI, 43-49) to 64 (IQR, 48.1-81.3; mean [SD], 64 [20]; 95% CI, 61-68) ($P < .001$).

Post Hoc Analysis

Post hoc analysis showed that patients with relapsing-remitting MS (n = 118), duration of disease of 10 years or shorter (n = 113), and those without sustained fever (defined as fever present on 3 readings at least 4 hours apart during a 24-hour period) during HSCT (n = 106) had significant improvements in EDSS score (eFigure 2 in the Supplement). Scores on the EDSS did not improve significantly for patients with secondary-progressive MS (n = 27), in those with a disease duration of longer than 10 years (n = 32), or in those with sustained peritransplant fever of greater than 38.5°C (n = 31) (eFigure 2 in the Supplement). In the mixed-effects analysis, both the difference in duration of disease (>10 years vs ≤10 years) and type of disease (secondary-progressive MS vs relapsing-remitting MS) were associated with a significantly ($P = .05$) increased posttranspant EDSS score. Sex, age, baseline EDSS score, and prior number of immune drugs were not significantly associated with posttransplant EDSS scores.

Discussion

In this cohort of patients with MS undergoing HSCT, the EDSS score improved (decreased by ≥1.0 point), with 50% and 64% of patients demonstrating improvement at 2 years and 4 years,

respectively. To our knowledge, this is the first report of significant and sustained improvement in the EDSS score following any treatment for MS. The significant improvements observed following HSCT in the NRS score, MSFC scores, SF-36 quality-of-life scores, and T2 lesion volume on MRI scan are consistent with and support the reported improvement in EDSS score.

Compared with our study, the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) trial[24] (treatment-naive patients) and the Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) trial[25] (patients received prior interferon treatment) of natalizumab vs placebo reduced the risk of sustained progression of disability but did not improve EDSS scores. The 5-year interim analysis of data collected on 4821 patients in the open-label Tysabri Observational Program (TOP) also failed to showed improvement in EDSS scores.[26] In the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) I (which involved treatment-naive patients) and CARE-MS II (which involved patients previously treated with beta interferon or glatiramer acetate) trials, alemtuzumab marginally reduced the risk of sustained accumulation of disability by −0.14 and −0.17 points on the EDSS, respectively.[27,28]

Because the minimal EDSS increment for scoring an individual patient is 0.5 and no previous study, to our knowledge, has demonstrated a decrease in EDSS score by 0.5 or more (improvement), a 1.0 decrease in EDSS score (improvement) in the treated patients, as shown herein and if substantiated in other studies, may set a benchmark for MS research based on reversal of disability rather than the traditional goal of slowing the accumulation of disability.

In our study, among the 132 patients who had complete sets of SF-36 questionnaires completed prior to HSCT and at their most recent evaluation after HSCT (median follow-up of 2 years), the SF-36 scores improved significantly (by 15 points for physical health, 20 for mental health, and 19 for total health). In the AFFIRM and SENTINEL trials, the SF-36 mental and physical component scores improved in the active treatment groups by 2.0 points or less.[29] Although the quality-of-life improvements in these trials were statistically significant, it is generally accepted that a clinically significant difference in SF-36 score requires a minimal change of 5 points.[30]

In our cohort of patients with MS, there was no treatment-related mortality and no early or late infectious cases of fungal, *P jirovecii*, cytomegalovirus, Epstein-Barr virus, or JC virus. Four patients developed late reactivation of dermatomal zoster, which was treated with oral acyclovir. In our trial, posttransplant immune dysfunction (ITP, hypothyroidism, and hyperthyroidism) occurred and was significantly more common with alemtuzumab (22.7%) compared with antithymocyte globulin (6.9%). Both MS and treatment of MS with alemtuzumab are associated with ITP[31-33] and thyroid dysfunction.[34]

Myeloablative transplant regimens cause irreversible bone marrow failure, thus mandating hematopoietic stem cell reinfusion to recover. Although, depending on the regimen, they may be relatively safe as reported in the Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS) trial,[35] the toxicity and late complications can be substantial with myeloablative regimens.[12] In contrast, nonmyeloablative regimens, as used herein, are designed for transient marrow suppression. Although not necessary for recovery, stem cell infusion shortens the interval of neutropenia and attendant complications.

Patient selection is important in determining outcome. In the post hoc analysis, the EDSS score did not improve in patients with secondary-progressive MS or in those with disease duration longer than 10 years. In our study, baseline EDSS score, older age, or prior number of immune-modulation or suppression regimens were not associated with a worse outcome. However, these findings may not be generalizable because we preselected patients with active inflammation and excluded those with late secondary-progressive MS.

Fever is an unfavorable prognostic factor for neurological recovery in patients with neuronal injuries related to cardiopulmonary bypass, cardiac arrest, cerebral vascular accident, traumatic closed head injury, and subarachnoid hemorrhage.[36,37] In MS, environmental heat is associated with acute pseudo-relapses and disabling fatigue.[38,39] In the post hoc analysis in our study, sustained fever during hospitalization for HSCT was associated with higher disability several years later. Due to early implementation of corticosteroids in our standard of care to prevent fever, the number of patients with sustained peritransplant fever was small, which decreased the statistical power of fever as a factor in the mixed-effects analysis.

This study has several important limitations. First, the study was conducted at a single academic institution, which may introduce the possibility for bias. However, all patients had clinical continuity with a local treating neurologist not affiliated with the study who would also identify relapses or need for additional treatment.

Second, a large number of patients were treated on a compassionate basis, rather than on the study protocol. Nevertheless, all patients had a diagnosis of relapsing-remitting MS or secondary-progressive MS and were treated with a nonmyeloablative regimen and followed up in an identical manner. In addition, by reporting all patients (similar to registry data), our results illustrate the risks of treatment that are unique to different nonmyeloablative regimens, the importance of patient selection, and peritransplant factors that influence neurological outcome and help to define the subset of MS patients for which HSCT is potentially beneficial within the clinical heterogeneity of patients who are most likely to be referred and treated with HSCT.

Third, improvement in function in patients with MS may be in part a consequence of continuing recovery from earlier relapses. However, to our knowledge, no other therapy for relapsing-remitting MS has demonstrated significant and sustained improvement in disability and quality of life and sustained lack of new disease activity despite absence of posttransplant disease-modifying therapy.

Fourth, long-term follow-up (ie, at ≥4 years) was not available for a substantial proportion of patients.

Fifth, because this is an observational cohort without a control group, inferences about causal effects of HCST cannot be made. Definitive conclusions will require a randomized trial; however, this analysis provides the rationale, appropriate patient selection, and therapeutic approach for a randomized study.

Conclusions

Among patients with relapsing-remitting MS, nonmyeloablative HSCT was associated with improvement in neurological disability and other clinical outcomes. These preliminary findings from this uncontrolled study require confirmation in randomized trials.

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