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Position Statement

Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation

Jeffrey A. Cohen[1,*], Laura E. Baldassari[1], Harold L. Atkins[2], James D. Bowen[3], Christopher Bredeson[2], Paul A. Carpenter[4], John R. Corboy[5], Mark S. Freedman[6], Linda M. Griffith[7], Robert Lowsky[8], Navneet S. Majhail[9], Paolo A. Muraro[10], Richard A. Nash[11], Marcelo C. Pasquini[12], Stefanie Sarantopoulos[13], Bipin N. Savani[14], Jan Storek[15], Keith M. Sullivan[13], George E. Georges[4]

[1] *Mellen Center for MS Treatment and Research, Cleveland Clinic, Cleveland, Ohio*
[2] *Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[3] *Multiple Sclerosis Center, Swedish Neuroscience Institute, Seattle, Washington*
[4] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[5] *Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado*
[6] *University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[7] *Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland*
[8] *Division of Blood and Marrow Transplantation, Stanford University, Stanford, California*
[9] *Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio*
[10] *Division of Brain Sciences, Department of Medicine, Imperial College London, London, United Kingdom*
[11] *Blood and Marrow Transplant Program, Colorado Blood Cancer Institute, Denver, Colorado*
[12] *Department of Hematology and Oncology, Medical College of Wisconsin and Center for International Blood and Marrow Transplant Research, Milwaukee, Wisconsin*
[13] *Department of Medicine, Division of Hematologic Malignancies and Cellular Therapy, Duke University Medical Center, Durham, North Carolina*
[14] *Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, Tennessee*
[15] *Blood and Marrow Transplant Program, University of Calgary, Calgary, Alberta, Canada*

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A B S T R A C T

Multiple sclerosis (MS) is a chronic, disabling, immune-mediated, demyelinating and degenerative disease of the central nervous system. Approved disease-modifying therapies may be incompletely effective in some patients with highly active relapsing disease and high risk of disability. The use of immunoablative or myeloablative therapy followed by autologous hematopoietic cell transplantation (AHCT) has been investigated in retrospective studies, clinical trials, and meta-analyses/systematic reviews as an approach to address this unmet clinical need. On behalf of the American Society for Blood and Bone Marrow Transplantation (ASBMT), a panel of experts in AHCT and MS convened to review available evidence and make recommendations on MS as an indication for AHCT. A review of recent literature identified 8 retrospective studies, 8 clinical trials, and 3 meta-analyses/systematic reviews. In aggregate, these studies indicate that AHCT is an efficacious and safe treatment for active relapsing forms of MS to prevent clinical relapse, magnetic resonance imaging-detectable lesion activity, and worsening disability and to reverse disability without unexpected adverse events. Based on the available evidence, the ASBMT recommends that treatment-refractory relapsing MS with high risk of future disability be considered a "standard of care, clinical evidence available" indication for AHCT. Collaboration of neurologists with expertise in treating MS and transplantation physicians with experience performing AHCT for autoimmune disease is crucial for ensuring appropriate patient selection and optimizing transplantation procedures to improve patient outcomes. Transplantation centers in the United States and Canada are strongly encouraged to report baseline and outcomes data on patients receiving AHCT for multiple sclerosis to the Center for International Blood and Marrow Transplant Research.

INTRODUCTION

Multiple sclerosis (MS), a chronic, immune-mediated, demyelinating and degenerative disease of the central nervous system, is a major cause of neurologic disability, leading to reduced quality

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* Correspondence and reprint requests: Jeffrey A. Cohen, MD, Mellen Center for MS Treatment and Research, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44915.
E-mail address: cohenj@ccf.org (J.A. Cohen).

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of life and substantial economic costs [1]. Manifestations can include visual impairment, weakness, incoordination, sensory loss, gait dysfunction, bowel and bladder dysfunction, sexual dysfunction, fatigue, and cognitive impairment. Most patients present between age 20 and 40 yr with a relapsing-remitting (RR) course due to multifocal inflammatory lesions that cause clinical relapses and magnetic resonance imaging (MRI)-detectable lesion activity (ie, new/enlarged T2-hyperintense or T1 gadolinium-enhancing lesions) [2,3]. After 10 to 15 years, most patients with RRMS transition to a secondary progressive (SPMS) course characterized by neurodegeneration and gradual neurologic decline independent of clinical relapses, although superimposed inflammatory disease activity can still occur [2]. Approximately 10% to 15% of patients present with primary progressive MS (PPMS), characterized by gradual neurologic worsening after onset with or without superimposed relapses and MRI lesion activity [2].

Patients with MS have varying rates of disability worsening. The extent of early inflammatory disease activity has a substantial impact on both short-term and long-term prognosis [4-6]. Therefore, no evidence of disease activity (NEDA)—absence of relapses, disability worsening on the Expanded Disability Status Scale (EDSS), or MRI lesion activity [7]—has been proposed as a goal for MS disease-modifying therapy (DMT) [8]. Currently, more than a dozen DMTs have regulatory approval in the United States and worldwide for treatment of relapsing MS, with varying mechanisms of action, routes of administration, and efficacy. However, despite therapy, a high proportion of patients fail to achieve NEDA [9]. Among these patients, a subset with highly active disease refractory to approved DMTs develop severe disability with the need for ambulation assistance within 5 years of onset [10]. In addition, all MS DMTs have potential safety concerns, the risk of which is cumulative with ongoing therapy. Thus, therapeutic options for patients with relapsing MS and ongoing disease activity despite approved DMTs or who develop adverse effects from therapy represent an important unmet clinical need. Recent treatment guidelines from the American Academy of Neurology [11,12] and European Academy of Neurology/European Committee on Treatment and Research in MS [13,14] do not address the management of such treatment-refractory patients with poor prognosis.

Immunoablation or myeloablation followed by autologous hematopoietic cell transplantation (AHCT) has been studied as a treatment option for several autoimmune diseases, including MS, systemic sclerosis, and Crohn's disease [15,16]. In MS, AHCT has been investigated as treatment of various phenotypes in both retrospective studies and clinical trials. Although the overall results support the benefit of AHCT in the treatment of a subset of patients with highly active relapsing forms of MS, this procedure is not yet integrated into routine clinical practice. In addition, the recent MS treatment guidelines from the American Academy of Neurology [11,12] and European Academy of Neurology/European Committee on Treatment and Research in MS [13,14] do not comment on a role for AHCT in treatment of MS. Guidelines from the American Society for Blood and Marrow Transplantation (ASBMT) published in 2015 designate MS as a "developmental" indication for AHCT [15].

In response to newly available data concerning the efficacy and safety of AHCT in MS and to establish best practices in relapsing MS, the ASBMT Practice Guidelines Committee created a Task Force of experts in AHCT and MS to review the current evidence and provide a recommendation on treatment-refractory relapsing MS as an indication for AHCT. This position paper presents expert opinion based on contemporary evidence available for MS as an indication for AHCT and is not intended to serve as a treatment guideline.

ASBMT DEFINITIONS FOR AHCT INDICATIONS

The guiding principles and processes that ASBMT follows when considering a disease or condition as an indication for transplantation have been described previously [15,17]. In brief, ASBMT criteria for classifying AHCT indications include (1) "standard of care" where indication for AHCT is well defined and supported by evidence; (2) "standard of care, clinical evidence available" where large clinical trials and observational studies are not available but AHCT has been shown to be effective therapy; (3) "standard of care, rare indication" for rare diseases where AHCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible; (4) "developmental" for diseases where preclinical and/or early phase clinical studies show AHCT to be a promising treatment option; and (5) "not generally recommended" where available evidence does not support the routine use of AHCT.

SUMMARY OF EVIDENCE

Search Strategy

The Embase and Ovid MEDLINE databases were searched using a combination of MeSH terms and key words for the following concepts: bone marrow or hematopoietic transplantation, multiple sclerosis, and trials, observational studies, or meta-analyses. Truncation and wildcard operators were used to obtain as comprehensive a set of results as possible. Search results were limited to English language and for article published between 2008 and January 2019. Conference abstracts and reports involving fewer than 10 patients with relapsing MS who underwent AHCT (with 1 exception) were excluded. All search results were manually reviewed by 1 author (L.E.B.).

Retrospective Studies

Eight retrospective studies evaluating the efficacy of AHCT in patients with MS using registries, country-level data, or hospital consortia were identified [18-25]. In aggregate, these studies consistently supported the efficacy of AHCT in patients with relapsing forms of MS based on relapse reduction, progression-free survival, disability improvement, and reduction of MRI lesion activity. Four key studies are summarized (Table 1).

Mancardi et al [19] reported outcomes in an Italian multicenter case series including 74 patients with MS (33 RRMS, 41 SPMS, mean age of 35.7 years) who underwent AHCT using a conditioning regimen consisting of BCNU, etoposide, cytosine-arabinoside (Ara-C), and melphalan (BEAM) and antithymocyte globulin (ATG) between 1996 and 2008. Patients who had at least a 1.0-point worsening in EDSS over the previous year despite DMT were included. The median duration of follow-up was 4.0 years. EDSS progression-free survival was 71% in RRMS patients at 5 years and was generally higher in younger patients. Among patients with MRI studies available, none had gadolinium-enhancing lesions (0 of 45; 0%) at 1 year and 2 of 24 patients (8.3%) had gadolinium-enhancing lesions and at 2 years. At 5 years, 85% of all patients were relapse-free, but among RRMS patients, 30% had experienced relapse during follow-up. In addition, 31% of RRMS patients with >1 year of follow-up had 6- to 12-month confirmed EDSS improvement of at least 1 point following AHCT. Transplantation-related mortality was 2.7% (2 of 74).

Burman et al [20] reviewed the experience with AHCT for treating MS at 7 Swedish centers from 2004 to 2013. A total of 52 patients were identified, 4 of whom were not included owing to concurrent autoimmune disease or uncertain MS diagnosis. Most of the patients in this series (n = 41) underwent AHCT using a conditioning regimen consisting of BEAM and ATG; 7 patients

Table 1
Summary of Key Retrospective Studies on Immunoablative or Myeloablative Therapy Followed by AHCT for MS

Characteristic	Italian Report (2012) [19]	Swedish Report (2014) [20]	Northwestern Report (2015) [21]	Review of CIBMTR/ EBMT Registries (2017) [24]
Study design				
Protocol	Retrospective case series	Retrospective case series	Retrospective case series	Retrospective registry review
Number of centers/sites	17	7	1	25
Recruitment period	1996-2008	2004-2013	2003-2014	1995-2006
Sample size, n	74	41 had at least 1 yr follow-up; toxicities only were reported for an additional 7	151 underwent transplantation; 145 with reported outcomes†	281 evaluable patients (CIBMTR, n = 111; EBMT, n = 170)
Inclusion criteria for disease severity	MS with severe clinical course in the past yr (worsening in EDSS ≥1.0 point despite DMT)	MS previously treated with DMT	RRMS who failed at least 1 DMT, with 2 or more treated relapses or 1 treated relapse with Gd^+ lesions at a separate time†	Receipt of AHCT for MS with minimal dataset available (disease course at baseline, EDSS at baseline, information on conditioning regimen and graft manipulation, and at least 1 follow-up visit)
Primary endpoint	EDSS progression-free survival	Relapse-free survival, MRI event-free survival, EDSS progression-free survival, and disease-free survival (defined as any one of: clinical relapse, MRI event, or progression of disability on EDSS of at least .5)*	Time to EDSS improvement and time to EDSS worsening, both of at least 1.0 point	Progression-free survival (12-mo confirmed EDSS increase of 1.0 point (or .5 point for EDSS ≥5.5)
Transplantation protocol				
Mobilization regimen	Cy (1.5-4 g/m^2) + filgrastim 5-12 μg/kg/d until harvest completion	Cy (2 g/m^2) + filgrastim (5-10 μg/kg/d for 6-7 d)	Cy (2 g/m^2) + filgrastim 5-10 μg/kg/d daily; hematopoietic cells collected on day 10	Chemotherapy combined with growth factor in 263 of 281 (93.6%), growth factor alone in 18 of 281 (6.4%)
$CD34^+$ selection	No	No	No	Yes in 123 of 281 (43.8%), no in 158 of 281 (56.2%)
Conditioning regimen	BEAM and rabbit ATG (7.5-10 mg/kg)	Most (n = 41) had BEAM and ATG, but some (n = 7) had Cy (200 mg/kg) and ATG	Cy (200mg/kg) plus either alemtuzumab 20 mg or rabbit ATG 6 mg/kg	Variable: "high intensity" in 53 of 281 (18.9%), "intermediate intensity" in 179 of 281 (63.7%), "low intensity" in 49 of 281 (17.4%); ATG in 232 of /281 (82.6%)‡
Patient characteristics				
MS phenotype	33 RRMS, 41 SPMS	40 RRMS, 5 SPMS, 2 PPMS, 1 PRMS	123 RRMS, 28 SPMS	46 RRMS, 186 SPMS, 32 PPMS, 17 PRMS
Age, yr	Mean, 35.7 (range 16-53)	Mean, 31 (range, 9-52)	Median, 37 (range, 18-60)	Median, 37 (range, 16-65)
EDSS, median (range)	6.5 (3.5-9)	5.5 (1.5-8.5) for RRMS	4.0 (3.0-5.5)	6.5 (1.5-9.0)
Disease duration, yr, median (range)	11.2 (1-28)	6.25 (.33-25)	5.1 (.8-22)	6.8 (<1-34)
Results				
Duration of follow-up	Median, 4.0 yr (range, .8 mo to 10.5 yr)	Mean, 4.0 yr (range, 1-9 yr)	Mean, 2.5 yr (6 months-5 yr)	Median 6.6 years
Primary outcome	EDSS progression-free survival at 5 yr for all patients was 66%, with significantly better outcomes for those with Gd^+ lesions present at baseline vs none at baseline (87% vs 46%; $P = .013$). Among RRMS patients, EDSS progression-free survival was 71% at 5 yr	At 5 yr post-AHCT: clinical relapse-free survival 87%; MRI event-free survival, 85%; EDSS progression -free survival, 77%; disease-free survival, 68% (no clinical relapse, MRI activity, or EDSS progression)	EDSS improved from 4.0 to 3.0 at 2 yr and to 2.5 at 4 yr ($P < .001$) Significant disability improvement in 41 of 82 patients (50%) at 2 yr and in 23 of 36 (64%) at 4 yr	Yearly EDSS available for 239 of 281 patients (85.1%); overall progression-free survival rate was 46%; among patients with RRMS or PRMS (n = 63), progression-free survival rate was 82% at 3 yr and 73% at 5 yr
Secondary outcomes	Among those with at least 1 yr of follow-up, 85% were relapse-free after up to 5 yr;	At 5 yr post-AHCT: 4 patients had experienced clinical relapse, 5 had MRI activity,	Relapse-free survival 80% at 4 yr; EDSS progression-free survival 87% at 4 yr	Mean EDSS increased by .94 point during 12 mo pre-AHCT and decreased by -.32

(*continued*)

Table 1 (*Continued*)

Characteristic	Italian Report (2012) [19]	Swedish Report (2014) [20]	Northwestern Report (2015) [21]	Review of CIBMTR/ EBMT Registries (2017) [24]
	the rate of relapse was 30% for RRMS vs 10% for SPMS ($P = .03$) For patients with MRI studies available, new Gd^+ MRI lesions detected in 0 of 45 patients between 6 mo and 1 yr and in 2 of 24 patients at 2 yr. Among RRMS patients with at least 1 yr of follow-up, 31% had confirmed EDSS improvement of >1 point at 6-12 mo	and 8 had EDSS progression (out of 41 evaluable patients)	MSFC, QOL, and SNRS improved significantly T2 MRI lesion volume decreased significantly	point during 12 mo post-AHCT Factors associated with neurologic progression post-AHCT included older age, progressive vs relapsing form of MS, and >2 previous DMTs
Overall survival, %	95.9 (71 of 74 patients); 1 patient died at 56 days post-AHCT of cerebral hemorrhage unrelated to transplantation	100	99.3; 1 patient died at 2.5 yr post-AHCT due to hypertensive cardiovascular disease	93 at 5 yr
Treatment-related mortality, %	2.7 (2 of 74 patients); 1 patient died at day 24 post-AHCT due failure to engraft and sepsis; 1 patient died at 1 mo due to encephalopathy of uncertain etiology	0	0	2.8 (8 of 281)

Cy indicates cyclophosphamide; Gd^+, gadolinium-enhancing; MSFC, Multiple Sclerosis Functional Composite; QOL, Quality of life; SNRS, Scripps Neurological Rating Scale.

* For this observational study, multiple endpoints were followed simultaneously without designation of a primary endpoint, as described by Burman et al [20].

† Of 151 patients who underwent AHCT, 55 were treated on the study protocol and 96 were treated off protocol on a compassionate basis (did not meet entry criteria). Also, among those who underwent AHCT, 6 were not included in the outcome analysis for reasons described by Burt et al [21].

‡ See Muraro et al [24] for details on the conditioning regimens used.

received a conditioning regimen of cyclophosphamide and ATG. Follow-up efficacy data for at least 1 year were available for 41 patients, 34 (83%) of whom had RRMS. At 5 years post-AHCT, relapse-free survival was 87%, and disease-free survival (defined as absence of death, clinical relapse, MRI lesion activity, or EDSS progression) was 68%. Safety results were reported for 48 patients. Transplantation-related mortality was 0%.

In a retrospective case series conducted at Northwestern University, 151 patients with MS (123 RRMS, 28 SPMS) underwent AHCT using a conditioning regimen consisting of cyclophosphamide and either alemtuzumab or ATG [21]. The primary outcome was improvement or worsening of disability, based on 1.0-point decrease or increase in the EDSS, respectively. Outcome data were available for 145 patients. The median EDSS improved from 4.0 to 3.0 (interquartile range [IQR], 1.5 to 4.0) at 2 years, and to 2.5 (IQR, 1.9 to 4.5) at 4 years. There was a significant decrease in EDSS in 41 of 82 patients (50%; 95% confidence interval [CI], 39% to 61%) at 2 years and in 23 of 36 patients (64%; 95% CI, 46% to 79%) at 4 years. At 4 years, relapse-free survival was 80%, and progression-free survival was 87%. Transplantation-related mortality was 0%.

Muraro et al [24] reported an analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) and European Blood and Marrow Transplant Group registries, which included 63 patients with RRMS (n = 46) or progressive relapsing (PR) MS (n = 17); the majority of patients (n = 218) had PPMS (n = 32) or SPMS (n = 186). Patients received different conditioning regimens depending on the transplantation center, but the majority (63.7%) received BEAM. The primary outcomes were progression-free survival, defined as absence of 12-month confirmed EDSS worsening or death, and overall survival. At 5 years, progression-free survival was 46% (95% CI, 42% to 54%) overall. In the patients with RRMS or PRMS (n = 63), progression-free survival was 82% (95% CI, 71% to 93%) at 3 years and 73% (95% CI, 57% to 88%) at 5 years. In contrast, progression-free survival in patients with SPMS (n = 186) was 33% (95% CI, 24% to 42%) at 5 years. This long-term follow-up study demonstrated an overall survival at 5 years of 93% (95% CI, 89% to 96%).

Single-Arm Clinical Trials

Six single-arm, phase 1 and 2 clinical trials of AHCT to treat RRMS published in the past 10 years were identified [26-32]. Although these studies used varying regimens for mobilization and conditioning, all demonstrated high efficacy of AHCT for RRMS, with marked benefits for MS disease activity-free survival, disability worsening, and disability improvement. Five of these single-arm clinical trials are summarized in Table 2.

A single-center, phase 1/2 trial reported by Burt et al [28] included 21 patients with RRMS who underwent AHCT between 2003 and 2005. Eligible patients had either 2 steroid-treated relapses in the previous year despite treatment with IFN-β for at least 6 months or 1 clinical relapse and gadolinium-enhancing lesions on brain MRI at separate times. Cyclophosphamide and filgrastim were used for mobilization of the autologous graft, followed by cyclophosphamide and either alemtuzumab or rabbit ATG for conditioning. The primary outcomes were progression-free survival, with progression defined as an increase in EDSS of at least 1.0 point after AHCT, as well as reversal of neurologic disability at 3 years post-AHCT. Progression-free survival at 3 years was 100%, and 81% of patients (n = 17) had an EDSS improvement of at least 1.0 point. The other 4 patients had either an EDSS improvement of .5 point (n = 2) or no change (n = 2). No deaths were reported.

Table 2
Summary of Key Single-Arm Clinical Trials on Immunoablative or Myeloablative Therapy Followed by AHCT for MS

Characteristic	Northwestern Report (2009) [28]	Russian Report (2012) [27]	Canadian Report (2016) [31]	HALT-MS (2015, 2017) [29,30]	Australian Report (2018) [32]
Identifier	ClinicalTrials.gov NCT00278655	Not available	ClinicalTrials.gov NCT01099930	ClinicalTrials.gov NCT00288626	ACTRN 12613000339752
Study design					
Protocol	Phase 1/2 clinical trial, single-arm	Phase 2 clinical trial, single-arm	Phase 2 clinical trial, single-arm	Phase 2 clinical trial, single-arm	Phase 2 clinical trial, single-arm
Number of centers/sites	1	1	3	3	1
Recruitment period	2003-2005	2006-2011	2001-2009	2006-2009	2010-2016
Sample size, n	21	95	26 were enrolled; 24 were transplanted	25 were enrolled; 24 were transplanted	35
Inclusion criteria for disease severity	RRMS with 2 steroid-treated relapses in the previous 12 mo despite IFN-β for at least 6 mo, or 1 clinical relapse and Gd^+ MRI lesions separate from relapse	Clinically definite MS having EDSS 1.5-8.0; most were refractory to conventional therapy	Ongoing disease activity despite 1 yr of DMT, consisting of 2 clinical relapses in prior 1 yr, or 3 relapses in prior 2 yr, or EDSS increase of $\geq$1.0 points in prior 18 mo	RRMS with failure of DMTs during prior 18 mo (2 or more clinical relapses with EDSS increase of $\geq$1.0 points)	RRMS with at least 1 relapse or one new Gd^+ MRI lesion in the past yr despite DMT SPMS with worsening and with at least 1 Gd^+ MRI lesion in the past yr despite DMT
Primary endpoint	EDSS progression-free survival (at least 1.0) and reversal of neurologic disability at 3 yr post-AHCT	Treatment response, defined as EDSS being stable or improved by at least .5 point	MS activity-free survival (defined as absence of clinical relapse, new or Gd^+ MRI lesions, or progression of disability on EDSS)	Time to treatment failure (death or MS disease activity defined as progression of disability on EDSS of at least 1.0-point, clinical relapse, or new MRI lesions)	Event-free survival (NEDA), defined as absence of clinical relapse, new/enlarging T2 or Gd^+ brain MRI lesions, or sustained EDSS worsening
Transplantation protocol					
Mobilization regimen	Cy (2 g/m^2) + filgrastim (10 μg/kg/d)	Filgrastim (10 μg/kg/d according to EBMT guidelines)	Cy (4.5 g/m^2) + filgrastim (10 μg/kg/d for 10 d)	Filgrastim (16 μg/kg/d for 4-5 d), prednisone (1 mg/kg/d for 10 d) was started 1 d before filgrastim was given	Cy (2 g/m^2) + filgrastim (10 μg/kg/d)
$CD34^+$ selection	No	No	Yes	Yes	No
Conditioning regimen	Cy 200 mg/kg and either alemtuzumab (20 mg) or rabbit ATG (6 mg/kg)	BM (BCNU/CCNU and melphalan) (n = 60) or a "mini-BEAM-like" regimen (BCNU/CCNU, etoposide, Ara-C and melphalan) (n = 35) $\pm$ horse ATG[†]	Busulfan (PK monitoring of first dose; mean total dose 10.9 mg/kg), Cy 200 mg/kg, rabbit ATG 5 mg/kg[*]	BEAM, rabbit ATG 5 mg/kg	BEAM, horse ATG 40 mg/kg
Patient characteristics					
MS phenotype	21 RRMS	42 RRMS, 35 SPMS, 15 PPMS, 3 PRMS	12 RRMS, 12 SPMS	25 RRMS (24 transplanted)	20 RRMS, 15 SPMS
Age, yr, median (range)	33 (20-53)	Mean 34.5	34 (24-45)	38 (27-53)	37 (21-55)
EDSS, median (range)	3.1 (2.0-5.5)	3.5 (1.5-8.0)	Median NA; range 3.0 – 6.0	4.5 (3.0-5.5)	Median NA; n=6 with EDSS <4, 16 with EDSS 4-6,13 with EDSS >6
Disease duration, yr	Median, 5 (range, 1.5-10)	NA	Mean, 6.1 $\pm$ 2.5	Median, 4.9 (range, .6-12)	Median, 6.9 (range, .7-21.6)
Results					
Duration of follow-up, yr	Mean, 3.1 (range, 2-4)	Mean, 3.8 (range, .8-5.5)	Median, 6.7 (range, 3.9-12.7)	Mean, 5.2 (range, 1-6)	Median, 3 (range, 1-5.5)
Primary outcome	EDSS progression-free survival at 3 yr, 100% EDSS improvement $\geq$1 point in 17 (81%), .5 point in 2	EDSS progression -free survival 82% at 5 yr (95% CI, 71.2%-89.1%) For those with baseline EDSS 1.5-3.0 vs 3.5-8.0, EDSS progression free	MS activity-free survival 69.6% (95% CI, 46.6%-84.2%) at 3 yr	Event-free survival at 5 yr 69.2% (90% CI, 50.2%-82.1%) EDSS progression-free survival, 91.3% (95% CI, 74.7%-97.2%) Clinical relapse-free survival, 86.9%	MS activity-free (NEDA) survival, 82% (95% CI, 65%-92%) at 1 yr, 65% (95% CI, 45%-79%) at 2 yr, and 60% (95% CI, 40%-70%) at 3 yr

(*continued*)

Table 2 (*Continued*)

Characteristic	Northwestern Report (2009) [28]	Russian Report (2012) [27]	Canadian Report (2016) [31]	HALT-MS (2015, 2017) [29,30]	Australian Report (2018) [32]
	(9.5%), no change in 2 (9.5%) at 2-3 yr	survival at 5 yr was 92% vs 73%, respectively (P= .01)		(95% CI, 69.5%-94.7%) MRI activity-free survival 86.3% (95% CI, 68.1%-94.5%)	In RRMS only, MS activity-free (NEDA) survival, 90% at 1 yr and 70% at 2 and 3 yr
Secondary outcomes	Improvement in SNRS, PASAT, T25FW, and SF-36	At 6 mo, 98.9% (89 of 90) had stable (58%) or improved (41%) EDSS For patients with RRMS at baseline, 97.5% (39 of 40) were clinical relapse-free long-term (mean, 3.8 yr)	35% with sustained EDSS improvement at 3 yr; no clinical relapse in 23 surviving patients, no new Gd^+ or T2-weighted MRI lesions post-AHCT	Median EDSS improvement of -.5 (IQR, -1.5 to 0; P = .001)	Sustained EDSS improvement in 13 patients (37%); of these, 12 had RRMS For RRMS patients, EDSS improvement was sustained out to 3 yr (mean decrease. -1.3 at 1 yr (p=0.008); -1.5 at 3 yr (p=0.0088) Significant reductions in Gd+ and T2 MRI lesion volumes between 6 months post-AHCT and last follow-up MRI
Overall survival, %	100	100	95	87.5%; 3 subjects died ≥ 2.5 yr post-AHCT, 2 due to MS disease progression, 1 with MS progression and further information not available	100
Treatment-related mortality, %	0	0	4.2%; 1 subject at 2 months post-AHCT due to hepatic sinusoidal obstruction syndrome and sepsis	0	0

PASAT indicates Paced Auditory Serial Addition Test; PK, pharmacokinetic; SF-36: Short Form-36 questionnaire; T25FW: timed 25-foot walk.

* The dose and route of administration of busulfan was changed during the duration of this study to minimize regimen-related toxic effects; see the appendix published online with Atkins et al [31] for details.

† See Shevchenko et al [27] for doses of drugs used in these preparative regimens.

A phase 2 study of AHCT in MS performed by Shevchenko et al [27] involved 95 patients with MS (42 with RRMS) who had EDSS 1.5 to 8.0, most of whom were refractory to previous DMT. Patients underwent AHCT with mobilization of the graft using filgrastim, and conditioning with a modified BEAM regimen plus horse ATG. The primary outcome was treatment response, defined as stable or improved EDSS (by at least .5 point) confirmed at 3 months. Outcomes were reported for 6 and 12 months and for longer follow-up at a mean of 3.8 years. Treatment response was 98.9% at month 6, 96% at month 12, and 80% at long-term follow-up. Thirty-nine of 40 patients (97.5%) with RRMS included in the clinical efficacy analysis were relapse-free at long-term follow-up. Interpretation of this study is complicated somewhat by restriction of the long-term follow-up analysis to patients who had not progressed or relapsed by month 36 and a substantial number of patients who discontinued the study between months 12 and 36. No deaths were reported.

The Canadian phase 2 trial included 26 patients (24 of whom underwent transplantation, including 12 with RRMS and 12 with SPMS) who had ongoing disease activity in the preceding year despite DMT [31]. Mobilization was accomplished with cyclophosphamide and filgrastim, and the graft was $CD34^+$-selected. The conditioning regimen contained busulfan, cyclophosphamide, and ATG. The primary outcome was MS activity-free survival, defined as absence of death, clinical relapse, confirmed worsening of EDSS, or new or gadolinium-enhancing brain MRI lesion. At 3 years, MS activity-free survival was 69.6% (95% CI, 46.6% to 84.2%). There were no relapses or gadolinium-enhancing lesions on sequential brain MRIs following AHCT, with plateau of the MS activity-free curve beyond 2 years with a median follow-up of 6 years. Despite an initial increase in the rate of brain atrophy at 6 months post-AHCT, there was slowing and stabilization at -0.32 ± 0.67% brain volume change per year after 24 months post-transplantation. Transplantation-related mortality was 4.2% (1 of 24 patients).

The HALT-MS phase 2 study included 25 patients with RRMS (24 of whom underwent transplantation), EDSS of 3.0 to 5.5, disease duration <15 years, and failure of DMT with ≥2 relapses in the preceding 18 months with a corresponding increase in EDSS of at least 1.0 point [29,30]. The transplantation protocol involved mobilization with filgrastim and prednisone, $CD34^+$ graft selection, and conditioning with BEAM and rabbit ATG. The primary outcome was event-free survival, defined as survival without MS relapse, worsening EDSS, or new MRI lesions (ie, equivalent to death or NEDA). At 5 years, overall event-free survival was 69.2% (90% CI, 50.2% to 82.1%). Progression-free survival was 91.3% (90% CI, 74.7% to 97.2%), clinical relapse-free survival was 86.9% (90% CI, 69.5% to 94.7%), and MRI activity-free survival was 86.3% (90% CI, 68.1% to 94.5%). Median EDSS improved by -.5 point (IQR, -1.0 to 0; P = .001). Transplantation-related mortality was 0%.

A single-center, phase 2 study conducted in Australia evaluated the efficacy of AHCT in 35 patients with either active RRMS (n = 20) or SPMS (n = 15) [32]. Patients underwent AHCT using cyclophosphamide and filgrastim for graft mobilization and then BEAM and ATG for conditioning. The primary outcome was MS disease activity-free survival (NEDA), defined as the absence of relapse, new/enlarging T2 lesions and/or new gadolinium-enhancing lesions on MRI after 6 months post-AHCT MRI, or confirmed EDSS worsening. Overall, NEDA was achieved by 82% of patients (95% CI, 65% to 92%) at 1 year, by 65% (95% CI, 45% to 79%) at 2 years, and by 60% (95% CI, 40% to 70%) at 3 years. In RRMS patients (n = 20), NEDA was achieved by 90% (95% CI, 66% to 97%) at 1 year and by 70% (95% CI, 41%

to 87%) at 2 and 3 years. Secondary outcome analysis demonstrated significant benefit, with EDSS improvement in 13 patients (37%), including 12 with RRMS. In the RRMS group alone, the mean decrease in EDSS was 1.3 at 1 year (P = .008) and 1.5 at 3 years (P = .0088). Significant benefit was also observed in reduction of gadolinium-enhancing lesion number and T2 lesion volume between 6 months post-AHCT and last follow-up MRIs. Transplantation-related mortality was 0%.

Randomized Controlled Trials

Two randomized controlled trials were identified (Table 3) [33,34]. ASTIMS was a phase 2 study comparing AHCT to mitoxantrone in 21 patients with MS (including 7 with RRMS), 9 of whom received AHCT and 12 of whom received mitoxantrone [33]. The number of new T2 lesions on brain MRI at 4 years was significantly lower in the AHCT group (rate ratio, .21; 95% CI, .1 to .48; P = .00016). No patients who received AHCT had any gadolinium-enhancing brain MRI lesions over 4 years, compared with 56% of patients on mitoxantrone. The annualized relapse rate was lower in the AHCT group compared with the mitoxantrone group (.19 versus .6; rate ratio, .36; 95% CI, .15 to .88; P = .026). No deaths were reported.

The randomized controlled phase 3 MIST trial compared the efficacy of AHCT using a nonmyeloablative conditioning regimen (cyclophosphamide 200 mg/kg over 4 days followed by rabbit ATG) and treatment with DMTs [34].The study population included 110 patients (randomized 1:1) with RRMS who had ≥2 relapses or 1 relapse plus gadolinium-enhancing lesions at different times in the preceding year despite treatment with DMT. Among patients in the control arm, 21 of 55 (38.2%) were treated with natalizumab, and the remainder (62%) were treated with various approved or off-label DMTs. None was treated with ocrelizumab or alemtuzumab. Crossover was allowed if there was an EDSS increase of 1.0 point at 1 year after treatment initiation. The primary outcome was 6-month confirmed disability worsening on EDSS of ≥1.0 point, which occurred in 5.7% (3 of 52) AHCT patients and 66.7% (34 of 51) DMT patients. The median time to the confirmed disability worsening was 24 months with DMT and was not calculated in AHCT owing to the small number of events (hazard ratio, .07; 95% CI, .02 to .24; $P < .0001$). In the AHCT group, 2.0% had relapse at 1 year and 15.4% at 5 years, compared with 69.2% and 85.2% in the DMT group, respectively ($P < .001$ at 1 year). Mean EDSS improved at 1 year from 3.38 ± 1.2 to 2.36 ± 1.4 in the AHCT patients but worsened from 3.31 ± 1.0 to 3.98 ± 1.7 in the DMT patients ($P < .001$). At 1 year, mean T2 lesion volume on MRI was decreased in the AHCT group but increased in the DMT group ($P < .001$). There were no deaths or grade 4 toxicities related to transplantation.

Adverse Events in Clinical Trials

Adverse events across the prospective clinical trials in AHCT for patients with MS were largely consistent with those expected from transplantation. Overall, treatment-related mortality was rare in the studies summarized above. One patient died at 62 days post-AHCT in the Canadian trial, which used a busulfan-containing regimen, due to hepatic necrosis following sinusoidal obstruction syndrome and *Klebsiella* sepsis [31]. No subsequent deaths or episodes of liver veno-occlusive disease occurred once oral busulfan was replaced with parenteral busulfan, affording better control of dosing. Otherwise, the reported deaths were related to MS disease worsening or comorbidities [29,30].

Meta-Analysis and Systemic Reviews

A meta-analysis by Sormani et al [35] evaluated the efficacy and safety of AHCT in both relapsing and progressive forms of MS in studies conducted between 1995 and 2016, comprising 764 patients in 15 studies (10 observational and 5 phase 1/2 clinical trials). The analysis indicated a pooled transplantation-related mortality estimate of 2.1% (95% CI, 1.3% to 3.4%). The rate of EDSS progression was 17.1% (95% CI, 9.7% to 24.5%) at 2 years and 23.3% (95% CI, 16.3% to 31.8%) at 5 years. The proportion of patients with NEDA was 83.0% (range, 70% to 92%) at 2 years and 67% (range, 59% to 70%) at 5 years. Studies with >44% of patients with RRMS reported lower 2-year progression rates compared with studies with <44% of patients with RRMS (7.8% versus 24.8%; P = .004). Transplantation-related mortality also decreased over time, from 3.6% (95% CI, 2.2% to 6.0%) in patients undergoing AHCT before 2005 to .3% (95% CI, 0 to 2.0%) in patients undergoing AHCT after 2005 (P = .014). In addition, transplantation-related mortality was higher in patients with more severe disability (ie, higher EDSS) at baseline (P = .001).

Another study by Sormani et al [36] evaluated rates of NEDA in patients with MS in studies of AHCT (n = 66) compared with DMTs (n = 216). AHCT resulted in NEDA rates of 78% to 83% at 2 years and 60% to 68% at 5 years. In contrast, studies of conventional MS DMTs, including those considered to be high efficacy, reported NEDA rates of 13% to 46% at 2 years.

Similarly, an analysis of the European Blood and Marrow Transplant (EBMT) registry comparing the efficacy of AHCT versus conventional DMTs by Muraro et al [37] demonstrated a higher rate of NEDA with AHCT compared with the rates reported in clinical trials of DMTs. Importantly, this analysis of the EBMT registry also demonstrated that treatment-related mortality has declined over time [37]. Among all patients who underwent AHCT for MS, overall treatment-related mortality was 2.0% during 1995 to 2016 (n = 829) but only .2% from 2012 to 2016 (n = 439). This decrease in treatment-related mortality is thought to reflect improved patient selection, refinement of transplantation protocols, and increased experience with AHCT in autoimmune disorders.

In summary, the retrospective studies and clinical trials of AHCT summarized above differed in design, study population, and transplantation protocol, and only 2 studies included a control group. Typically, the AHCT studies enrolled patients with more active or severe disease compared with the studies of conventional DMTs. Despite these limitations, it is apparent that after AHCT, many patients with MS experienced rapid, complete, and durable control of inflammatory disease activity, with resultant improvement in long-term clinical outcomes. Where data for similar MS populations are available, outcomes with AHCT appear to be superior compared with reports for conventional DMTs.

POSITION STATEMENT

The ASBMT Task Force recommends revising the recommended indication for AHCT in MS to “standard of care, clinical evidence available”, for patients with relapsing forms of MS (RRMS or progressive MS with superimposed activity) who have prognostic factors that indicate a high risk of future disability, including ongoing clinical relapse or MRI lesion activity despite treatment with available DMTs, especially if disease activity continues despite treatment with high-efficacy DMTs and/or worsening disability. This revision of our previous “developmental” guideline [15] is based on the evidence from retrospective studies, clinical trials, and meta-analyses/systematic reviews summarized above.

Table 3
Summary of Key Randomized Controlled Clinical Trials of Immunoablative or Myeloablative Therapy Followed by Autologous Hematopoietic Cell Transplantation for MS

	ASTIMS (2015) [33]	MIST (2018) [34]
Identifier	EUDRACT 2007-000064-24	ClinicalTrials.gov NCT00273364
Study design		
Protocol	Phase 2 clinical trial, AHCT vs mitoxantrone	Phase 3 clinical trial, AHCT vs conventional DMT
Number of centers/ Sites	7	4
Recruitment period	2004-2009	2005-2016
Sample size, n	21 (9 to AHCT)	110 (55 to AHCT, 52 in primary analysis)
Inclusion criteria for disease severity	Despite DMT during previous yr, .5-1 point worsening of EDSS, and 1 or more Gd^+ MRI lesions	Despite DMT during previous yr, at least 2 clinical relapses, or 1 relapse with Gd^+ MRI lesions at a different time during the yr
Primary endpoint	Cumulative number of new T2 lesions on brain MRI during 4 yr post-randomization	6-month confirmed EDSS worsening $\geq$1.0 point, after at least 1 yr of treatment or post-AHCT
Transplantation protocol		
Mobilization regimen	Cy (4 g/m^2) + filgrastim (5 μg/kg/d)	Cy (2 g/m^2) + filgrastim (5-10 μg/kg/d)
$CD34^+$ selection	No	No
Conditioning regimen	BEAM, rabbit ATG 7.5 mg/kg	Cy 200 mg/kg, rabbit ATG 6 mg/kg
Patient characteristics		
MS phenotype	7 RRMS, 13 SPMS, 1 PPMS with relapses	RRMS
Age, yr, median (range)	35.5 (19-46)	34 (18-54) for AHCT group
EDSS, median (range)	6 (5.5-6.5)	3.0 (1.5-6.5) for AHCT group
Disease duration, yr, median (range)	10.2 (2-23)	4.7 (0.8-14) for AHCT group
Results		
Follow-up duration	4 yr	Up to 5 yr
Primary outcome	Over 4 yr, median number of new T2-weighted MRI lesions was 2.5 in AHCT vs 8 in mitoxantrone (rate ratio, 0.21; 95% CI, .1-.48; $P = .00016$)	Disability worsening occurred in 5.8% (3/52) AHCT vs 66.7% (34/51) DMT; median time to progression, 24 mo in DMT, not calculated in AHCT due to small number of events (hazard ratio, .07; 95% CI, .02-.24; $P < .001$)
Secondary outcomes	Over 4 yr: None of those who received AHCT had Gd^+ MRI lesions; 56% of those on mitoxantrone had at least 1 Gd^+ MRI lesion ($P = .029$) ARR was 0.19 in AHCT vs. 0.6 in mitoxantrone, (rate ratio 0.36, 95% CI 0.15-0.88; $P = .026$) EDSS progression was 57% in AHCT vs 48% in mitoxantrone (log-rank test, $P = .50$)	At 1 yr, relapse occurred in 2.0% (1/51) AHCT and 69.2% (36/52) DMT ($P < .001$); At 5 yr, relapse occurred in 15.4% AHCT and 85.2% DMT At 1 yr, mean EDSS improved from 3.38 $\pm$ 1.2 to 2.36 $\pm$ 1.4 with AHCT and worsened from 3.31 $\pm$ 1.0 to 3.98 $\pm$ 1.7 with DMT ($P < .001$) At 1 yr, mean T2 lesion volume on MRI decreased in the AHCT group, but increased in the DMT group ($P < .001$)
Overall survival, %	100	100
Treatment-related mortality, %	0	0

ARR indicates annualized relapse rate.

PATIENT SELECTION AND TRANSPLANTATION REGIMEN

Collaboration of neurologists with expertise in treating MS and transplantation physicians with experience performing AHCT for autoimmune disease is crucial for appropriate patient selection and optimizing transplant procedures to improve patient outcomes [37-40]. Patients most likely to benefit from AHCT include those of relatively younger age with relatively short disease duration, a relapsing form of MS (RRMS or progressive MS with superimposed activity), accumulating disability but still ambulatory, and ongoing disease activity despite DMT [37-40]. Patients with progressive MS without recent inflammatory disease activity (ie, clinical relapse or MRI lesion activity within the previous 1 to 2 years) are less likely to benefit. Some patients with other demographic or disease characteristics (eg, patients with early MS who have failed only a limited number of DMTs but are considered at high risk for future disability or some patients with progressive disease without recent activity) may benefit from AHCT, but there is less supportive evidence for AHCT in those populations.

This position paper does not provide recommendations on preferred methods for mobilization and stem cell collection, graft manipulation (eg, $CD34^+$ selection), cell dose, conditioning regimen, or post-transplantation supportive care. The studies discussed above vary in terms of intensity of conditioning regimens and other procedural aspects. Nevertheless, all of the regimens summarized above demonstrated potent efficacy, and all are reasonable options. Clinicians considering AHCT are advised to refer to eligibility criteria and treatment regimens detailed in the studies summarized above and to published guidelines [37-40]. The intensity of the conditioning regimen that represents the optimal trade-off in level and durability of efficacy versus safety and tolerability in MS remains uncertain. The relationships between both efficacy and safety with patient characteristics, including age, level of disability, and presence of comorbid conditions, are complex. Formal clinical trials to optimize patient selection and transplantation protocols and to develop novel regimens are encouraged to improve outcomes.

DATA REPORTING TO CIBMTR

As AHCT becomes available to patients with treatment-refractory relapsing MS, collection and analysis of baseline and outcomes data will be critical to developing better approaches to transplantation and planning future research. Thus, transplantation centers in the United States and Canada and international centers affiliated with the CIBMTR are strongly encouraged to report data on patients who undergo AHCT for MS. Although data collection is a core practice in the transplantation field, areas such as AHCT for autoimmune diseases present additional challenges, given that disease-specific information is often not available to transplantation centers and there is often a lack of expertise in reporting such information. Again, collaboration between neurologists and transplantation physicians is key to allow the collection of the standardized and comprehensive data necessary to advance the knowledge base about AHCT for MS.

CONCLUSION

In summary, the ASBMT endorses AHCT as a “standard of care, clinical evidence available” for treatment-refractory relapsing MS. This document is not a treatment guideline, but is intended to provide guidance to physicians, patients, payers, policy makers, and other stakeholders on coverage decisions and the appropriate use of this procedure for MS.

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REFERENCES

1. Kobelt G, Thompson A, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler*. 2017;23:1123–1136.
2. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278–286.
3. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006;129(Pt 3):606–616.
4. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain*. 2003;126(Pt 4):770–782.
5. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology*. 2009;73:1616–1623.
6. Novotna M, Paz Soldán MM, Abou Zeid N, et al. Poor early relapse recovery affects onset of progressive disease course in multiple sclerosis. *Neurology*. 2015;85:722–729.
7. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol*. 2009;8:254–260.
8. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Mult Scler Relat Disord*. 2015;4:329–333.
9. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol*. 2015;72:152–158.

10. Gholipour T, Healy B, Baruch NF, Weiner HL, Chitnis T. Demographic and clinical characteristics of malignant multiple sclerosis. *Neurology*. 2011; 76:1996–2001.
11. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777–788.
12. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:789–800.
13. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler*. 2018;24:96–120.
14. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur J Neurol*. 2018;25:215–237.
15. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1863–1869.
16. Sullivan KM, Majhail NS, Bredeson C, et al. Systemic sclerosis as an indication for autologous hematopoietic cell transplantation: Position statement from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2018;24:1961–1964.
17. Majhail NS, Giralt S, Bonagura A, et al. Guidelines for defining and implementing standard episode of care for hematopoietic stem cell transplantation within the context of clinical trials. *Biol Blood Marrow Transplant*. 2015;21:583–588.
18. Krasulová E, Trneny M, Kozák T, et al. High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a single centre 10-year experience. *Mult Scler*. 2010; 16:685–693.
19. Mancardi GL, Sormani MP, Di Gioia M, et al. Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: the Italian multi-centre experience. *Mult Scler*. 2012;18:835–842.
20. Burman J, Iacobaeus E, Svenningsson A, et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. *J Neurol Neurosurg Psychiatry*. 2014;85:1116–1121.
21. Burt RK, Balabanov R, Han X, et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurologic disability in patients with relapsing-remitting multiple sclerosis. *JAMA*. 2015;313:275–284.
22. Shevchenko JL, Kuznetsov AN, Ionova TI, et al. Long-term outcomes of autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multple sclerosis: physician's and patient's perspectives. *Ann Hematol*. 2015;94:1149–1157.
23. Casanova B, Jarque I, Gascón F, et al. Autologous hematopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: comparison with secondary progressive multiple sclerosis. *Neurol Sci*. 2017; 38:1213–1221.
24. Muraro PA, Pasquini M, Atkins HL, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. *JAMA Neurol*. 2017;74:459–469.
25. Ruiz-Argüelles G, León-Peña AA, León-González M, et al. A feasibility study of the full outpatient conduction of hematopoietic transplants in persons with multiple sclerosis employing autologous non-cryopreserved peripheral blood stem cells. *Acta Haematol*. 2017;137:214–219.
26. Shevchenko YL, Novik AA, Kuznetsov AN, et al. High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation as a treatment option in multiple sclerosis. *Exp Hematol*. 2008;36:922–928.
27. Shevchenko JL, Kuznetsov AN, Ionova TI, et al. Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis. *Exp Hematol*. 2012;40:892–898.
28. Burt RK, Loh Y, Cohen B, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. *Lancet Neurol*. 2009;8:244–253.
29. Nash RA, Hutton GJ, Racke MK, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report. *JAMA Neurol*. 2015;72:159–169.
30. Nash RA, Hutton GJ, Racke MK, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology*. 2017;88:842–852.
31. Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haematopoietic stem-cell transplantation for agressive multiple sclerosis: a multicentre single-group phase 2 trial. *Lancet*. 2016;388:576–585.
32. Moore JJ, Massey JC, Ford CD, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2019. https://doi.org/10.1136/jnnp-2018-319446. Accessed February 12, 2019.
33. Mancardi GL, Sormani MP, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. *Neurology*. 2015;84:981–988.
34. Burt RK, Balabanov R, Burman J, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. *JAMA*. 2019;321:165–174.
35. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a meta-analysis. *Neurology*. 2017;88:2115–2122.
36. Sormani MP, Muraro PA, Saccardi R, Mancardi G. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. *Mult Scler*. 2017;23:201–204.
37. Muraro PA, Martin R, Mancardi GL, Nicholas R, Sormani MP, Saccardi R. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. *Nat Rev Neurol*. 2017;13:391–405.
38. Saccardi R, Freedman MS, Sormani MP, et al. A prospective, randomized, controlled, trial of autologous haematopoietic stem cell transplanatation for aggressive multiple sclerosis: a position paper. *Mult Scler*. 2012;18:825–834.
39. Scolding NJ, Pasquini M, Reingold SC, et al. Cell-based therapeutic strategies for multiple sclerosis. *Brain*. 2017;140:2776–2796.
40. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv*. 2017;1:2742–2755.