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Autologous Hematopoietic Stem Cell Transplant in Multiple Sclerosis
Recommendations of the National Multiple Sclerosis Society

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IMPORTANCE Autologous hematopoietic stem cell transplant (AHSCT) for multiple sclerosis has gained increasing interest in recent years. Despite the availability of many US Food and Drug Administration–approved disease-modifying therapies, some patients do not respond adequately and others may have very early aggressive disease that prompts consideration of alternative, highly effective, long-lasting therapy. The National Medical Advisory Committee of the National Multiple Sclerosis Society has reviewed recent literature on AHSCT for the purpose of making recommendations about its use based on current knowledge, as well as pointing out areas of controversy and issues requiring further research.

OBSERVATIONS Studies on AHSCT have repeatedly demonstrated high efficacy and a durable outcome in people with relapsing multiple sclerosis. Recent studies have shown considerable improvement in the safety of the procedure, with much lower mortality rates than were reported earlier. Consensus is emerging about the characteristics of the best candidates for the procedure. Questions remain about the ideal protocol, particularly about the best conditioning regimen to be used to kill immune cells. Larger randomized clinical trials are needed to address the question of whether AHSCT has advantages over the most efficacious disease-modifying agents currently available. One such trial (Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Multiple Sclerosis [BEAT-MS) is currently in progress.

CONCLUSIONS AND RELEVANCE The National Multiple Sclerosis Society believes that AHSCT may be a useful treatment option for people with relapsing multiple sclerosis who demonstrate substantial breakthrough disease activity (ie, new inflammatory central nervous system lesions and/or clinical relapses) despite treatment with high-efficacy disease-modifying therapy or have contraindications to high-efficacy disease-modifying therapies. The best candidates are likely people younger than 50 years with shorter durations of disease (<10 years). The procedure should only be performed at centers with substantial experience and expertise. Ideally, recipients of the procedure should be entered into a single database, and further research is needed to establish ideal cell mobilization and immune-conditioning regimens.

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Multiple sclerosis (MS) is an immune-mediated inflammatory and neurodegenerative disease of the central nervous system, usually characterized by relapses and remissions of neurological symptoms and variable accumulation of disability over time. Approximately 10% of patients have a gradually progressive course from onset. Despite numerous effective US Food and Drug Administration–approved disease-modifying therapies (DMTs) with differing mechanisms of action, routes of administration, and clinical trial results, some individuals continue to experience disease activity evidenced by new magnetic resonance imaging (MRI) activity, relapses, and/or progression of disability. For those with early and highly active MS, the risk of disability accumulation is high, and for many in this group, the current DMTs may provide suboptimal effectiveness. In addition, the risks and contraindications of several DMTs may preclude their use in certain individuals. For these individuals, other MS disease-modification strategies are needed.

Cell-based therapies, an active area of MS research, may be able to effectively address unmet treatment needs in MS. Various therapeutic approaches are under study, including autologous hematopoietic stem cell transplant (AHSCT), mesenchymal stem cells, induced pluripotent stem cells, and oligodendrocyte progenitor cells. Of these various therapies, a growing body of evidence supports potential use of AHSCT in MS. In AHSCT, following mobilization, stem cells are extracted from an individual. A conditioning regimen follows to deplete immune cells, including those believed to be autoreactive in MS. Extracted cells are then infused to reconstitute a less reactive immune system. Some debate continues about the relative role of the immu-

noablative conditioning regimen itself vs that of the reconstituted immune system. However, researchers have demonstrated, for example, that after the transplant, there is a reduction of autoreactive effector T cells, particularly TH17 cells. In addition, pretransplant, the peripheral blood shows the presence of mucosal-associated invariant T cells, which are proinflammatory. After the transplant, there is a significant reduction in this T-cell population, as well as increases in regulatory $CD4^+$, $CD25^{high}$, $CD127^-$, and Fox $P3^+$ cells.[1-4]

In 2015, an international consensus conference was held to discuss the state of various cell-based therapy research and make recommendations on further research needed to establish safety and potential efficacy. Based on the evidence for the use of AHSCT in MS, the consensus group recommended that AHSCT may be beneficial for individuals with MS with the following characteristics: younger age (<50 years), shorter disease duration (<5 years), active MS (based on MRI activity, relapses, and/or progression), ambulatory status, and demonstration of ongoing disease activity despite the use of approved DMTs.[5] The consensus group also recommended that additional research is needed, particularly comparative studies of high-efficacy DMTs and AHSCT that would demonstrate effectiveness and comparative safety.

More recently, the American Society for Blood and Marrow Transplantation (ASBMT) published a position statement on the use of AHSCT in MS. Based on an extensive review of the current AHSCT research, the ASBMT recommended AHSCT for a specific subset of the MS population. Similar to those of the 2015 international consensus group, the recommendations include individuals with active relapsing MS, those at high risk for future disability, and those with MS refractory to DMTs, particularly high-efficacy DMTs. The ASBMT, using nomenclature specific to that organization, recommended that AHSCT in MS be considered a "standard of care, clinical evidence available."[6(p845)]

The purpose of this communication is to assess the current status of AHSCT as a disease-modifying treatment for MS. We will then make recommendations about its use.

Appropriate Candidates for AHSCT

When considering any therapeutic intervention, physicians and patients must weigh the prospective benefits vs the potential risks. For AHSCT, the risk lies in the possible consequences of immunoablation, most notably serious and sometimes unusual infections. The prospective benefit, on the other hand, is long-lasting freedom from MS disease activity.

Numerous studies, as summarized in the recent position statement by the ASBMT, have demonstrated a high degree of efficacy and durability of outcome in patients with active relapsing forms of MS. Studies have included retrospective analyses, single-arm clinical trials, and 2 small randomized clinical trials, as well as an extensive meta-analysis and another extensive analysis of the European Blood and Marrow Transplant Registry. In particular, the meta-analysis by Sormani et al[7] described rates of no evidence of disease activity of 78% to 83% at 2 years and 60% to 68% at 5 years, substantially exceeding those seen with DMTs, which ranged from 13% to 46% at 2 years.

On the risk side of the equation, AHSCT for MS has clearly become safer in recent years, likely because of selection of candidates more well suited to the procedure and changes in immunoablation regimens. Data from the European Blood and Marrow Transplant Registry indicated an overall mortality rate of 2.0% for procedures performed between 1995 and 2016 (829 transplants), but only a 0.2% rate for those done between 2012 and 2016 (439 transplants).[8,9] Furthermore, in contrast with serious adverse events in patients treated with DMTs, which are more likely to occur over time, most of the serious adverse events with AHSCT are likely to occur early, during the period of immunoablation. Some of that reduction in the risk of serious complications likely results from selection of more appropriate patients for transplant, but randomized clinical trials will be necessary to establish both the relative safety and efficacy of AHSCT compared with DMTs.

Most authors have concluded that the likelihood of benefit from AHSCT is much smaller for patients with progressive MS without recent disease activity. In addition, patients who are older and have greater disability have greater risk for serious complications or death associated with the procedure.[10,11] In its position statement, the ASBMT stated, "Patients most likely to benefit from AHCT [autologous hematopoietic cell transplantation] include those of relatively younger age with relatively short disease duration, a relapsing form of MS (RRMS [relapsing-remitting MS] or progressive MS with superimposed activity), accumulating disability but still ambulatory, and ongoing disease activity despite DMT."[6(p853)] A report from the International Conference on Cell-Based Therapies for Multiple Sclerosis sponsored by the International Advisory Committee on Clinical Trials (a joint committee of the US National Multiple Sclerosis Society and the European Committee for Treatment and Research in Multiple Sclerosis) similarly noted that "Patients most likely to benefit from I/AHSCT [immunoablation followed by autologous hematopoietic stem cell transplant] are relatively young e.g. 50 years of age or less, with relatively short disease duration e.g. 5 years or less, have active relapsing-remitting multiple sclerosis and accumulating disability but still are ambulatory, and have ongoing disease activity despite DMT."[5(p2781)] The workshop report further recommended "a formal, multicenter, randomized phase 3 trial, comparing I/AHSCT head-to-head versus currently available highly effective therapy(ies) in a defined patient population."[5(p2781)]

Even in the face of the apparent agreement among many experts about the profile of patients who should be considered for AHSCT, a number of specific questions remain. How young should patients be? How long should disease duration be (and should one count from symptom onset or time of diagnosis)? How much disease activity should an appropriate candidate have? Should clinical activity be required, or will silent MRI activity suffice? Should the patient have tried more than 1 DMT before consideration of the procedure? Should continued disease activity while taking a highly efficacious DMT be required before AHSCT (and which agents should be considered highly efficacious)? Should a patient presenting with very active disease and other risk factors for so-called aggressive MS be considered for AHSCT as a first-line therapy?

Answers to these questions remain elusive at present in the absence of specific data. However, some guidance may be taken from the inclusion and exclusion criteria for a randomized clinical trial (Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Multiple Sclerosis [BEAT-MS]; NCT04047628, sponsored by the Immune Tolerance Network of the National Institutes of Health) that has recently begun and will compare AHSCT with highly

efficacious DMT.[12] Candidates for this trial must be aged 18 to 55 years, still be ambulatory without aids (Expanded Disability Status Scale >2.0 and ≤5.5), and have "highly active treatment-resistant relapsing MS."[12] The last requirement is defined as 2 or more episodes of treatment failure in the 24 months (and at least 1 episode within 12 months) prior to screening. Each episode of treatment failure must occur after at least 3 months of treatment with a US Food and Drug Administration–approved DMT (or rituximab), and at least 1 of those episodes must occur after treatment with a DMT other than interferon beta or glatiramer acetate. At least 1 episode must be a clinical relapse, and MRI evidence of activity must include at least 2 unique or active lesions in the brain or spinal cord. Highly efficacious DMT for this trial includes only natalizumab, ocrelizumab, rituximab, and alemtuzumab. This trial should help to clarify the relative efficacy and risk of AHSCT compared with DMT.

In a similar vein, Muraro et al[8] suggested that an appropriate candidate for AHSCT would be a person younger than 45 years with a short duration of disease (less than 10 years) with relapsing-remitting MS (or, if progressive MS, with disease for only for a short time). The patient would have recent clinical or MRI inflammatory activity (in the previous 12 months) and an Expanded Disability Status Scale score lower than 6 (unless it was very recently up to 6.5 because of inflammatory activity). The candidate should have undergone a regiment of high-efficacy DMT that did not work and should not have considerable comorbidities.

Ideally, today, a patient considering AHSCT should think about participating in a randomized clinical trial, if possible. This would assure the patient of quality care with an acceptable protocol and provide the personal satisfaction of knowing they are contributing to answering a very important question for people with MS. If the patient is not interested in a clinical trial or none is readily available, he or she should fall into the categories described, have a thorough and frank discussion with a knowledgeable MS physician, and if proceeding with AHSCT, undergo the procedure only at a highly reputable and experienced center (and, in the US, one in which the transplant physician is a member of the ASBMT).

Optimal Treatment Location

Stem cell treatments are offered at a variety of centers throughout the US and internationally, and many clinics may lack adequate expertise and quality assurance oversight. Determining the professional standing of a center prior to seeking treatment is highly recommended. Several organizations provide accreditation to centers that agree to adhere to a set of quality standards. The Foundation for the Accreditation of Cellular Therapies[13] is a nonprofit corporation cofounded with the International Society for Cellular Therapy (ISCT) and the ASBMT for the purposes of voluntary inspection and accreditation in the field of cellular therapy. The European counterpart to the Foundation for the Accreditation of Cellular Therapies is the Joint Accreditation Committee of the International Society for Cellular Therapy and Europe and European Society for Blood and Marrow Transplantation (JACIE),[14] which is Europe's only official accreditation body in the field of hematopoietic stem cell transplant (HSCT) and cellular therapy. It promotes high-quality patient care and medical and laboratory practice through a profession-led voluntary accreditation scheme. In addition to accreditation, centers performing AHSCT for MS should have transplant teams that include not only hematologist-oncologists with extensive experience in AHSCT but also neurologists with expertise in MS diagnosis and treatment. Comparing outcomes across centers is complicated by the lack of standardized processes and patient selection. Recently, the AHSCT accrediting agencies (FACT, JACIE, and the European Society for Blood and Marrow Transplantation) embarked on an effort to standardize benchmarking of outcomes for AHSCT across 7 European countries, the US, and Australia.[15] The results of these efforts should help to establish standardized outcome measures, increase accountability, and allow meaningful comparisons across centers performing AHSCT.

Protocol for AHSCT in People With MS

Protocols for treating MS with AHSCT procedures differ significantly among centers publishing reports on the use of these techniques. All protocols use a mobilization stage to stimulate release of precursor cells into the blood for harvesting and subsequent preservation. These mobilization protocols involve the use of granulocyte-colony stimulating factor or granulocyte-macrophage–colony stimulating factor to stimulate cell proliferation. Because these agents can also provoke MS relapses, an immunosuppressive drug, usually cyclophosphamide, is also administered. The stem cells are harvested from the blood by passing it through a cell separator, and selected cells are frozen for preservation until the subsequent transplant. Once sufficient cells have been separated from the blood and preserved, patients are given a conditioning regimen designed to kill current immune cells. The conditioning regimens used in published studies vary in the intensity of the immune suppression they induce (**Table**).[4,16-19] At one end of the intensity spectrum are high-intensity myeloablative conditioning protocols that suppress bone marrow blood cell formation and can cause damage to the bone marrow, while at the other end of the spectrum are nonmyeloablative regimens, termed *lymphoablative*, which are less immunosuppressive and target primarily the lymphocyte populations. Some regimens, generally using the bis-chloroethylnitrosourea, etoposide, cytarabine, and melphalan (BEAM) protocol, are considered to have intermediate intensity between these poles.[4,17,18,20,21] Proponents of higher-intensity regimens, such as those including busulfan, argue for increased efficacy with the more intensive regimens, with higher rates of effective MS disease activity suppression and longer durability of benefit, albeit at the cost of increased risk of infections and other complications, including potential mortality.[16] Proponents of the nonmyeloablative, lower-intensity regimens maintain that their approach produces high efficacy with less risk of complications.[19]

An additional variable across studies concerns whether the harvested cells are processed before transfusion. In some protocols, harvested cells are manipulated, which refers to selecting for the presence of a stem cell marker called *CD34* to eliminate mature lymphocytes that might be mixed among the harvested cell population and thereby reduce the risk of reinfusing mature autoreactive lymphocytes that might reinitiate the MS inflammatory process. Other protocols do not manipulate the graft because of the increased complexity of this step and the current lack of evidence for the benefit of graft manipulation on MS outcomes.

Table. Clinical Trials of Autologous Hematopoietic Stem Cell Transplant Reports Since 2015

Source	Identifier	Protocol	Sample size, No.	Conditioning regimen	Primary outcome	Mortality, %
Canadian report[16]	NCT01099930	Phase 2 single-arm clinical trial	26 Enrolled; 24 who received transplant	Busulfan, mean total dose, 10.9 mg/kg; cyclophosphamide, 200 mg/kg; rabbit ATG, 5 mg/kg	Activity-free survival at 5 y: 69.6%	4.2
HALT-MS[17]	NCT00288626	Phase 2, single-arm clinical trial	25 Enrolled; 24 who received transplant	BEAM; rabbit ATG, 5 mg/kg	Event-free survival at 5 y: 69.2%; progression-free survival: 91.3%	0
Australian report[4]	ACTRN12613000339752	Phase 2 single-arm clinical trial	35	BEAM; horse ATG, 40 mg/kg	NEDA at 1 y: 82%; NEDA at 2 y: 65%; NEDA at 3 y: 60%	0
ASTIMS[18]	EudraCT 2007-000064-24	Phase 2 clinical trial AHSCT vs mitoxantrone	21 Total; 9 randomized to AHSCT	BEAM; rabbit ATG, 7.5 mg/kg	Over 4 y, median new T2 lesions 2.5 in AHSCT group vs 8 in mitoxantrone group (rate ratio, 0.21; $P < .001$)	0
MIST[19]	NCT00273364	Phase 3 clinical trial AHSCT vs conventional DMT	110 Total; 55 randomized to AHSCT; 52 in primary analysis	Cyclophosphamide, 200 mg/kg; rabbit ATG, 6 mg/kg	Confirmed disability worsening, 5.8% in AHSCT group vs 66.7% in DMT group	0

Abbreviations: ASTIMS, Autologous Stem Cell Transplantation International–Multiple Sclerosis; ATG, antithymocyte globulin; BEAM, bis-chloroethylnitrosourea, etoposide, cytarabine, and melphalan; DMT, disease-modifying therapy; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; HALT-MS, High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis; MIST, Multiple Sclerosis International Stem Cell Transplant; NEDA, no evidence of disease activity.

These variations in conditioning regimens and graft manipulation, in addition to differences in the populations recruited and treated across published studies, make cross-study comparisons of one AHSCT regimen with another unreliable. To date, to our knowledge, no study comparing one AHSCT protocol with another in a controlled population exists to guide the choice among these protocols.

Ultimately, optimal conditioning regimen selection depends on balancing expected efficacy with the safety of the procedure in the population of patients with MS for whom it will be used. It is possible that optimal regimens may differ in different patients with MS, although no basis for selecting among them based on individual patient characteristics currently exists.

Treatment Course and Follow-up

The initial process of AHSCT mobilization and leukapheresis and harvest generally takes about 5 to 15 days. This is followed by an ablation regimen and finally transplant of the autologous stem cell graft. The patient is usually admitted to a hospital for 3 weeks for the ablation and transplantation regimen, as well as recovery from these procedures. After this period, the patient may be discharged home. Follow-up after transplant should include the following:

- Neurological evaluations: these should take place within 2 weeks after discharge, and then every 2 to 4 months by a neurologist.
- Cognitive evaluation: these should occur at baseline and within 1 year of AHSCT by neuropsychologists trained in MS care.
- Medical evaluation: monitoring for the appearance of infections, administration of vaccinations, and monitoring of prophylactic antibiotic and antiviral treatments is recommended immediately following transplant and every 2 to 3 months for 2 years by a hematologist or internist.
- An MRI of the brain and spine: this should be obtained within 6 months after discharge, and then at minimum annually, to evaluate for new lesion formation and brain volume changes. Administration of contrast may facilitate the identification of new lesions.
- Serum evaluations: tests should be performed at discharge and then every 4 weeks for 1 year (including tests of liver enzymes, measures of kidney function, and, periodically, thyroid panels), plus evaluations of complete blood cell counts with differential, $CD4^+$, $CD8^+$, and B cell ($CD19^+$) counts.
- Psychological and supportive care: these should be offered during hospitalization and/or at discharge, and patients should be followed every 1 to 2 months or as needed.

Costs

Another potential consideration in weighing the decision between AHSCT and pharmacotherapy is cost. The estimated cost for AHSCT today is approximately $150 000,[22] whereas treatment with DMTs currently entails a mean annual wholesale price of $80 000 or more, continuing indefinitely.[23]

Registries

Because AHSCT is a relatively uncommon therapy, it is critical to capture outcomes in longitudinal registries and open-label studies. Randomized clinical trials of AHSCT are limited because of small numbers of appropriate participants, study design challenges, and challenges in funding for nonpharmaceutical trials. It is, therefore, critical to capture both clinical and imaging outcomes as well as to

retain biosamples, if possible, in standardized registries, wherever possible. The collection of such data will continue to inform the safety and efficacy of AHSCT, as well as provide new insights into the immunological mechanisms.

Conclusions

Based on the current evidence and the recommendations from the International Conference on Cell-Based Therapies for Multiple Sclerosis and the Society of Blood and Bone Marrow, the National Multiple Sclerosis Society believes that AHSCT may be a useful treatment option for people with MS who demonstrate substantial breakthrough disease activity (new inflammatory central nervous system lesions and/or clinical relapses) despite treatment with high-efficacy DMT or have contraindications to high-efficacy DMTs and are younger than 50 years, with disease duration less than 10 years. In addition, the National Multiple Sclerosis Society believes that:

- AHSCT for people with MS should only occur at centers with experience and expertise in both MS care and stem cell transplant.
- People with MS treated with AHSCT should be entered into a single database for long-term follow-up.
- Research is needed to establish standards for cell mobilization and immune-conditioning regimens.
- Continuing research on comparative effectiveness of AHSCT and high-efficacy DMT is needed.

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