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CADTH Horizon Scan

Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Multiple Sclerosis

CADTH

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Key Messages

- Autologous hematopoietic stem cell transplantation is an emerging health technology for treating multiple sclerosis, in particular for relapse-remitting forms of the disease. In 2019, transplant societies in the US and Europe both indicated the procedure may be provided as a standard of care for a subset of people with multiple sclerosis based on age and clinical classification criteria. The Canadian Multiple Sclerosis Working Group indicated in their 2020 treatment optimization recommendations that autologous hematopoietic stem cell transplantation may be considered for younger people (aged 18 to 31) who are early in their treatment course. The procedure is offered in 2 provinces, Alberta and Ontario, as an experimental treatment.
- Results from a phase III randomized controlled trial, a systematic review of single-arm trials, and retrospective analyses from European transplant registries provides evidence that the procedure may provide effective disease control for patients who show high disease activity despite receiving disease-modifying therapies. Evidence also shows that the safety profile of the procedure has been improving over the past 25 years.
- Although cost-effectiveness studies are not yet available, the one-time procedure may have important economic implications and may have the potential to provide cost-savings to health systems, as it may reduce the need for ongoing disease-modifying therapies that may be required for patients throughout their lives.
- At least 3 additional phase III randomized controlled trials are ongoing and aim to provide a stronger evidence base to inform optimal treatment regimens and appropriate eligibility criteria. As results from these studies develop, this horizon scan aims to provide health care stakeholders in Canada with an early overview of the technology and existing evidence, while highlighting considerations related to health equity, the need for multidisciplinary care, and transplant centre infrastructure that would be important if there is to be wider use across Canada should emerging evidence demonstrate value.

Purpose

The purpose of this horizon scan is to present health care stakeholders in Canada with an overview of information related to autologous hematopoietic stem cell transplantation for the treatment of multiple sclerosis (MS), a description of some of the published clinical studies, and a summary of some important considerations related to the potential implementation of the technology should emerging evidence demonstrate value. This report is not a systematic review and does not involve critical appraisal or include a detailed summary of study findings. It is not intended to provide recommendations for or against the use of the technology.

Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE via OVID, the websites of Canadian and major international health technology agencies, ongoing clinical trials, as well as a focused internet search. The main search concept was autologous hematopoietic stem cell transplantation for MS. No filters were applied to limit the retrieval by study type. Comments, newspaper articles, editorials,

and letters were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2015 and March 24, 2021.

Regular alerts updated the search until project completion; only citations retrieved before May 14, 2021 were incorporated into the analysis.

One author screened the literature search results and reviewed the full text of all potentially relevant studies. For research examining the clinical effectiveness, safety, and suitability of autologous hematopoietic stem cell transplantation, studies with and without comparator groups were included. Other types of stem cell transplants used for MS were excluded. Grey literature reports and other information sources were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this horizon scan was reviewed by 2 clinicians with expertise in neurology and stem cell transplantation, respectively.

Background

MS is a chronic, inflammatory, autoimmune disorder that primarily affects the central nervous system.[1] In people with MS, inflammation destroys the myelin sheath surrounding nerve fibres, causing neurodegeneration and disrupting the ability of the nervous system to transmit signals throughout the body.[1] It is a slow, progressing, neurologic disorder, where early symptoms may include fatigue, visual blurring, and some difficulties in walking.[1,2] In advanced stages, people with MS can face paralysis, loss of speech, and loss of mobility, severely impacting their day-to-day life.[1,2] In Canada, 90,000 people or about 1 in 400 live with MS.[3] It is also the most common neurologic disorder affecting younger adults, with people typically having an onset of symptoms in their early 30s followed by formal diagnosis a few years later.[4,5] The average age at diagnosis in Canada is 37 years and the disease is 2 to 3 times more common among females than males.[4,5]

There are 4 clinical courses or phenotypes of MS. These clinical courses are characterized by disease activity (which describes the occurrence of clinical relapses and/or brain lesions) and disability progression (which describes the increase in disability or worsening of symptoms).[6,7] The most common course, relapsing-remitting MS (RRMS), affects about 85% of people with MS and is marked by periods of distinct symptom flare-up (relapse), followed by periods of remission, when symptoms may completely resolve or some symptoms may persist permanently.[7,8] People may also develop progressive forms of MS when symptoms continue to worsen over time, either at the onset of the disease (primary-progressive) or after a period of having RRMS (secondary-progressive).[7,8]

More than a dozen disease-modifying therapies (DMTs) are available to people with MS in Canada.[9] DMTs aim to reduce the frequency and intensity of relapses, the accumulation of lesions in the brain, and the progression of disability.[9] Primarily for people with RRMS, these drugs have shown to be highly effective in improving clinical outcomes over the short-term (3 years or less).[10] However, despite effective DMTs, up to 90% people with RRMS are likely

to develop progressive forms of MS within 10 to 20 years of disease onset.[11,12] A longitudinal study showed that within 7 years of being treated with DMTs, 7.9% of people maintained no evidence of disease activity (NEDA), a composite measure describing the occurrence of clinical relapses and the development of brain lesions.[13] Moreover, first- and second-line DMTs may fail to improve outcomes for some people or may have limited effects on disease control, while still causing people to experience adverse effects.[14-17]

Autologous hematopoietic stem cell transplantation (AHSCT), also referred to autologous hematopoietic cell transplantation, is a well-established immune reconstitution therapy for many blood cancers and is an emerging therapy for treating people with MS and other autoimmune disorders.[18,19] The procedure has the potential to provide a therapeutic option for people with aggressive or highly active RRMS for whom drug-based DMTs have had limited effect in disease control. AHSCT is not currently offered as part of routine care and protocols about the procedure are still be refined in research trials. As the therapy is intended to be a one-time procedure (compared to ongoing DMTs), AHSCT may alleviate the need for DMTs that may cause adverse events and incur recurring health care costs.[18] In particular, given that MS onset tends to be in one's 30s, if the safety and effectiveness of AHSCT can be well-established, it has the potential to improve the quality of life and reduce the treatment-related side effects and financial cost associated with DMTs over a longer time period.[20]

Although research about the type and dosing of regimens and eligibility criteria for AHSCT is emerging, guidelines from Canada, the US, and Europe recommend that AHSCT may be offered as a treatment option for a subset of patients with MS who qualify based on their age and clinical presentation.[19,21-23] Across the world, more than 1,500 people with MS have received AHSCT.[19] Within Canada, centres have led foundational clinical research into AHSCT for MS, but there has been limited use outside of research settings. This horizon scan aims to inform Canadian health care stakeholders about the emerging technology, ongoing clinical research to assess its safety and effectiveness as compared to DMTs, and implementation considerations for wider uptake should emerging evidence demonstrate value.

The Technology (Procedure)

AHSCT aims to partially or completely destroy autoreactive immune cells that cause damage to the CNS with a conditioning regimen and then redevelop or reconstitute the immune system with stem cells from the same person.[19] The procedure produces an "immune system reset" that limits disability progression and disease activity, and may help enable disease recovery.[24] The AHSCT procedure involves multiple steps including pre-assessment, conditioning, transplantation, and post-transplant rehabilitation. The entire procedure is delivered over 2 to 6 months and ongoing monitoring occurs for 3 years or more.[25] Specifically, the procedure involves the following steps.

Step 1. Pre-transplant assessment and priming: A multidisciplinary team initially assesses whether the procedure is suitable for candidates based on their age and clinical presentation. People with MS and their caregivers are informed about the procedure's short- and long-term benefits and risks. If a person is currently taking DMTs, these are discontinued between 6 weeks and 6 months before the immunoablation, depending on the type of DMT.[19,26] Pre-habilitation may be provided with support for exercise, nutrition, and other aspects of self-managed care to help reduce the risk of complications following transplantation.[25]

Step 2. Stem cell mobilization and harvesting: Peripheral whole blood is collected from the person undergoing transplantation and white blood cells are separated through a process of leukapheresis.[19] Cells may be collected several weeks or months before the transplant.[27]

Step 3. Immune system conditioning: Approximately 10 days before the transplant, the patient is admitted to a hospital to receive a conditioning regimen consisting of chemotherapy with or without an antibody therapy, such as anti-thymocyte globulin (ATG), that aims to either partially or completely ablate the immune system.[19,28] Several conditioning regimens with different doses and intensity or toxicity levels have been used and are also under active investigation. These include:

- high-intensity regimens that incorporate busulfan (BU) and aim to completely ablate the immune system[18]
- intermediate-intensity regimens that are myeloablative use BEAM (BiCNU-carmustine, etoposide, cytosine arabinoside [Ara-C], and melphalan)[19]
- intermediate-intensity regimens that are non-myeloablative primarily use cyclophosphamide (CP).[19]

Different regimens offer a trade-off between effectiveness and the potential for adverse events.[29] BU can penetrate the blood-brain barrier and be more effective in disease control by targeting immune cells throughout the central nervous system but is also associated with a higher rate of severe side effects, particularly liver toxicity and sinusoidal obstruction syndrome.[28] Intermediate-intensity regimens of BEAM or CP may be less effective in limiting disease activity but are less likely to have severe side effects.[19] European transplant guidelines recommend only using BEAM-ATG or CP-ATG (most common), while in Canada, the BU-CP-ATG regimen is the primary regimen used.[18,19] Research trials directly comparing the safety and effectiveness of different regimens are currently lacking but trials are underway to determine the optimal dosing for individual regimens.[20]

Step 4. Transplantation: After 2 days of the last conditioning regimen, patients receive their previously harvested autologous cells.[28]

Step 5. Post-transplant rehabilitation: Following the transplant, patients receive supportive care, which includes close monitoring for infections and other adverse events, physical therapy, speech and language therapy, and support for performing daily tasks.[25] Most patients are discharged from the hospital 4 weeks after the transplant and continue to receive regular scans, rehabilitation, and close monitoring for 3 to 6 months.[25] Periodic follow-up with the transplant program, in conjunction with a patient's neurologist, may occur for several years but continues for at least 3 years.[25]

Availability

Under the *Food and Drugs Act*, autologous cell therapies are defined as drugs and are regulated by federal approval.[30] However, lymphohematopoietic cells, such as those used in AHSCT, that are minimally manipulated and are used for the same function in the same patient (homologous) after transplantation are exempt from this regulation.[30] Autologous bone marrow transplantation procedures are also exempt from the less stringent *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*.[31] More than a dozen

transplant centres in Canada are, however, regulated by international standards set by FACT, the Foundation for the Accreditation of Cellular Therapy, which has requirements for onsite inspections, reporting, and audits.[32] Provincial colleges of physicians and surgeons also maintain an oversight on transplant procedures.[33] AHSCT for people with MS is offered as an experimental treatment in Canada at limited centres in Alberta and Ontario for people who qualify based on age criteria and clinical evaluation by an MS neurologist and a transplant surgeon.[34]

Who Might Benefit?

Published recommendations and guidelines from Alberta Health Services, the US National Multiple Sclerosis Society, the ASTC (or American Society for Transplantation and Cellular Therapy, formerly known as the American Society for Blood and Marrow Transplantation), and the EMBT (or European Society for Blood and Marrow Transplantation) recommend that AHSCT can be offered to eligible people with RRMS who are 45 years of age or younger (US recommendations indicate 50 years of age or younger).[19,21,22,34] The Canadian MS working group on treatment optimization recommends that people between the ages of 18 and 31 years may be considered for the procedure.[23] Older people with MS typically have a higher level of disability at baseline and have a higher risk of severe complications, which could reduce the likelihood of treatment success.[21] Approximately 5,000 people living with MS in Canada are younger than 31 years and 22,000 people are younger than 50 years of age and could be potential candidates based on these age criteria.[4,35] While eligibility criteria includes this wide age range, the average age among clinical trial participants has been 35.7 years.[36]

Guidelines also indicate that AHSCT may be offered to people who show a high level of disease activity despite receiving DMTs.[19,21,23] Approximately 25% of people on first-line DMTs experience initial treatment failure, in which case they are most often transitioned to another first-line DMT.[14] There is limited evidence, beyond consensus statements, describing when a person receiving first-line DMTs should be transitioned to second-line treatments such as alemtuzumab, fingolimod, and natalizumab.[37] In practice, people are typically transitioned when they experience 2 or more relapses over a period of 12 months, or have fewer relapses but show evidence of new brain lesions.[19,34,38] It is uncertain the proportion of people in Canada who are either dissatisfied with their current DMT because of its adverse effects or who show signs of high disease activity despite receiving second-line therapies. Estimates from Scotland suggest that between 2% and 10% of people living with MS may be eligible for the procedure each year.[39]

Other clinical factors like disease duration, level of disability, and overall health will affect the procedure's suitability for candidates. It is possible that with a stronger evidence base showing the safety and effectiveness of the procedure in specific populations, the eligibility criteria may be expanded to consider people earlier in their treatment pathway. For example, rather than reserving AHSCT for people with high disease activity, a low-intensity regimen of AHSCT may be appropriate for people with less aggressive forms of MS for whom DMTs do provide some level of disease control.[40] However, the current evidence base has not yet explored AHSCT as an alternative to DMTs for all people with MS; rather, it is being investigated specifically for people with aggressive forms of MS for whom DMTs provide limited disease control.

Summary of the Evidence

A CADTH Rapid Review[41] summarized and critically appraised results from comparative studies, which included 2 randomized control trials (RCTs),[42,43] 4 retrospective cohort studies,[44-47] and 2 evidence-based guidelines.[19,22] These studies compared the safety and effectiveness of AHSCT (both myeloablative and non-myeloablative conditioning regimens) to DMTs. The 2 RCTs included:

- The Autologous Hematopoietic Stem Cell Transplantation trial in MS (ASTIMS),[42] which was a multi-centre, phase II RCT coordinated by the EBMT comparing AHSCT to a DMT across centres in Italy and Spain. The trial was designed as a proof-of-concept study and therefore had limited participants, with a total of 21 people randomized to receive either AHSCT (myeloablative) or mitoxantrone (MTX).[42] Authors concluded that AHSCT was associated with a significantly fewer number of brain lesions compared to MTX.
- The Multiple Sclerosis International Stem Cell Transplant (MIST)[43] trial was a multi-centre, phase III RCT conducted in the US, England, Sweden, and Brazil. It is the largest and only phase III RCT with AHSCT for the treatment of MS to have been completed to date.[18] The trial enrolled 110 participants (n = 55 in each arm) who were randomized to receive either AHSCT (non-myeloablative regimen) or standard DMTs available at the time of the study. The authors of the MIST trial described significantly better outcomes in disability progression, rate of relapses, and quality of life in the AHSCT intervention arm compared to the DMT arm.

Findings from those studies and additional studies that did not meet the inclusion criteria for the Rapid Review, as there was no comparator group, were synthesized for this horizon scan. These additional studies included a systematic review and meta-analysis[36] of 14 single-arm trials (and the ASTIMS study), together with other primary studies that had no comparators, non-systematic reviews, and grey literature reports that examined clinical effectiveness, safety and long-term effects on health and well-being, patients' perspectives, and cost implications.

Clinical Effectiveness

Several measures are used to assess the effectiveness of treatments for people with MS. The Expanded Disability Status Scale (EDSS) is the most common validated instrument used to describe disability status and progression.[48] An increase in score is associated with increased disability and worsening of symptoms.

The MIST trial showed that, at 2 years, a clinically meaningful disability progression of EDSS of 1.0 or greater was observed in 5.19% of participants in the AHSCT arm compared to 62.5% in the DMT arm.[43] At 5 years, disability progression was 9.71% in the AHSCT arm compared to 75.3% in the DMT arm.[43] A meta-analysis of 14 single-arm trials and the ASTIMS study showed that, at 2 years, the pooled rate of EDSS of 1.0 or greater was 17.1% of participants who received AHSCT.[36] The meta-analysis included patients with both relapse-remitting and progressive forms of MS. In studies with a greater proportion of patients with RRMS, disability progression at 2 years was 7.8%.[36] A single-arm, retrospective study that conducted long-term follow-up of patients in Italy with RRMS who had received AHSCT showed that disability worsening-free survival at 5 years was 85.5% and at 10 years was 71.3% of participants;[49] that is to say, disability progression at 5 years was 14.5% and at 10 years was 28.7% of participants.

The rate of relapse or development of brain lesions detectable by MRI are additional measures used to assess treatment effectiveness. In the MIST trial, 9.61% and 15.4% of participants in the AHSCT arm and 79.6% and 85.2% of participants in the DMT arm had relapses at 2 and 5 years, respectively.[43] The ASTIMS study reported that participants in the AHSCT arm had 79% fewer brain lesions (mean number of new brain lesions) compared to participants who received MTX at 4 years.[42]

NEDA — a composite measure that incorporates the occurrence of clinical relapses, increasing disability, and the development of brain lesions — is increasingly being used to assess the effectiveness of treatments.[50] The Sormani et al. meta-analysis showed that NEDA at 2 years was 83.4% and at 5 years was 67.0% for RRMS patients who received AHSCT.[36] Results from retrospective comparative studies show significantly higher NEDA at 3 years among patients who received AHSCT compared to patients who received DMTs.[46,47] For example, a retrospective comparative study from Sweden showed that NEDA at 3 years was 88% for RRMS patients who received AHSCT compared to 33% for those who received the DMT alemtuzumab.[45]

Quality of life outcomes have been reported in some studies, including the MIST trial, showing AHSCT was associated with significantly improved scores after 1 year compared to baseline and compared to participants who received DMTs.[40,43] Overall, results from both RCTs and other comparative studies suggest that AHSCT can have clinically meaningful effectiveness for people with RRMS in extending the length of disease progression-free survival and slowing or halting disease activity as compared to DMTs.[19,20,40,44] In some people, AHSCT may be associated with disability and symptoms improvement.[40,51] Clinical effectiveness among patients with progressive forms of MS has been found to be moderate and both American and European transplant societies suggest the need for further research.[19,22]

Safety

Treatment-related mortality was a major concern in early trials, but the rate of mortality has been reduced over time. Analysis from the EBMT registry showed that treatment-related mortality between 1995 and 2000 was 7.3%; between 2001 and 2007, it was 1.3%; and between 2008 and 2016, it was less than 1.0%.[20,52] Among 8 studies with 20 or more transplant recipients published between 2016 and 2020, 1 study reported treatment-related mortality.[20] This study was a Canadian phase II trial using a high-intensity BU regimen and reported 1 treatment-related death among 24 patients (4%).[28] Better survival over time is attributed to refined eligibility criteria, such as restricting the procedure to younger patients with RRMS who have less disability, improved conditioning regimens, and transplant centres having greater experience in delivering the procedure and providing supportive care.[15,19,20,25]

Most adverse events are reported to occur within 1 month of receiving the procedure and are largely related to the toxicity of conditioning regimens.[20,40] Similar to most cell transplant procedures, there is risk of respiratory and urinary tract infections, gastrointestinal damage, and organ damage.[18] Intermediate-intensity regimens using BEAM or CP are considered to have less severe adverse effects than high-intensity regimens that use BU, which may increase the risk of severe liver toxicity, requiring intensive care support.[18,40]

Late adverse events, reported 6 months or more following the procedure, include a 2% risk of malignancies and a 5% to 26% risk of secondary autoimmune dysfunction, in particular thyroid disease, as reported by various single-arm and retrospective studies.[18,28,44,52,53] However, 1 review noted that higher rates of secondary autoimmune dysfunction may occur

among people treated with certain DMTs.[18] Studies with longer follow-up periods (e.g., 10 years or more) would help characterize the long-term risk profile of the procedure.

The risk of infertility is an important concern among all patients treated with transplant conditioning regimens, especially for eligible candidates of AHSCT with MS, as they are more likely to be in child-rearing ages. A retrospective single-arm study of 43 females treated with AHSCT at 4 centres in Italy between 1999 and 2019, showed that 30 out of 43 females (70%) had complete recovery in menstrual cycles within 6 months of their transplant.[54] All transplant recipients were treated with intermediate-intensity regimens and females who resumed menstrual cycles were more likely to be younger, with a mean age of 30.2 years compared to 37.6 years, which has been reported previously.[54,55] Three transplant recipients reported full-term pregnancies without any complications and 1 recipient reported infertility.[54] In a single-arm trial that used a high-intensity regimen for AHSCT, 2 transplant recipients reported having children after their transplant by using previously harvested gametes.[28] Male infertility is a concern among patients receiving AHSCT for other conditions, but limited information pertaining to AHSCT for MS was identified.[56] Overall, there is a risk of the procedure affecting fertility, but it seems to vary depending on the regimen and patient characteristics.[20,40]

Cost Implications

AHSCT may provide economic benefits and cost-savings if it is provided as a one-time procedure compared to ongoing DMTs that may be administered over the lifetime of people with MS.[20] There is also the potential for benefits associated with limiting disability progression, which may affect a person's employment, social well-being, and quality of life.[20]

No cost-effectiveness analysis studies comparing AHSCT to DMTs were identified and such analysis may be challenging given the diversity of conditioning regimens, varied treatment and supportive care practices, and a wide range of costs for DMTs. One study has reported the cost of AHSCT for the treatment of MS compared to DMTs specific to their hospital in the US. The mean total cost of the AHSCT procedure, including the direct costs of treatment and care and indirect overhead costs, was US$85,184.[57] In comparison, the average annual cost of DMTs reported was between US$80,000 and US$100,000 per patient.[57]

A budget impact analysis from the UK found the net cost of AHSCT may range from approximately £10,000 to £19,000 per patient.[39] The analysis did not consider net savings over the lifetime of a patient from potentially avoiding DMTs or costs associated with long-term adverse effects related to DMTs and ongoing disease management.

In Canada, DMTs cost between $13,000 to $50,000 annually per patient.[9] AHSCT that is not specifically for the treatment of MS has been reported to cost $60,990 (2015 rate) in 1 Canadian jurisdiction but can increase depending on the length of hospital stay following the procedure.[58] More up-to-date cost estimates for providing AHSCT to patients with MS in Canadian centres, including the costs related to pre-assessment and long-term follow-up, were not identified and would be important for assessing AHSCT in Canadian settings.

Patients' Perspectives

Using a questionnaire, 1 cross-sectional study from the Netherlands assessed the views and awareness of AHSCT among people with MS; 113 of the 137 people with MS (83%) reported having heard about the procedure.[59] However, 25% of respondents reported that they perceived themselves to have sufficient knowledge about the risks and benefits of AHSCT

compared to 60% who reported having sufficient or excellent knowledge about DMTs.[59] People who had MS for 10 years or less, greater disability (EDSS higher than 3.5), and who were dissatisfied with their current treatments were more likely to consider AHSCT as a potential therapeutic option for themselves.[59]

Case studies from people with MS and their caregivers in Scotland indicated that, for many, the disease can have a large impact on their lives and their ability to take part in daily activities.[39] One of the primary reasons people with MS and their families sought AHSCT was to avoid the adverse effects associated with DMTs and their worry about increasing disability progression.[39] Some people who were considering AHSCT but did not qualify for the procedure in the UK reported travelling out of country on their own expense to seek treatment. Some individuals from Canada have also been reported to seek AHSCT abroad.[60,61]

Ongoing Research Developments

Following the MIST trial, at least 3 phase III RCTs are underway across the world to assess the safety and efficacy of AHSCT compared to the most recently developed DMTs, which may not have been available at the time of earlier studies (Table 1). These trials have varied eligibility criteria but are generally limited to younger people with RRMS (younger than 55 years of age) who show high disease activity but with limited comorbidities or other health concerns that may lead to an increased risk of treatment-related complications.[20] Trials investigating other cell therapies, such as mesenchymal stem cells, are also ongoing for progressive forms of MS and may be of interest but are not shown in Table 1.[62]

Although a high-intensity regimen with BU has been tested in studies and is currently being used in different centres in Canada, none of the current RCTs identified are incorporating BU. Instead, active trials are investigating intermediate-intensity regimens of BEAM-ATG or CP-ATG. Stem cell selection and purification before transplantation is part of Canadian AHSCT protocols but is not being included in current trial protocols because of limited evidence of providing benefit and potentially increasing costs.[18,19] These differences could have important implications for future protocol development in Canada. No ongoing trials that are directly comparing different AHSCT regimens were identified, but the EBMT has suggested that analyses from European registries may help examine the differences in outcomes between different regimens.[20]

Overall, these phase III trials, together with ongoing retrospective analyses of registry databases in Europe, aim to provide a stronger evidence base for AHSCT in the next 5 to 10 years and will help inform clinical guidelines and eligibility criteria across the world.[19]

Operational Considerations

Cost of AHSCT

The upfront health care costs of delivering AHSCT are likely to be high and would need to be considered in relation to drug-based DMTs and the costs associated with their ongoing administration.[20] However, a key aspect of AHSCT is the potential for reducing disability

progression, which may have a large impact on the health, social, and economic well-being of people with MS.[20] The risks associated with the procedure and benefits to both the transplant recipient and potential cost-savings to the health system related to long-term disease management may vary based on many different factors unique to individual patients. It is also not yet known whether transplant recipients who redevelop disease activity following AHSCT would still require or benefit from DMTs later on.

Table 1: Active Phase III Clinical Research Trials Investigating AHSCT for People With MS

Name of study and country	Study design	Study duration and sample size	Population	AHSCT regimen and comparator	Outcomes
NCT04047628 **Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS)** **US and UK**	Phase III RCT, multi-centre: • 21 sites	Up to 6 years follow-up during the period Dec. 2019 to Dec. 2026 n = 156	18 to 55 years Highly active RRMS with ≥ 2 episodes of prior treatment failure in previous 24 months	**Intervention:** BEAM-ATG **Comparator:** Best available DMT from natalizumab, alemtuzumab, ocrelizumab, or rituximab	**Primary:** • Relapse-free survival up to 3 years **Secondary:** • Number of relapses • Disease activity • Changes in disability • Adverse events
NCT03477500 **RCT Comparing Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab in MS (RAM-MS)** **Norway, Sweden, Netherlands, and Denmark**	Phase III RCT, multi-centre: • 8 sites	Up to 5 years follow-up, during the period March 2018 to March 2024 n = 100	18 to 50 years Highly active RRMS	**Intervention:** CP-ATG **Comparator:** Alemtuzumab	**Primary:** • NEDA (2 years) **Secondary:** • Time to first sign of new disease activity • Changes in disability • QoL • Other clinical outcomes
NIHR Registration 16/126/26 **Autologous Stem Cell Transplantation versus Alemtuzumab or Ocrelizumab in Relapsing Remitting Multiple Sclerosis (STAR-MS)** **UK**	Phase III RCT, multi-centre: • 19 sites	Up to 2 years follow-up, during the period Jan. 2019 to June 2024 n = 198	16 to 55 years Highly active RRMS	**Intervention:** CP-ATG **Comparator:** Alemtuzumab or ocrelizumab	**Primary:** • NEDA (2 years) **Secondary:** • Time to first sign of new disease activity • Changes in disability • QoL • Other clinical outcomes

AHSCT = autologous hematopoietic stem cell transplantation; ATG = antithymocyte globulin; CP = cyclophosphamide; DMT = disease-modifying therapy; MS = multiple sclerosis; NEDA = no evidence of disease activity; QoL = Quality of life; RCT = randomized controlled trials; RRMS = relapsing-remitting multiple sclerosis.

In Canada, the cost of DMTs is covered by private drug plans (52%), public plans (41%), and out-of-pocket expenses (7%).[63] The range of costs covered by public plans also varies between 27% to 90% across different jurisdictions.[63] Therefore, the potential cost-savings to public plans from relying less on DMTs may vary between different jurisdictions.

Health Equity

Prior to the AHSCT procedure, counselling candidates and their families about the benefits and risks of the procedure, both short- and long-term, are an important part of informed consent.[25] In particular, all candidates who consent to AHSCT and may desire to have children in the future should be provided options for gamete preservation.[40] Access to fertility treatments vary based on provincial and territorial jurisdictions, which could have important implications for health equity and equitable uptake of the procedure across Canada if emerging evidence demonstrates value.[64]

The transplant procedure itself requires a strong commitment from candidates and their caregivers. Patients would be required to stay at or near the transplant centre for several months and, for many, that would require travelling away from their homes, which may not be feasible.[34] Caregivers also play an important role in rehabilitation and recovery, and are an essential part of supporting transplant receipts to resume daily activities after the procedure.[25] Not all eligible candidates for the procedure may have that critical caregiver support. Moreover, any additional out-of-pocket expenses for rehabilitation therapy or time away from work may be additional barriers for some candidates.

Transplant Centre Infrastructure

More than 20 blood and marrow transplant centres exist in Canada and could potentially offer the therapy to eligible candidates by modifying their existing protocols for AHSCT.[65] Many aspects of care are similar to AHSCT used for other conditions, but there are some additional considerations. People with MS may be more likely to develop seizures, certain fever-induced neurologic symptoms, and urinary bladder dysfunction, which could increase the risk of infection.[19,25] Therefore, supportive care protocols used for other patients undergoing transplants, such as oncology patients, may need to be modified accordingly. During and following the procedure, patients would require support from both caregivers and a wide range of health professionals to facilitate rehabilitation and favourable long-term outcomes.[25]

Offering AHSCT on a wider scale beyond experimental treatment in Canada would require a shift in how care is delivered for people with MS. Most people with MS receive the majority of their care through specialist neurology clinics.[25] AHSCT requires a multidisciplinary approach, with members from a range of expertise, including but not limited to neurology, hematology, transplantation, infectious diseases, specialist therapy, and rehabilitation.[25] In particular, close collaboration between neurologists and the transplant team would be required at all stages of the procedure including assessment and follow-up, which could add more complexity than other transplant procedures. The existing funding models in jurisdictions can also pose challenges for transplant centres in accepting patients with conditions other than cancer because of limited resource capacity and budgets.[66] Increased funding and resources for transplant centres would likely be required to increase access to AHSCT for non-oncology care.[66]

Transplant centre experience is considered 1 of the major reasons for better outcomes and the improved safety of AHSCT over the past 25 years.[67] Centres that can bring together these

different specialties and adopt best practices for setting eligibility criteria, administering optimal treatment regimens, and providing appropriate supportive care may have the most potential for favourable outcomes.[67] The EBMT Autoimmune Disorders Working Party[68] maintains a registry database in Europe and facilitates knowledge sharing among centres. Leveraging existing networks of provincial transplant societies and CTTC–Cell Therapy Transplant Canada[69] may similarly help to monitor outcomes in different centres, operationalize the procedure on a wider scale, and ensure equitable access to care is provided across Canada.

Final Remarks

AHSCT for the treatment of MS is an emerging health technology that has existed for more than 25 years and has a growing evidence base assessing its clinical effectiveness for reducing disability progression and disease activity compared to DMTs.[18,19] Researchers in Canada have played a key role in developing and refining the procedure in the past 10 years and it is offered as an experimental treatment at limited centres in Alberta and Ontario. There remains some uncertainty about the procedure's safety profile, optimal protocol design, and its role in the treatment course of people with MS.[18] However, refinements in treatment regimens have contributed to increased safety, reducing the risk of severe adverse events and treatment-related mortality.[20] Transplant societies from the US and Europe recommend that AHSCT can be offered as standard of care for younger people with RRMS who show high disease activity despite receiving DMTs.[19,22] The Canadian MS Working Group has similarly recommended that the therapy may be considered for younger candidates between the ages of 18 and 31 years who are early in their treatment course.[23] Ongoing developments with phase III RCTs currently underway across the world aim to further assess 2 key aspects of the procedure: the safety and efficacy of different intermediate-intensity conditioning regimens and the appropriate eligibility criteria for candidates.[20] Although the emerging evidence base shows likely improved outcomes compared to DMTs, AHSCT is not intended to replace DMTs altogether. Instead, AHSCT may offer a potential alternative for people who are still early in their disease progression but show a high level of disease activity despite being on first- or second-line DMTs. Operationalizing the procedure across Canada on a wider scale, should emerging evidence demonstrate value, would need to consider aspects of heath care costs, health equity, increasing resources for transplant centres, and leveraging established frameworks, including FACT and CTTC–Cell Therapy Transplant Canada, for monitoring and sharing protocols and outcomes data.

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