Autologous Hematopoietic Stem Cell Transplants as a Treatment for Multiple Sclerosis

doi: 10.35493/medu.48.26

AUTHORS:
SONALI MEHTA[1] & ARHAAN KAMAL[2]
[1] Bachelor of Health Sciences (Honours Biochemistry), Class of 2027, McMaster University
[2] Bachelor of Science (Honours Sensory Motor Systems), Class of 2027, McMaster University

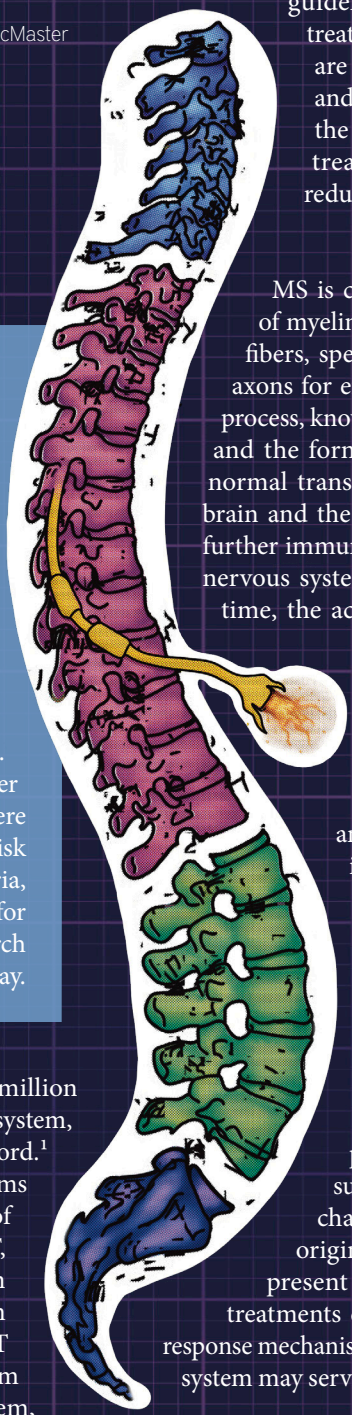
ARTIST:
SUMAIYYA MAHMOOD[3]
[3] Bachelor of Science (Honours Life Sciences), Class of 2028, McMaster University

ABSTRACT

Multiple sclerosis (MS) presents through progressive loss of motor function due to the demyelination of axons throughout the nervous system. It is categorized as an autoimmune disease with a variety of subclassifications based on the recurrence of degenerative events. This review examines the efficacy of autologous hematopoietic stem cell transplantation (AHSCT) in reducing the symptoms related to MS compared to traditional disease-modifying therapies (DMTs) such as ocrelizumab and ofatumumab. Within current literature, AHSCT has shown success in increasing quality of life as well as halting degenerative events. In preliminary studies, AHSCT has shown greater improvement when used prior to DMTs. However, severe limitations hinder the availability of AHSCT, such as the risk of neuroablative illness, highly specific treatment criteria, and high costs. AHSCT is a promising treatment for alleviating MS symptoms, and necessary research on its long-term efficacy is currently underway.

INTRODUCTION

MS is a chronic autoimmune disease affecting over 2.8 million individuals globally. The disease targets the central nervous system, causing degeneration of neurons in the brain and spinal cord.[1] This damage often leads to disability and long-term symptoms which reduces quality of life. As such, the ongoing pursuit of innovative treatment options has become crucial. AHSCT, a therapy introduced in 1997, has shown high efficacy in recent years, with numerous studies suggesting long-term increases in quality of life and reductions in disability.[1] AHSCT involves the extraction and purification of a patient's stem cells, which are then used to "reboot" the immune system, halting the autoimmune attacks characteristic of MS progression.[1,2] Despite the strides taken in recent years, AHSCT as a treatment for MS remains uncertified by many government institutions, including the United States Food and Drug Administration, due to immunoablative illnesses, strict patient qualification guidelines, and high cost-related barriers to treatment.[1,2] For these reasons, further studies are required to determine the ideal timeline and immune conditioning needed to increase the efficacy of the procedure. Individualized treatment plans have shown promise in reducing the risk of immunoablative illnesses.[2]



BACKGROUND

MS is characterized by autoimmune degradation of myelin, which is responsible for insulating nerve fibers, speeding up electrical signals and protecting axons for efficient and reliable communication.[1] This process, known as demyelination, leads to inflammation and the formation of scar tissue, which disrupts the normal transmission of electrical signals between the brain and the rest of the body.[1,2] Lesions may result in further immune responses on the central and peripheral nervous system, increasing disease progression.[2] Over time, the accumulated damage to myelin and nerve fibers can cause irreversible disability.[1]

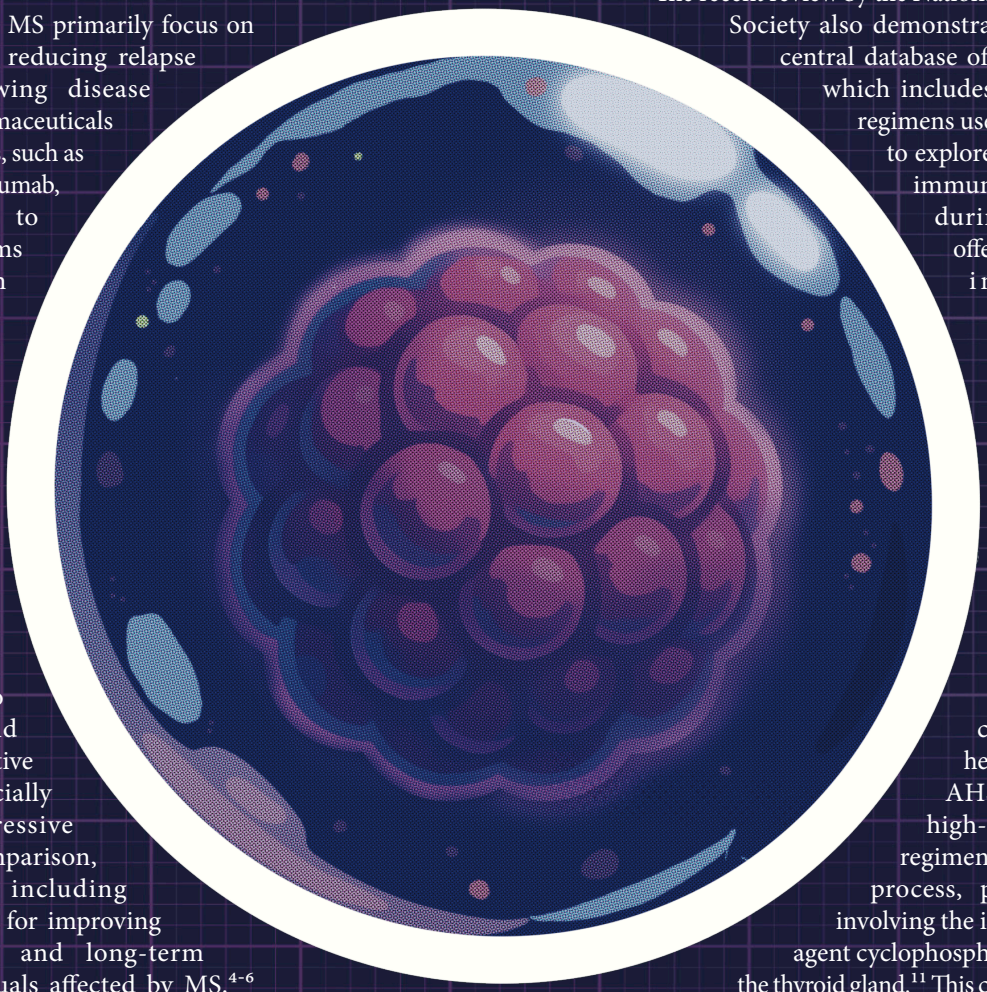
MS is widely believed to result from a combination of genetic predispositions and environmental triggers. Viral infections, vitamin D deficiency, and smoking has also been shown to increase an individual's chance of developing MS. MS is more common in women and is typically diagnosed in young adults, although it can occur at any age.[2] Studies of the underlying molecular mechanisms which cause the observable traits of MS identify the CD8+ mucosal-associated invariant T cell type to be present in higher amounts in individuals with the disease. This type of immune cell is implicated in the production of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-17, causing the characteristic inflammation in MS. Diseases originating from immune system dysfunction present a hurdle in determining pathology and treatments due to the interwoven nature of immune response mechanisms. Reintegration of an individual's immune system may serve as a wide-sweeping method of treatment.[3]

THERAPEUTIC MECHANISMS

During AHSCT treatment, a patient's hematopoietic stem cells are collected from their blood or bone marrow, purified, and

stored for later use.[4] The patient then undergoes high-dose chemotherapy or immunosuppressive therapy, which eliminates the pathogenic T cells that mistakenly target myelin.[1,4] Following the completion of immunosuppressive therapy, purified stem cells, which include regularly functioning lymphocytes, are reintroduced into the patient's body. These stem cells then migrate to the bone marrow, and a new, healthier immune system is regenerated.[4] On a molecular level, post-AHSCT immune systems indicated greater regulation of microRNA (miRNA) expression, consequently upregulating genes such as *FOXO1* and *BAK*, which promote regulatory lymphocyte activity and inflammation suppression respectively. These epigenetic modifications, in tandem with a decrease in the presence of inflammatory cytokines, lend further evidence to the notion that AHSCT creates a sustainable immune system wherein disease progression is halted.[5]

Current treatments for MS primarily focus on managing symptoms, reducing relapse frequency, and slowing disease progression, with pharmaceuticals playing a key role. DMTs, such as ocrelizumab and ofatumumab, are commonly used to manage relapsing forms of MS. These modern drugs, which are monoclonal antibodies targeting receptors on the surface of B cells, aim to reduce autoimmune responses, the frequency of flare-ups, and the development of brain lesions associated with the disease. However, these treatments do not offer a cure, and they may not be effective for all patients, especially those with progressive forms of MS. In comparison, novel treatments including AHSCT hold promise for improving the quality of life and long-term outcomes for individuals affected by MS.[4-6]



CASE STUDIES AND CLINICAL TRIALS

Preliminary studies of the effect of DMT and AHSCT on disease progression in relapse-remitting MS (RRMS) indicate a significant decrease in disease status in AHSCT compared to DMT use.[7] A randomized controlled study by Burt et al. measured disease status using the Expanded Disability Status Scale (EDSS).[7] Individuals who underwent AHSCT demonstrated an improved (lower) EDSS score, while participants who continued DMT treatment showed a worsened (higher) score.[7] The fundamental goal for MS treatments is to achieve no evidence of disease activity (NEDA) status.[8] NEDA status designates a lack of any apparent symptoms or progression of neurological damage for individuals with MS.[8]

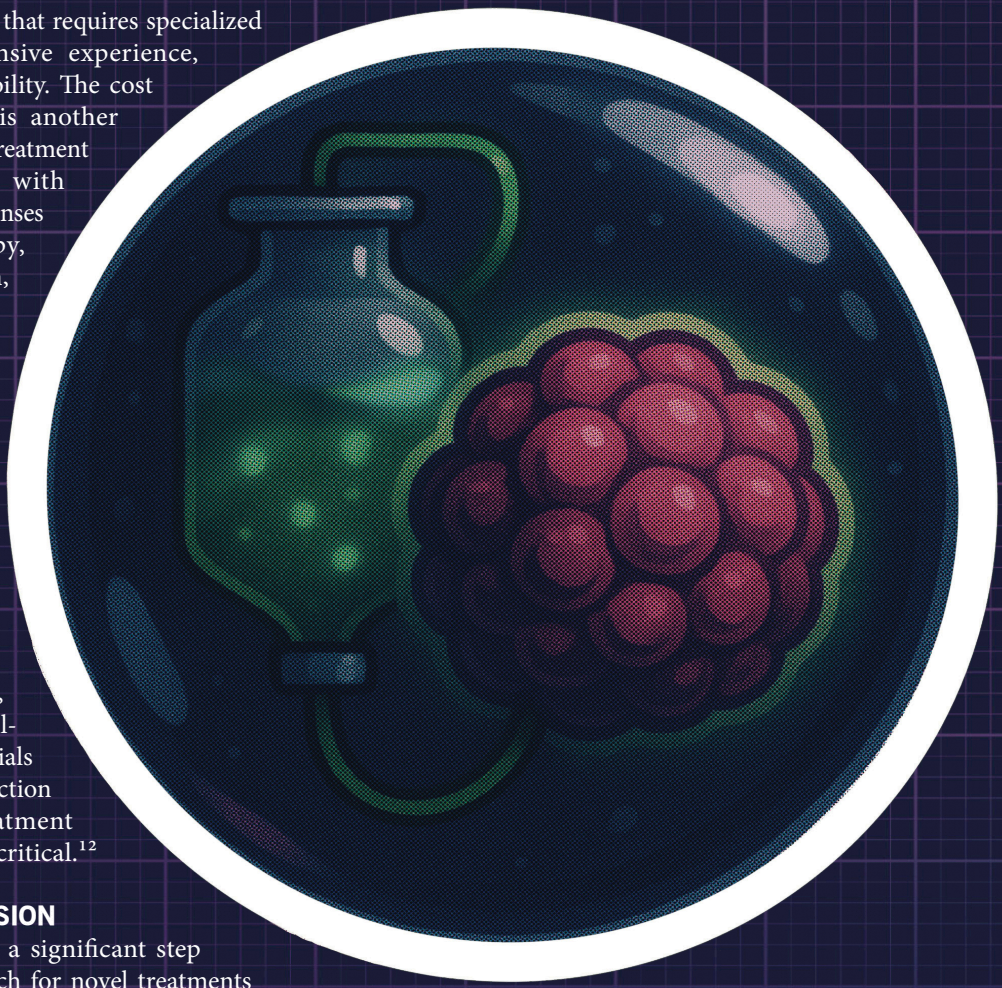
A retrospective study by Sormani et al. shows that 54.5% of stem cell transplant patients exhibit NEDA status 3 years post-AHSCT, whereas DMTs indicate 11.5% of individuals with NEDA status. This study highlights the efficacy of AHSCT relative to DMTs.[8] Current AHSCT qualification guidelines state that DMTs must show inefficacy prior to AHSCT use.[9] Contrary to these guidelines, a retrospective study by Das et al. highlights the potential of AHSCT as a first-line treatment.[9] This study evaluated the treatment of 20 individuals with a qualitatively aggressive form of MS, finding high efficacy in reducing disease activity within 30 months post-transplant and an 85% rate of NEDA status.[9] These findings provide a basis for further study regarding the timing of AHSCT, its impact on disease activity reduction, and the potential benefits of early treatment.[9] There are currently no conclusive large-scale trials where a specific immune conditioning regimen for AHSCT has been determined. The recent review by the National Multiple Sclerosis Society also demonstrates the need for a central database of patient outcomes, which includes the conditioning regimens used. Research has yet to explore the progression of immunoablative illnesses during AHSCT and offers a path for further investigation.[10]

LIMITATIONS

Several limitations regarding the usage of AHSCT in treating MS must be carefully considered.[11] Endocrine complications, such as thyroid dysfunction, are among the most common long-term health issues following AHSCT.[11] The use of high-dose conditioning regimens in the transplant process, particularly those involving the immunosuppressive agent cyclophosphamide, can damage the thyroid gland.[11] This can also be influenced by prior exposure to chemotherapy, particularly total body irradiation, which can directly damage thyroid follicular cells and disrupt hypothalamic-pituitary-thyroid axis regulation.[11]

AHSCT may also lead to cardiovascular complications. For instance, anthracycline-induced cardiotoxicity is a dose-dependent condition characterized by damage to the myocardium. The use of anthracyclines is important to prepare patients for AHSCT as they suppress the existing immune system and create space for the reinfusion of autologous stem cells. This drug induces the formation of reactive oxygen species, leading to lipid peroxidation, mitochondrial DNA damage, and impaired ATP production. This results in myocyte apoptosis and fibrosis,

progressively weakening the heart's contractile capacity. Moreover, doses exceeding 250 mg/m² significantly increase the risk of cardiovascular complications, especially when combined with chest radiation, which exacerbates vascular damage and myocardial fibrosis. These processes lead to reduced left ventricular function and an increased risk of congestive heart failure.[11] AHSCT for MS also requires strict patient eligibility criteria, which currently lacks long-term efficacy and safety data.[10] Ideal candidates are typically younger than 45 years, have a relatively short disease duration, and demonstrate active RRMS or early-stage progressive MS despite high-efficacy DMT.[10] Candidates must also have a relatively low EDSS score and minimal comorbidities.[10]As such, there is a need for further comparative studies to better understand the relative risks and benefits of AHSCT compared to other highly efficacious DMTs.[10] Moreover, AHSCT is a resource-intensive procedure that requires specialized centers with extensive experience, limiting its accessibility. The cost of the procedure is another significant barrier. Treatment costs associated with AHSCT include expenses for chemotherapy, stem cell collection, and post-transplant care, which can exceed $100,000. Insurance coverage is not always sufficient, further exacerbating the financial burden on patients. The procedure's long-term effects remain uncertain, and the need for well-controlled clinical trials to refine patient selection and improve treatment protocols remains critical.[12]



CONCLUSION

AHSCT represents a significant step forward in the search for novel treatments for MS, particularly for individuals with aggressive RRMS. By offering a potential means to reset the immune system and achieve prolonged periods of remission or even NEDA status, AHSCT provides hope for improved quality of life and disease management. However, the considerable risks, high costs, and accessibility challenges associated with the procedure necessitate cautious adoption. Rigorous clinical trials and long-term studies are essential to fully understand the efficacy, safety, and cost-effectiveness of AHSCT. As research advances, refining the procedure to mitigate risks, improving patient selection criteria, and addressing economic barriers will be critical steps toward making AHSCT a more accessible and viable option. Ultimately, AHSCT holds promise as a transformative therapy that could reshape MS treatment.

REVIEWED BY: MOHAMMAD KARIMI (PHD STUDENT)

Mohammad Karimi is a PhD student conducting research in the Bhatia Program at McMaster University. He is focused on applying high-throughput and systems-biology approaches to investigate the heterogeneity of Acute Myeloid Leukemia and identify potential therapeutic candidates.

EDITED BY: FIRDOSE KHAN & PATRICIA ZHANG