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Position Statement

Autologous Haematopoietic Stem Cell Transplant (AHSCT) for MS

Background

AHSCT (or bone marrow transplant) is a procedure that has been used to treat a small percentage of people with Multiple Sclerosis (MS) in Australia and internationally. The procedure comprises a number of stages performed over several weeks. Drugs are first used to mobilise haematopoietic (blood and immune system) stem cells from the bone marrow into the blood. Blood is then collected from the patient and the stem cells are separated and frozen.

The patient then receives a 'conditioning' treatment with chemotherapy agents which destroys the cells of the immune and blood system. The extent and duration of immune system suppression can be variable depending on the chemotherapy protocol used (for more information visit here). The patient's own (autologous) haematopoietic stem cells are then thawed and reinfused to overcome the effects of the chemotherapy resulting in a recovery of blood and immune cells over several months. During this time, the patient has severely reduced immune function and is vulnerable to infections and bleeding problems as white blood cells and platelets are affected.

AHSCT is thought to 'reset' the immune system to a less inflammatory or injurious state, reducing the autoimmune attack on the central nervous system. There is no evidence that the procedure initiates stem cell-mediated repair of the nervous system.

A number of international observational studies[1–5] of several hundred patients have been published with some patients being followed for 3 to 10 years. The data from the large European Bone Marrow Transplant Registry demonstrated, at three years of follow-up, that in approximately 64% of people with MS treated with intermediate intensity chemotherapy regimens, inflammatory disease is halted with no evidence of relapses, active brain lesions or disability progression[5]. This is an improvement compared to the period between 1995 and 1999 where approximately 55% of people with MS experienced halting of the disease[1]. While these case series included patients with both relapsing remitting and progressive MS, there has more recently been an increase in the ratio of patients with relapsing remitting to progressive MS undergoing treatment.

A study published in 2021 following people with MS for up to 10 years after treatment at different Italian centres found that 78.1% of people with relapsing remitting MS remained relapse free five years following treatment[3]. After ten years, this dropped to 63.5%. After 5 years, 85.5% of people with relapsing remitting MS had no disability worsening, which decreased to 73.1% after 10 years. For people with progressive forms of MS, 71% had no disability worsening after 5 years which

decreased to 57.2% after 10 years. Another 2021 study which looked at over 500 patients treated between 2003 and 2019 in a single hospital in the US showed that the proportion of people with relapsing remitting MS who remained relapse-free 5 years after treatment was 80.1%[4]. After 4 years, 95% did not experience disease progression. On average, there was significant improvement in disability at 5 years post-treatment[4]. For people with secondary progressive MS, 66% did not experience disease progression up to 4-years post-transplant. While there was some improvement in disability up to 1 year post transplant, longer follow up didn't continue to show improvement.

Overall, most studies show that the risk of disease activity returning gradually increases over time following the treatment[3,4,6] (see here for more information). As with other MS therapies, in some people undergoing AHSCT, there may be a reversal of disability but it is not widespread[4,6]. Other patients may continue to experience disease activity and disability progression (worsening) despite treatment with AHSCT. In people with progressive forms of MS or relapsing remitting MS of longer duration, the benefits of the procedure may be less and accumulation of disability may continue[1,2,4,6,7]. Treatment should be accompanied by recorded long-term follow-up through registries or clinical trials to contribute to ongoing understanding of AHSCT as an intervention for MS

Overall, the current data shows that patients who are relatively young (under 40 years) and still in the active inflammatory phase of the disease (new and active lesions on MRI scans and/or relapses) appear to do better in comparison to patients who are older and/or have no active inflammatory lesions[1,4,6–10]. This is similar to what is seen for some high efficacy disease modifying therapies (DMTs), such as fingolimod[11], alemtuzumab[12,13] and natalizumab[14].

The intense immune suppression of the procedure is associated with severe and potentially life-threatening complications mainly due to infections, however, the risk of death has declined in recent years with advances in supportive care. Experience with AHSCT in patients predominantly with blood cancers in Australia suggests this procedure has a mortality rate of around 1% in the immediate 100 days following transplant (Transplant Related Mortality, TRM)[4]. The European Bone Marrow Transplant Registry data shows that over the last two decades the TRM has significantly improved, with recently reported levels of around 0.2%[9]. Data from the single US hospital study looking at patients treated between 2003 and 2019 recorded a TRM of 0.19%[4]. A number of recently published smaller studies in MS have recorded no deaths (see here for more information). To date there have been no deaths among the approximately 100 people with MS who have received AHSCT in Australian teaching hospitals[15] (Australian MS AHSCT Registry and Australasian Bone Marrow Transplant Recipient Registry).

The risk of infections from bacteria, viruses and fungi remains significant[16]. These infections can result in prolonged hospital stays and may also be associated with neurological worsening[8]. Chemotherapy can be neurotoxic and often patients will

become worse in the immediate post-transplant period due to a combination of infection, deconditioning and the chemotherapy itself. Experience with treating blood cancers over many years, as well as autoimmune disorders, suggests that there may also be longer term adverse effects of AHSCT, such as effects on heart, liver, kidney and bone health, reduction in fertility, secondary cancers and secondary autoimmunity[16].

The risks from treatment will differ depending on the form of chemotherapy used, which may vary slightly from centre to centre. This should be discussed with the treating transplant centre. Over recent years, there has been a trend towards the use of lower intensity chemotherapy regimens for the treatment of autoimmune diseases, which appear safer and better tolerated but still highly efficacious.

There has been one international phase 3 clinical trial that has compared the efficacy between AHSCT and some approved DMTs on MS activity and progression[17]. This study followed 110 people with active relapsing remitting MS over a period of up to five years. On average, participants treated with AHSCT had fewer relapses and less disability progression compared to participants on the approved DMTs. There were also no deaths. However, it is worth noting that only 35% of the DMT group were taking a high efficacy DMT (natalizumab). Further research is required to directly compare the efficacy of AHSCT with other high efficacy DMTs, such as ocrelizumab and other B cell depleting therapies, which weren't included in this trial. These trials are currently underway in several countries around the world and are awaited with interest.

While the long-term effects of AHSCT on the course of MS are still being investigated, the growing evidence base indicates that people with inflammatory MS and who are still experiencing disease activity (relapses or new MRI lesions) despite treatment with available high efficacy DMTs may benefit from AHSCT. There are still significant risks associated with the procedure and therefore this would require careful consideration and planning in consultation with the patient's healthcare team.

MS Australia (with initial support of the MS Society of Western Australia) is funding the Australian MS AHSCT Registry and working with haematologists and neurologists to gather and analyse further data on Australians with MS treated with this procedure. This will contribute to the continuing international effort to better understand the role that AHSCT may play in the range of treatments available for MS.

In the interim, MS Australia provides the guidelines below, to assist those who may be considering AHSCT for the treatment of MS.

Recommendations

As each person's situation is unique and as MS Australia does not have a direct role in the treatment of MS, it cannot recommend any specific treatment for people living with MS. Decisions about any MS treatments, taking into consideration the potential benefits, risks and side effects for an individual's particular circumstances, should be made in careful consultation with each individual's neurologist.

The following recommendations reflect a synthesis of expert views, developed in consideration of current international data on AHSCT for MS (safety and outcomes) in the context of what is known about approved MS therapies, as of January 2022. Should further high-quality evidence emerge concerning the efficacy and safety of AHSCT, then these recommendations will be altered accordingly.

Interim recommendations:

- **The clinical role of AHSCT requires further evaluation in clinical trials and thus is not currently recommended as routine therapy for MS. However, in circumstances where either high efficacy DMTs have failed or are contraindicated (not suitable due to other conditions or risk factors) then it may be reasonable to consider AHSCT for those with active disease. Typical features of such a state might include these disease events, despite treatment with a high efficacy DMT:**

    - One or more gadolinium enhancing lesions on the most recent MRI scan; or
    - Accumulation of new typical T2 lesions on MRIs 6 months apart; or
    - More than 2 clinical relapses in the past 2 years

- **The following factors would be considered as being reasons against considering AHSCT (contraindications):**
    - No relapses on a high efficacy DMT;
    - Progressive disease without relapses or new MRI activity;
    - Age greater than 50 years. The risks associated with AHSCT increase with age, and current data suggests poor response to treatment in this age group;
    - Expanded Disability Status Scale (EDSS) score of 7.0 or greater, except in circumstances of rapidly evolving malignant (or Marburg's) MS, or patients rendered paraplegic by severe spinal lesions early in the disease course;
    - No evidence of inflammatory disease on MRI (no recent new T2 or Gadolinium enhancing lesions);
    - Other medical complications or conditions that may increase the risks associated with AHSCT.

- **MS Australia also recommends that those considering this intervention are assessed and referred to an Australian Haematology Unit, by a neurologist experienced in the diagnosis and treatment of MS and:**
    - The Haematology Unit should be in a major teaching hospital in Australia and has significant clinical experience in treating autoimmune disorders by AHSCT – international studies indicate this reduced the incidence of mortality associated with the procedure in people with MS[1,18].
    - The treatment should be approved by the ethics committee of the hospital and provided as part of a clinical trial and/or inclusion in a registry with long-term follow-up and monitoring to ensure contribution to further understanding of AHSCT as an intervention for MS.

In circumstances where AHSCT is considered an appropriate therapy for an individual, neurologists experienced in the treatment of MS should be able to advise on a suitable Haematology Unit that may be able to provide this treatment.

The above criteria are guidelines aimed at assisting people with MS in understanding the factors that may be taken into consideration by treating clinicians. Provision of AHSCT for MS or other autoimmune disorders in Australia remains entirely at the discretion of the treating hospital and the criteria for treatment may differ to the recommendations in this document.

MS Australia has formed these recommendations in consultation with clinicians and members of the research and MS communities (see below).

As the MS Australia-supported Australian MS AHSCT Registry continues its analysis of the Australian data and further data becomes available from international registries and trials, this position will be revised.

MS Australia will continue to advocate for Australian neurologists and haematologists to work together to deepen our understanding of the safety and efficacy of AHSCT for MS.

For more information and references please visit https://www.msaustralia.org.au/ahsct/autologous-haematopoietic-stem-cell-transplant

References

1. Farge D, Labopin M, Tyndall A, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. *Haematologica*. 2010;95(2):284-292. doi:10.3324/haematol.2009.013458
2. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2012;47(6):770-790. doi:10.1038/bmt.2011.185
3. Boffa G, Massacesi L, Inglese M, et al. Long-Term Clinical Outcomes of Hematopoietic Stem Cell Transplantation in Multiple Sclerosis. *Neurology*. Published online January 20, 2021. doi:10.1212/WNL.0000000000011461
4. Burt RK, Han X, Quigley K, Helenowski IB, Balabanov R. Real-world application of autologous hematopoietic stem cell transplantation in 507 patients with multiple sclerosis. *J Neurol*. Published online October 11, 2021:1-14. doi:10.1007/s00415-021-10820-2
5. 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(27):2742-2755. doi:10.1182/bloodadvances.2017010041
6. Rebeiro P, Moore J. The role of autologous haemopoietic stem cell transplantation in the treatment of autoimmune disorders. *Intern Med J*. 2016;46(1):17-28. doi:10.1111/imj.12944
7. Mancardi G, Saccardi R. Autologous haematopoietic stem-cell transplantation in multiple sclerosis. *Lancet Neurol*. 2008;7(7):626-636. doi:10.1016/S1474-4422(08)70138-8
8. Burt RK, Balabanov R, Han X, et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. *JAMA*. 2015;313(3):275-284. doi:10.1001/jama.2014.17986
9. 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(7):391-405. doi:10.1038/nrneurol.2017.81
10. Sharrack B, Saccardi R, Alexander T, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant*. 2020;55(2):283-306. doi:10.1038/s41409-019-0684-0
11. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Lond Engl*. 2016;387(10023):1075-1084. doi:10.1016/S0140-6736(15)01314-8
12. Coles AJ, Wing MG, Molyneux P, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol*. 1999;46(3):296-304. doi:https://doi.org/10.1002/1531-8249(199909)46:3<296::AID-ANA4>3.0.CO;2-#
13. Paolillo A, Coles AJ, Molyneux PD, et al. Quantitative MRI in patients with secondary progressive MS treated with monoclonal antibody Campath 1H. *Neurology*. 1999;53(4):751-757. doi:10.1212/wnl.53.4.751
14. Brandstadter R, Katz Sand I. The use of natalizumab for multiple sclerosis. *Neuropsychiatr Dis Treat*. 2017;13:1691-1702. doi:10.2147/NDT.S114636
15. 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;90(5):514-521. doi:10.1136/jnnp-2018-319446

16. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2012;47(3):337-341. doi:10.1038/bmt.2012.5
17. 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(2):165-174. doi:10.1001/jama.2018.18743
18. Pasquini MC, Voltarelli J, Atkins HL, et al. Transplantation for autoimmune diseases in north and South America: a report of the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 2012;18(10):1471-1478. doi:10.1016/j.bbmt.2012.06.003

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