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Position Statement

Autologous Haematopoietic Stem Cell Transplant (AHSCT) for MS

Background

AHSCT (or bone marrow transplant) is an immunosuppressive chemotherapy treatment combined with reinfusion of blood stem cells to re-build the immune system. It has been used to treat a small percentage of people with multiple sclerosis (MS) in Australia and internationally.

AHSCT consists of a preliminary treatment (a drug or a combination of drugs) to mobilise haematopoietic (blood and immune system) stem cells from the bone marrow. Blood is then collected from the patient and the stem cells are separated and stored. 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 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 and so reduce the autoimmune attack on the central nervous system. There is no current evidence that the procedure initiates stem-cell mediated repair of the nervous system.

A number of international observational studies[1,2] of several hundred patients have been published with some patients being followed for five to eight years. The data from the large European Bone Marrow Transplant Registry suggests that in approximately 55% of people with MS, treated with a range of different chemotherapy regimens, at three years of follow-up, inflammatory disease is halted with no evidence during the follow-up period of relapses, active brain lesions or disability progression[1]. After 5 years approximately 45% of people remain progression free[1]. This case series included patients with both relapsing remitting and progressive disease. Other smaller studies have shown similar results, with remission of disease seen in these studies in at least 63% of patients followed for a minimum of three years[6]. Most studies also show that the risk of disease activity returning gradually increases over longer periods of follow-up[6] (see here for more information). In some, but not all, of the people with MS who respond to AHSCT, some reversal of disability has been noted in some studies[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 have been much less clear and accumulation of disability usually continues[1,2,6,7].

Patients who are relatively young (under 40 years) and still in the active inflammatory phase of the disease appear to do better in comparison to patients who are older and/or have no active inflammatory lesions[1,6,7]. This is similar to results seen in trials of other highly effective treatments for relapsing remitting MS.

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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 entire published period from 1996 to 2007, 13 of 345 people with MS treated with a number of different conditioning regimes died of transplant related causes, with a 100 day TRM of 2%[1]. However a lower 100 day TRM of 1.3% was recorded for people with MS treated between the years 2001 and 2007[7]. A number of recently published smaller studies in MS have recorded no deaths (see here for more information). To date there has been no mortality among the approximately 50 people with MS who have received AHSCT in Australian teaching hospitals (unpublished data, Australian MS AHSCT Registry and Australasian Bone Marrow Transplant Recipient Registry). Despite the decline in mortality from the procedure, the risk of infections from bacteria, viruses and fungi remains significant[5]. These infections can result in prolonged hospital stays, and may also be associated with neurological worsening[8]. 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[5]. These risks will differ depending on the form of chemotherapy used, and this should be discussed with the treating haematology centre.

Large scale randomised clinical trials have not been conducted to determine the efficacy of AHSCT in comparison with approved MS medications, and most importantly its long term effects on the course of MS have not been definitively established. The overall efficacy of the treatment is, therefore, considered to be unknown. Combined with the potential risks associated with the procedure, this means that Australian hospitals and clinicians are appropriately cautious in their approach to AHSCT for MS.

MS Research Australia (with the 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 Research 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 Research 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.

MS Research Australia understands and acknowledges that people with MS will wish to explore all potential avenues of treatment. However, rigorous evidence for the efficacy and safety of AHSCT in relation to other MS therapies, and the most appropriate circumstances

for its use, is required for Australian hospitals and clinicians to provide this intervention with equity and with greater confidence in the potential outcomes.

The following interim 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 standard MS therapies, as of December 2015. 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 remains uncertain and thus at the present time cannot be recommended as routine therapy for MS. However, in circumstances where either other appropriate therapies 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, rapidly evolving disease. Typical features of such a state might include:**
    - One or more gadolinium enhancing lesions on the most recent MRI scan despite other treatments; or
    - Accumulation of greater than two 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 highly activity disease-modifying treatment
    - Age greater than 50 years. The risks associated with AHSCT increase with age, and current data suggests poor response to treatment;
    - Duration of disease more than 10 years. Treatment appears to show less evidence for effectiveness in MS of longer duration;
    - 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 Research Australia also recommends that those considering this intervention are assessed and referred to a Haematology Unit, by a neurologist experienced in the diagnosis and treatment of MS and:**
    - The Haematology Unit should be in a major teaching hospital and has significant clinical experience in treating autoimmune disorders by AHSCT – international studies suggest that this may reduce the incidence of mortality associated with the procedure in people with MS.[1, 3]
    - The treatment should be ethically approved by the hospital and provided as part of a clinical trial and/or inclusion in a registry with long-term follow-up to ensure contribution to further understanding of AHSCT as an intervention for MS.

In circumstances where AHSCT is considered to be a possible avenue to pursue 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 Research Australia has formed these recommendations in consultation with clinicians and members of the research and MS communities (see below).

As the MS Research 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 Research 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.

References

1. Farge, D., M. Labopin, A. Tyndall, A. Fassas, G.L. Mancardi, J. Van Laar*, 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): p. 284-92.
2. Snowden JA, Saccardi R, Allez M, Ardizzone S, Arnold R, Cervera R, Denton C,Hawkey C, Labopin M, Mancardi G, Martin R, Moore JJ, Passweg J, Peters C, Rabusin M, Rovira M, van Laar JM, Farge D; EBMT Autoimmune Disease Working Party (ADWP); Paediatric Diseases Working Party (PDWP). Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2012 Jun;47(6):770-90. doi:10.1038/bmt.2011.185. Epub 2011 Oct 17.
3. Pasquini, M.C., J. Voltarelli, H.L. Atkins, N. Hamerschlak, X. Zhong, K.W. Ahn*, 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*, 2012. **18**(10): p. 1471-8.
4. Australasian Bone Marrow Transplant Recipient Registry 2014, Australasian Bone Marrow Transplant Recipient Registry: Annual Data Summary 2013, ABMTRR, Darlinghurst, NSW, Australia http://www.abmtrr.org/index.php/annual-data-summary/
5. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C, Burns LJ, Chaudhri N, Davies S, Okamoto S, Seber A, Socie G, Szer J, Van Lint MT, Wingard JR, Tichelli A; Center for International Blood and Marrow Transplant Research (CIBMTR); American Society for Blood and Marrow Transplantation (ASBMT); European Group for Blood and Marrow Transplantation (EBMT); Asia-Pacific Blood and Marrow Transplantation Group (APBMT); Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ); East Mediterranean Blood and Marrow Transplantation Group (EMBMT),; Sociedade Brasileira de Transplante de Medula Ossea (SBTMO. Recommended screening and preventive practices for long-term survivors after hematopoietic cell

transplantation. Biol Blood Marrow Transplant. 2012 Mar;18(3):348-71. doi: 10.1016/j.bbmt.2011.12.519. Epub 2011 Dec 13.
6. Rebeiro P, Moore J. The role of autologous haemopoietic stem cell transplantation in the treatment of autoimmune disorders. Intern Med J. 2015 Nov 2. doi: 10.1111/imj.12944. [Epub ahead of print] Review.
7. Mancardi G, Saccardi R. Autologous haematopoietic stem-cell transplantation in multiple sclerosis. Lancet Neurol. 2008 Jul;7(7):626-36. doi:10.1016/S1474-4422(08)70138-8. Review.
8. Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K, Yaung K, Helenowski IB, Jovanovic B, Spahovic D, Arnautovic I, Lee DC, Benefield BC, Futterer S, Oliveira MC, Burman J. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis.*JAMA.* 2015 Jan 20;313(3):275-84. doi: 10.1001/jama.2014.17986.

For more information and references please visit www.msra.org.au/autologous-haematopoietic-stem-cell-transplant-ahsct-ms

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