Autologous Haematopoietic Stem Cell Transplant for Multiple Sclerosis

Background and progress in research

Autologous Haematopoietic Stem Cell Transplant (AHSCT), also known as bone marrow transplant, is an experimental form of treatment that aims to reset, or ‘reboot’ the immune system to prevent the autoimmune attack on the central nervous system.

International data indicates that AHSCT may benefit a small proportion of people with MS who are still in the active inflammatory phase of the disease who do not respond to currently available approved treatments. However, it remains a risky procedure with a mortality rate of up to 2% when performed in major teaching hospitals. Mortality rates may be higher in less experienced centres.

This level of risk, the lack of larger scale randomised clinical trials and the availability of a number of clinically proven MS medications, mean that clinicians and hospitals continue to take a cautious approach to AHSCT. MS Research Australia is working with clinicians in the Australian MS AHSCT Register to gather further Australian data on this procedure.

This article reviews the current status of international research into AHSCT for MS.

History of AHSCT for MS

AHSCT has been used for a very small proportion of people with MS world-wide since 1995, following the discovery that a patient who had both leukaemia and MS went into remission for their MS following a bone marrow transplant to treat the leukaemia. Some data from studies of animals with MS-like disease also suggest that the disease could be improved with autologous stem cell transplant (Burt et al, 1995).

A small pilot study of AHSCT for MS was carried out in 1997 in Greece (Fassass et al 1997) with the outcomes providing evidence for benefit in some patients and supporting further larger studies.

This has been followed by several small scale clinical trials, larger case series, and a small number of ongoing randomised trials. This international data is described in more detail below, and indicates that the treatment may be most effective in people with MS who show active inflammatory lesions in brain and spinal cord MRI scans. The results for those who have already entered the secondary progressive phase have been less convincing and AHSCT does not appear to have any efficacy in primary progressive MS.

While AHSCT is a commonly used procedure for people with life-threatening blood cancers, it does carry with it a high risk of serious adverse events and even death (mortality).

A mortality rate of up to 7% was noted in the earlier studies and is primarily associated with the intensive chemotherapy that amongst other side-effects, destroys the immune system and leaves patients temporarily vulnerable to severe infections. The mortality rate has since declined, but remains at a significant rate of between 1.3% for autoimmune diseases overall.
In patients with MS the risk of death associated with AHSCT is approximately 2% in the immediate 100 day period following transplant and rises to 3.7% over the following 5 years (Farge et al 2010).

While severe cases of MS can be fatal the advent of a number of highly effective disease modifying therapies for MS in recent years has led to good control of MS in the majority of individuals. In this light, the high mortality rate and uncertain benefits mean, in many countries including Australia, AHSCT has been largely restricted to patients with severe MS that did not respond to other forms of treatment.

**What is AHSCT?**

Autologous (meaning ‘self’) AHSCT uses adult blood stem cells harvested from the blood or bone marrow of the patient. Haematopoietic stem cells are able to generate new cells of the blood and immune system.

Following a chemical treatment to mobilise stem cells from bone marrow and increase the number of stem cells in the blood, stem cells are harvested from the patient’s blood and frozen. The patient then receives chemotherapy to destroy the immune system. One of two forms of chemotherapy is usually used for MS - BEAM-ATG (intermediate intensity) or Cyclophosphamide-ATG (low intensity). The stored stem cells are then infused back into the patient’s blood stream. These stem cells repopulate the bone marrow and restore the immune system.

The theory behind this form of treatment is that the chemotherapy removes the majority of auto-reactive immune cells that have been attacking the patient’s brain and spinal cord. The stem cell transplant then effectively, ‘reboots’ the immune system.

**Clinical trials and case series**

A number of observational case series of patients undergoing AHSCT for severe MS, have been published in the peer-reviewed scientific literature over the last 10 to 15 years.

The largest case series has been an analysis of the combined data from the European Bone Marrow Transplant Register, published in 2010 (Farge et al, 2010), which looked at AHSCT carried out at centres throughout Europe for a range of severe autoimmune diseases and included 345 patients with MS. The follow-up period of the patients in this series, ranges from less than one year to 10 years following transplant. The overall mortality rate was 5% (for all autoimmune diseases, 2% in the MS patients) and the data showed that 55% of the MS patients were free of disease progression at 3 years and 45% at 5 years following the procedure.

Other published studies include the combined results from individual European countries, including Greece (up to 15 year follow-up of 35 patients with aggressive MS - Fassas et al, 2011), Italy (74 patients with a follow up of between 4 and 10 years – Mancardi, et al 2012) and Sweden (48 patients with up to 9 years follow-up - Burman et al, 2014). Case series from single clinical centres have also been published, including from the Czech Republic (26
patients with a median of 4 years follow-up - Krasulova et al, 2010) and Russia (95 patients with different types of MS followed up over an average of 4 years - Shevchenko et al, 2012) and the USA (21 patients with relapsing remitting MS with an average follow-up of 3 years - Burt et al, 2009).

Directly comparing the outcomes of the various studies is difficult as patient selection criteria, proportion of relapsing remitting and progressive patients, treatment protocols, and follow-up measures vary between the studies. However, there are common themes emerging from all of the data.

**Effects on disability, relapses and lesions**

Five year progression free survival (a measure of the probability of disease activity within the first 5 years following the treatment) is highly variable between the published studies, ranging from 92% in the Russian study to 55% for the European Bone Marrow Transplant Registry. The majority of studies have shown significant reduction or complete disappearance of relapses and no new or gadolinium enhancing lesions in MRI scans for a majority of patients with relapsing disease.

All of the studies indicate that patients who have gadolinium enhancing lesions on MRI scans prior to AHSCT (indicating active inflammation) appear to do much better (cessation of relapses, reduction of active lesions seen on MRI and stabilisation or improvement of EDSS* score), compared to those who do not have active lesions.

(* EDSS is a nonlinear scale of 0 – 10 representing disability ranging from no disability (zero) through to death (ten*))

For example, the recently published Swedish study shows that 5 year progression free survival for patients with gadolinium enhancing lesions is 79%, compared to 46% in those without gadolinium enhancing lesions.

While EDSS scores appear to stabilise, or in some cases improve, in many people with relapsing remitting disease, all of the studies show that recovery from more long standing progressive disease is unlikely and in fact disability continues to accumulate. For example, the study from the Czech Republic showed that overall 70% of patients showed no disease progression at 3 years following the treatment but at 6 years only 29% of patients remained free of disease progression (Krasulova et al, 2010). In the Italian study (Mancardi et al, 2012) 18 patients were followed for more than 7 years. Of these, 44% remained stable or had sustained improvement in disability score, while 56% showed a slow accumulation of disability, despite an early period of stabilisation or improvement.

The majority of the studies indicate that the outcomes are better for people younger than 40 years, those with disease duration of less than 5 years and those with active relapsing disease.

**Different responses of Relapsing and Progressive forms of MS to AHSCT**

There has been a growing recognition among researchers and clinicians that the relapsing
remitting form of MS and the progressive form of MS may be driven by different mechanisms.

Relapsing MS is primarily driven by the T and B cells of the adaptive immune system which invade the brain and carry out a destructive attack on the myelin that insulates nerve fibres. Progressive MS, on the other hand appears to have become ‘uncoupled’ from this inflammatory activity, and may be driven more by an ongoing lower-level of ‘slow-burning’ inflammation driven by the innate immune system cells present in the brain contributing to the progressive degeneration of the nerve fibres themselves.

Italian researchers used MRI studies to show that despite almost complete and long term suppression of inflammation (relapses and gadolinium enhancing lesions) by AHSCT in 10 patients with secondary progressive MS, there was continued significant loss of brain tissue as shown by measures of whole brain volume (Inglese et al, 2004).

In a study carried out in Germany, the brains of five MS patients who had previously received AHSCT were examined after their death (Metz et al, 2007). This detailed study of the brain tissue, nerve fibres and myelin showed that loss of myelin and degeneration of nerve fibres had continued in these patients after the AHSCT despite a great reduction in inflammation.

These studies and the other case series in which both relapsing remitting and secondary progressive MS have been treated, indicate that AHSCT may be effective in suppressing the aggressive inflammation in MS, but is unlikely to prevent continued damage to nerve fibres in people who have already moved into the secondary progressive phase of the disease.

In 2012, the European Bone Marrow Transplant Register published updated guidelines for the use of AHSCT in a range of autoimmune diseases, based on their own data and examination of other studies. Their recommendations are that the ideal target patients for AHSCT in MS are those in the relapsing remitting phase with high inflammatory activity (both clinically and by MRI with gadolinium enhancing lesions) and who are rapidly deteriorating despite one or more lines of approved treatments. Secondary progressive patients should be considered only when some inflammatory activity is still present as shown by new T2 MRI lesions on two subsequent scans or new gadolinium enhancing lesions. Patients who have already lost the ability to walk should not be offered the treatment, other than those with the ‘malignant’ or Marburg form of MS (rapid evolution of disease and disability progression within one year of onset).

Risks and side-effects
As mentioned the number of transplant related deaths vary between the most recent studies, from none reported in the Russian, Czech and Swedish studies, to 2.7% in the Italian multi-centre study.

The experience of the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases published in 2010 describes an overall mortality rate of 2%
for MS patients in the immediate 100 day period following AHSCT and this was closely related to the level of experience of the transplant centres (Farge et al 2010).

The mortality rate for HSCT should be considered in the context of the well-established risks, determined in extensive clinical trials, for the other pharmaceutical therapies currently approved for use in MS, as well as the severity of disease in any given individual.

Examples of common adverse events relating to the AHSCT procedure include thrombocytopenia (low platelet levels in the blood), neutropenia (low white blood cells), hair loss, fever, fatigue, anaemia and liver toxicity. A range of infectious diseases can also occur in the acute treatment period due to the temporary loss of the immune system. Some of these infections can be very serious, including sepsis (whole body inflammation caused by severe infection) and require treatment in an intensive care unit. In the longer term the most commonly reported side-effects are the reactivation of viral infections such as herpes zoster (chicken pox/shingles) and cardiotoxicity (heart damage). AHSCT is likely to make most patients infertile thus sperm or ova cryopreservation should be considered in patients undergoing the treatment.

Some studies have indicated that there is an increased risk of thyroid disease (e.g. Burman et al). An increased risk of developing a secondary autoimmune disorder following AHSCT for autoimmune diseases has also been documented in a series of patients treated in the USA (Loh et al, 2007) who found that nearly 2% of patients treated with the ATG conditioning protocol developed secondary autoimmune disease. The rate was higher in those who received alemtuzumab as a conditioning treatment and this is a known side effect of this medication. Alemtuzumab (Lemtrada), eliminates only T and B cells of the immune system and is now a TGA-approved medication for MS. It is no longer used as a conditioning treatment for AHSCT.

**Can AHSCT make MS worse?**

In the majority of the studies reported above there has been no evidence reported for the AHSCT treatment causing an exacerbation or escalation of MS progression, although MS relapses have been documented in association with the fever and infections resulting from the chemotherapy. However, a number of studies have raised concerns that AHSCT can exacerbate neurodegeneration and brain tissue loss (atrophy) in the immediate period following chemotherapy. The Canadian MS Bone Marrow Transplant Study Group, published data on brain volume measured by MRI scans before and after AHSCT in nine secondary progressive MS patients (Chen et al, 2006). The rate of brain atrophy in the month immediately following AHSCT was 10 times faster than the rate of brain tissue loss prior to AHSCT. At longer periods of follow-up (up to 3 years), the rate of brain atrophy was no different to the period before treatment. This suggests that the chemotherapy causes a rapid but short lasting loss of brain volume which is then followed by a steady rate of brain tissue loss consistent with the rate prior to transplant. The same is seen in the immediate period after Tysabri treatment and is believed to be due to a reduction in inflammation related oedema (swelling caused by fluid).
Dutch and British researchers showed that damage to brain tissue is exacerbated by chemotherapy in patients undergoing AHSCT for MS and cancer (Petzold et al, 2010). They tracked levels of neurofilament in the blood before and after chemotherapy. Neurofilament is a protein normally found inside neurons, and is only released into the blood when neurons are damaged. Levels of neurofilament were increased in the blood for up to 3 months following chemotherapy and this increase was much greater in the people with secondary progressive MS compared to those with cancer.

Italian researchers also showed that there was an initial rapid loss of brain tissue in the early period following AHSCT, but the rate of brain atrophy then slowed down significantly in the second year (Roccataglia et al, 2007 and Rocca et al, 2007). These researchers suggest that the long term rate of atrophy in their small study was slower than observed in people with rapidly progressing secondary progressive MS seen in other studies, however, a direct comparison group would be needed in the same study to confirm this.

What does AHSCT do to the immune system?
Researchers have examined the profile of immune cells found in the blood of people with MS following AHSCT. They have found that T-cells that react to components of myelin do not completely disappear following AHSCT. These ‘self’ reactive cells can expand to larger numbers again from the very few ‘self’ reactive immune cells that may remain in the body following AHSCT. So the potential for further autoimmune disease activity is still present. However, the researchers also found that the balance of pro-inflammatory versus anti-inflammatory immune cells has changed considerably in the reconstituted immune system following AHSCT. In particular, one type of pro-inflammatory cell that is capable of activating other T cells is greatly reduced. This suggests that while the cells that can mount an autoimmune attack are still present, the activation of these cells may be less likely to occur (Sun et al, 2004 and Darlington et al, 2012).

Ongoing trials and studies
Randomised controlled trials (RCT) remain the gold-standard for determining the efficacy and safety of new interventions for diseases. In an RCT, patients are randomly assigned to receive either the experimental treatment or a placebo or active comparator (such as the best available treatment).

A placebo controlled trial in which patients were ‘blinded’ to which group they were in is not possible for AHSCT. Researchers in the European Blood and Marrow Transplantation Group, the Centre for International Blood and Marrow Research and the AHSCT in MS International Study Group have proposed a format for an international multi-centre randomised controlled trial of AHSCT against the ‘best available approved treatment’ (which may differ in each country) (Saccardi et all, 2012). This trial is yet to get underway.

The Autologous Stem Cell Transplantation International MS Trial (ASTIMS) was a collaboration of Italian and British researchers. The trial, designed in 2003 was stopped in
2010 due to very slow enrolment of patients. The patients that were treated in this trial continue to be followed-up with regular MRI scans and clinical examinations. For more information see www.astims.org/multiple-sclerosis-study.html

Professor Richard Burt of Northwestern University, Chicago, USA is conducting an ongoing trial in collaboration with currently four other centres in the UK, Italy and USA, in which patients are randomised to receive either AHSCT treatment or a standard MS treatment such as interferon beta, glatiramer acetate, Tysabri or Gilenya. The trial is set to run until December 2017 (for more information click here).

In Australia, a phase II observational trial (no comparison treatment) is running at St Vincent’s Hospital in Sydney. To date approximately 14 patients have been treated and studied under this trial from both Canberra Hospital and St Vincent’s (for more information click here).

MS Research Australia, in collaboration with a committee of Australian neurologists and haematologists is coordinating and funding (with the support of the MS Society of Western Australia) an Australian MS AHSCT Registry. This is not a clinical trial, but will gather clinical and MRI data on patients who have undergone this procedure in Australia. The goal will be to analyse the data to determine the outcomes in relation to patient characteristics and develop guidelines for treatment (for more information on the registry click here)

References


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