High-dose Immunosuppressive Therapy and Autologous Haematopoietic Stem Cell Transplant (HDIT/HSCT)

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1. Introduction

The aim of this treatment is to "reset" the immune system, so that it will stop attacking the person's own central nervous system. This is done by first collecting the patient's own multipotent haematopoietic stem cells (HSCs) from either the bone marrow or blood. The patient is then given high-dose chemotherapy to deplete the immune system by destroying the cells within the bone marrow. Finally, the stem cells are re-introduced to the peripheral blood where they develop into red and white blood cells and re-establish their immune system [1].

Because this is such a high-risk procedure, it has traditionally been used for the treatment of life-threatening cancers. However, the success rates of the procedure have been continually increasing and so 20 years ago, it began to be investigated for use in autoimmune diseases such as MS.

2. Clinical Trial Evidence

2.1. Sormani et al. Meta-Analysis

There have already been several clinical trials for HDIT/HSCT in MS, completed outside of New Zealand. A recent meta-analysis by Sormani et al. has summarised the studies done to date [2]. They included all published studies of HDIT/HCT in any form of MS from 1995 to 2016. The three end points evaluated were transplant-related mortality, rate of disease progression, and no evidence of disease activity status. Progression events were defined according to an increase of Expanded Disability Status Scale score (EDSS) (1 point for baseline EDSS ≤5.5, 0.5 points for baseline EDSS >5.5, confirmed at 6 or 12 months). Patients were defined as presenting no evidence of disease activity (NEDA) over a given period of time if they did not experience any clinical relapse, disability progression, or any new MRI lesion (T2 or gadolinium-enhancing) over that period.

The authors included 15 studies with a total of 764 patients contributing 2,680 patient-years. The median age was 35.7 years and median EDSS was 5.6. Over all 15 studies, 44% of patients were classified as having relapsing-remitting multiple sclerosis (RRMS).

Transplant-related mortality is perhaps the most important outcome to first assess. Sormani et al. found that 2.1% of patients died within 100 days of stem cell transplantation. However, further analysis showed that in studies done after 2005, only one death was reported out of 349 patients (0.3% TRM), whereas the TRM was 3.6% in the 415 from the older studies. An important distinction illustrating the increasing safety of the procedure. A lower risk of TRM is also associated with patients who were younger at the time of transplantation, had RRMS rather than progressive MS and with a lower baseline EDSS.

Rate of disability progression (as defined above) found throughout the studies was 17.1% at 2 years after transplantation. However, this varied widely among the studies and the only factor noted as having a significant effect on this was an RRMS diagnosis, as opposed to a progressive one. In the studies which included less than 44% of RRMS patients, the rate was 24.8%, and in those with more than 44% of patients with RRMS, the rate was 7.8%. The authors note that this is comparable, if not perhaps a little higher than studies of new disease modifying treatments (DMTs) in RRMS. Such as the recent results from the recent ocrelizumab study which show a disability progression rate of 6.9% at 24 weeks [3]. However, it must be pointed out that it is difficult to compare outcomes from a clinical trial for a DMT and those for a study of HDIT/HSCT. The patients eligible for the latter generally have more aggressive or advanced MS than those enrolled in clinical trials. For example, in the HALT-MS Clinical Trial which examined HDIT/HSCT[4] the inclusion criteria required that patients have RRMS with a baseline EDSS of between 3.0 and 5.5. Importantly, they must have had failure of disease modifying treatments, defined as 2 or more clinical relapses during 18 months of treatment that were associated with an increase in the EDSS score (by 1.0 for pre-relapse EDSS score of 3.0–3.5 or by 0.5 for an EDSS score of 4.0–5.5 and sustained for ≥4 weeks). Compare this to the randomised controlled trial which was recently undertaken for Ocrelizumab, a new disease modifying treatment[3]. In this trial, patients were also required to have RRMS, but allowed a more permissible baseline EDSS of 0.0 – 5.0. The mean EDSS was between 2.75 (±1.29) and 2.86 (±1.24) for the four groups. Importantly, the demographic results show that between 71.4% and 75.3% of the included population had had no previous treatment with a disease modifying treatment. This high percentage, combined with a low baseline EDSS score indicates a less severe degree of MS.

The ultimate aim of any MS treatment is an outcome of no evidence of disease activity (NEDA), and this was assessed in 5 of the 15 studies (274 patients), 2 years after transplantation. The proportion of NEDA patients at this timepoint was an impressive 83.4%. For those studies where NEDA was measured at 5 years, the proportion was 67%. This is where HDIT/HSCT and DMTs can be easily separated as this is much higher than reported for even the most effective DMTs [5].

2.2. HALT-MS Clinical Trial

One of the most recent and impressive clinical trials included in the Sormani et al. analysis is the HALT-MS clinical trial [4], the 5-year results from which have been published in February 2017. The study includes a small sample size (n=24), but the most impressive results to date from a HDIT/HSCT study. The sample population was 100% RRMS, with an EDSS of 3.0-5.5 at baseline, MRI visible brain lesions, disease duration of <15 years and experiencing treatment failure on DMT.

Most importantly, there were no treatment-related deaths. Event-free survival (EFS) was the primary outcome, and defined as survival without death or disease activity from any one of: disability progression, relapse, or new lesions on MRI. At four years post-transplant, 73.8% of participants retained this outcome, and 69.2% at 5 years. 7 out of the 24 participants did not maintain EFS by the close of follow-up, however relapse activity was reduced in these participants,

compared to pre-treatment. This was achieved without post-transplant maintenance therapy with DMTs.

3. New Zealanders Seeking Treatment Internationally

HDIT/HSCT is currently an approved treatment for MS in several countries around the world, including Russia, Israel, India and Mexico. Some MS patients in New Zealand are now viewing treatment internationally as a viable option and taking on huge financial costs to have the treatment overseas. There have been many personal stories reported on in the media [6–8], and pages can be found on the Give A Little website where some fundraisers are trying to meet goals of up to $200,000 to fund their treatment [9,10]. It is clear that some New Zealanders are taking matters into their own hands.

However, this option not only poses a financial burden, but also a considerable health risk. The standards of medical care in the countries offering this treatment are not always the same as enjoyed in New Zealand. Should the treatment not go to plan, the patient be harmed by the treatment, or be the victim of medical misadventure, they may be in a situation where they do not have any method of recourse in the country where the treatment was done. Fortunately for the patient, if they can return to New Zealand, further treatment would most likely be covered by ACC, as long as they meet certain conditions such as; the treatment was given by a registered health professional, and the patient is normally a New Zealand resident[11]. However, this would be at a great cost to the New Zealand health system and require that New Zealand health professionals provide support without having any involvement in the initial treatment or treatment decisions.

The best option for the New Zealand MS community is to have an HDIT/HCT treatment available in New Zealand, which has been evaluated by the Ministry of Health as being effective and providing sufficient benefit to warrant the risks. This would also ensure that only the patients who the evidence shows would benefit from HDIT/HSCT, could undergo the treatment.

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