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The use of Autologous Haematopoietic Stem Cell Transplants in patients with Relapsing Remitting Multiple Sclerosis: A Meta-Analysis

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INTRODUCTION

Multiple Sclerosis (MS) is a progressive incurable autoimmune disease affecting the myelin sheaths and occasionally the underlying axons in the central nervous system. MS is a condition made up of 4 sub-types with Relapsing-Remitting MS (RRMS) affecting 85% of MS sufferers. RRMS has a wide and varied range of clinical presentations but most commonly involves fatigue, dysarthria, dysphagia, muscle weakness, incontinence as well as cognitive impairment.

Around 65% patients with RRMS will subsequently progress to Secondary Progressive MS (SPMS) where symptoms get progressively more severe with no remission or plateau. The disease at this stage is typically more treatment resistant as the phase is characterised as a period of irreversible axonal degeneration.

There has been an increase in the number of drugs available for MS including around 10 disease modifying drugs including the newly approved CD52 antagonist, Alemtuzumab (1,2). Despite this, less than 20% of patients experience no evidence of disease activity after 4 years of treatment (3). Along with poor prognosis, the cost of gold standard Disease Modifying Therapies (DMT) treatment can be prohibitively high for many healthcare systems.

One alternative to DMTs is the use of Autologous Haematopoietic Stem Cell Transplantations (aHSCTs) to selectively remove aberrant immune cells.

The use of this method has been reported numerous times since 1999, but studies published so far have frequently used patient groups with varying levels of disease progression across all MS sub-types while also using different primary and secondary outcomes to measure success. This means that despite over 1000 patients being described in literature, it is very difficult to describe with certainty the prognosis of RRMS after treatment with aHSCT. As RRMS is by far the most common sub-type, demonstrating the safety and efficacy of its treatment with this intervention could lead to widespread adoption in a clinical setting.

AIM

To describe in as much detail as possible the safety and efficacy of using aHSCTs in patients with Relapsing-Remitting Multiple Sclerosis in the form of a meta-analysis. Secondary aims include comparing these results to the safety and efficacy of current gold standard disease modifying therapies as well as suggesting subsequent studies that could be undertaken that would best develop current understanding.

METHODS

Search Strategy

Studies were identified and collected through several different databases including Google Scholar, PubMed, Web of Science, Cochrane library, clinicaltrials.gov, controlled-trials.com and finally the European Society for Blood and Marrow Transplantation- Autoimmune Disease Working Party (EMBT-ADWP). The dates search limits were between 1st January 1999 and 1st May 2020. Search terms included 'Multiple Sclerosis' and '(Autologous) h(a)ematopoietic stem cell transplantation'.

Data Analysis

The primary outcome measurement in this meta-analysis was Expanded Disability Status Score (EDSS); where this was unavailable Progression Free Survival was used as a proxy. Secondary outcomes included percentage Event Free Survival, Progression Free Survival, Treatment Related Mortality (defined as death within 100 days of aHSCT) and general mortality.

EDSS is a universally accepted scale measuring from 0-10 with 0.5-point increments for assessment of MS disease severity with 0 representing an individual not suffering from MS to 10, indicating that a patient has died due to MS.

RESULTS

Ten studies [4-13] including 319 patients with RRMS, who failed initial DMTs, were included in the review. All patients were initially alemtuzumab naïve. Mean baseline in the studies EDSS were 1.5-6.3. Six studies used myelo- and lympho-ablative BEAM-ATG conditioning; the others used lympho-ablative cyclophosphamide with ATG (or alemtuzumab in a minority of patients).

Event-free survival to five years was highly variable between studies ranging from 0% to 100%. Progression free survival saw similarly high levels of variation.

The available data showed a mean EDSS reduction from a baseline of 4.07 (2dp) to 3.18 at five-year follow-up. Studies with lower pre-aHSCT EDSS experienced the greatest reduction in EDSS.

All-cause mortality across the studies was 2.19% (2dp); treatment related mortality was 0.63%.

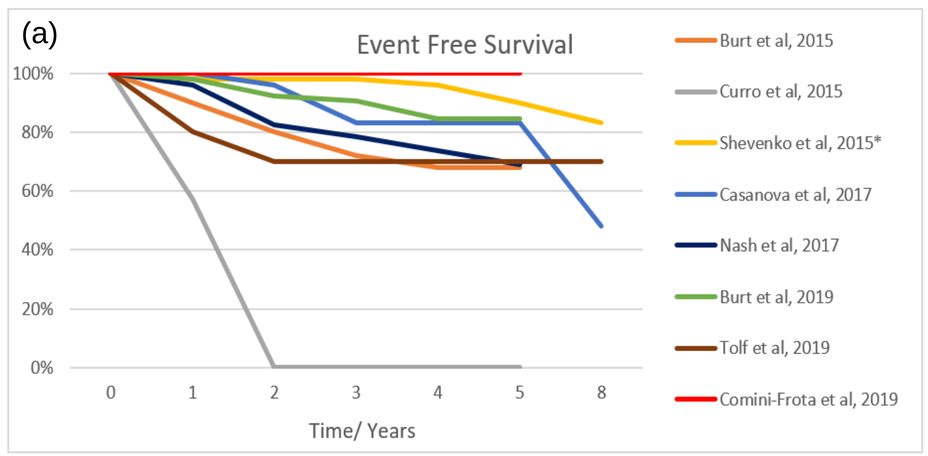

Figure 1: Visualisation of secondary outcome measures up to 8 years post aHSCT.

(a) Event free survival. Mancardi et al did not include data on event free survival so was not included. Shevchenko et al defined an event as a relapse or progression only with all other studies included new MRI lesions, so true event free survival is likely to be lower. Note the lack of data for years 7 and 8. (b) Progression free survival.

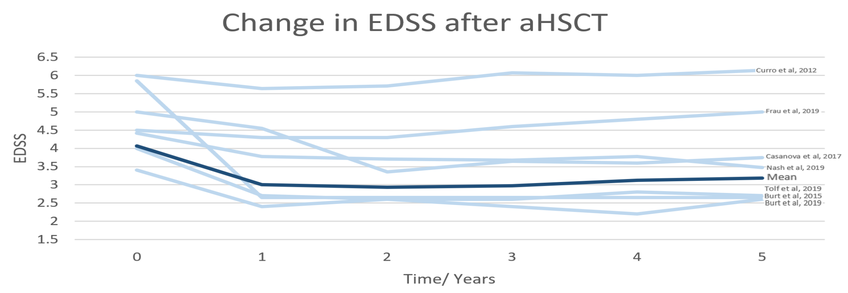

Figure 2: EDSS change to 5 years.

Light blue lines indicate individual studies, Dark blue lines indicate mean EDSS change for the treatment arm. Three papers did not report annual EDSS change so were excluded.

CONCLUSIONS

After relatively recent refinement to aHSCT that reduces mortality and morbidity, it is a plausible treatment for patients with auto-immune conditions such as RRMS. Compared to DMTs, its offers greater efficacy and cost effectiveness. The benefits are seen particularly in younger patients, those with a lower EDSS, and a shorter disease duration and patients who have not yet progressed to secondary progressive MS.

With this study and additional trials, particularly those with adverse effects and long-term outcome beyond 5 years as primary outcomes, it is hoped that aHSCT will become a mainstream treatment for patients with early-stage RRMS.

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