A Global Study of Haematopoietic Stem Cell Transplantation in Multiple Sclerosis and Other Neurodegenerative Disorders

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Abstract

Aim: The aim of this research is to understand the uptake of haemopoietic stem cell transplantation (HSCT) in neuroimmunological disorders like multiple sclerosis (MS).

Methods: A global internet survey was conducted of people having had HSCT, comparing demographics, treatment protocol, and effectiveness.

Results: Of 271 participants useful data was available in 223. 73.5% were female in the age range of 35-54 years, most had a household income greater than US$50,000 and the majority of participants were from Australia and the United States of America. 94.6% had MS. Most had their treatment in Russia (38.7%) and 78.1% had non-myeloablative transplants. Nearly half of the participants spent between US$50,000 to US$74,999. 54.5% of neurologists were not supportive of their patients having HSCT. 85.5% of participants believed HSCT helped them manage their disease from weeks to years after transplantation. 9.45% would recommend the treatment. The average reduction in Expanded Disability Status Score after transplantation was 1.2 [95% CI; 0.97-1.41; N=197; $p < 0.0001$; t: 10.7, df 196].

Conclusions: Participants were supportive of HSCT despite the costs and would recommend it to others. The data suggest some benefit in minimizing disability in MS and provides justification for large randomized controlled trials.

Introduction

Stem cells are defined as “unspecialized or undifferentiated cells with the ability to self-renew and to differentiate to produce specialized cell types in the body”.[1] Stem cells have specific functions and characteristics. Primarily, stem cells are able to divide and renew themselves for long periods of time. In addition, they are unspecialized; i.e. they do not have specialized cell functions. Therefore, they can give rise to specialized cells. Stem cells undergo differentiation, becoming more specialized at each step. There are multiple types of stem cells currently used. Embryonic stem cells are obtained from the inner cell mass of a blastocyst and are formed 3–5 days after sperm fertilization. These cells are typically used in IVF. Tissue-specific stem cells are somatic stem cells which generate different cell types for specific tissue or organs and are generally used when treating injury and/or disease. Mesenchymal stem cells are grown from other tissues, like fat and cord blood, and can make bone, cartilage and fat cells. They are important for making and repairing skeletal tissues. Finally, induced pluripotent stem cells are engineered in the laboratory by converting tissue specific cells to behave like embryonic stem cells. They are currently being used in disease modelling and premature aging research, congenital heart disease and cancer research. Stem cells can be obtained in two primary ways: autologous (sourced from the patient themselves) or allogenic (sourced from a donor).[1]

Hematopoietic Stem Cell Transplantation (HSCT) occurs when patients are intravenously infused with autologous or allogeneic stem cells to re-establish hematopoietic function.[2] There are two main procedural conditioning regimes which involve the delivery of maximally tolerated doses of multiple

chemotherapeutic agents: myeloablative and non-myeloablative. Myeloablative regimens are designed to kill all residual cells to cause immunosuppression.[2] Non-myeloablative regimes are immunosuppressive.[2] More than 50 000 HSCTs are performed worldwide every year and the number is increasing annually by approximately 10–20%.

A major use of stem cells is treating neuroimmunological conditions. A common neuroimmunological disorder is multiple sclerosis (MS), which is characterized by persistent inflammation in the brain and spinal cord causing the destruction of CNS neurons and myelin.[3] MS causes neurological disability, which can occur over a period of a few weeks.[4] In addition, the disease is most often progressive, in which disability accumulates over years and ultimately 40% of patients require a wheelchair within a period of 10 years from initial diagnosis.[4] The disease is incurable; however, over the past 30 years, stem cell therapy has gained credence as a treatment.[4] In order to stimulate the regeneration of myelin, one strategy used is the demyelination by stimulation of endogenous stem cells.[3] There are now a number of clinics both within Australia and globally that offer stem cell treatment for MS and other neuroimmunological disorders.

This paper aims to investigate the utilization of HSCT in neuroimmunological disorders on a global basis: who is having it, where the treatment is being performed, and what are the costs. Treatment specifics—including treatment location, myeloablative and non-myeloablative procedures, and waiting times—are examined. Neurologists attitudes to HSCT are considered, along with patient satisfaction. Data will be informative in providing information on the viability of HSCT as a legitimate therapy. There is a great concern that people are spending money on treatment that is unproven.

Methods

Data was gathered using an internet survey, which was performed via the social media platform, Facebook, and facilitated through SurveyMonkey. A series of 21 questions was developed. These questions were designed to gain a broad understanding of the demographics of patients undergoing HSCT, information on treatment protocol and overall success of the treatment (see **Supplementary Table 1**). The survey was then posted on Facebook. Participants self-selected to complete the survey. Participants were informed that they were partaking in an anonymous study to gain a wider understanding of the use of stem cells to treat neuroimmunological disorders. Statistical analyses of the Expanded Disability Status Score (EDSS), used in MS to measure function, were measured by the participant's neurologist before and after transplantation and was analyzed using the paired *t* test.

Ethics approval of the protocol and procedures was provided by Neurodegenerative Disorders Research Pty Ltd Human Research Ethics Committee (NDR.HREC) (#NDR-2018-0309). All research was performed in accordance with NDR.HREC guidelines. Informed consent was obtained from all participants who took part in the study.

Results

There were 271 participants. Of these, 223 had HSCT; 45 participants are not included in the analysis.

Of the participants that received HSCT, 73.5% were female. Most were in the age range 35–54 years (Table 1). The majority of participants had a household income greater than US$50,000 (Table 2). The greatest number of participants came from Australia and the United States (Fig. 1).

Table 1
Percentage of respondents in relation to age

Age	Respondents (%)
18–24	1.34
25–34	4.03
35–44	31.84
45–54	39.91
55–64	19.20
65 & over	3.59

Table 2
Percentage of respondents in relation to total household income

Total household income (US$)	Respondents (%)
< $18,000	3.14
$18,000-–$29,999	8.07
$30,000–$49,999	7.62
$50,000–74,999	17.94
$75,000–$99,999	22.87
$100,000–$149,999	17.49
> $150,000	20.63

94.6% of participants were suffering from MS. 2.7% had Chronic Inflammatory Demyelinating Polyneuropathy. There were two participants with Stiff Person's Syndrome, and one person for each of clinically isolated MS, scleroderma, Polyneuropathy, Organomegaly, Endocrinopathy, Myeloma Protein Syndrome (POEMS) and neuromyelitis optica (NMO).

The preponderance of participants had their treatment in Russia (38.7%) (Fig. 2). 78.1% of participants had non-myeloablative treatment, the others myeloablative.

Treatment costs ranged from less than US$15,000 to greater than US$150,000, with nearly half of the participants spending between US$50,000 to US$74,999 (Table 3 **).** Most participants waited from 3 to > 12 months before treatment (Table 4).

Table 3
Percentage of respondents in relation to treatment cost

Total household income (US$)	Respondents (%)
< $15,000	7.65
$15,000-–$29,999	0.90
$30,000–$49,999	10.36
$50,000–74,999	45.50
$75,000–$99,999	17.12
$100,000–$149,999	12.16
> $150,000	6.31

Table 4
Percentage of respondents in relation to waiting times prior to treatment

Waiting time (months)	Respondents (%)
< 1	4.50
1–2	6.31
3–5	31.53
6–8	21.17
9–11	12.61
> 12	23.86

54.5% of neurologists were not supportive of their patient receiving HSCT treatment. Post-treatment, 65.5% of neurologists continued patient care. In addition, 65.0% of participants continued to see the same neurologist before and after stem cell treatment.

83.33% of participants were satisfied with the level of post-treatment care. Participants saw five types of medical specialists following HSCT: neurologist, hematologist, general practitioner, rheumatologist and physiotherapist. On average, additional costs amounted to approximately US$13,800, including travel and accommodation for family members, meal costs, etc.
Of the 223 participants that have had HSCT, 85.5% either agreed or strongly agreed that the treatment has been successful in managing symptoms of their disease. Participants reported that their symptoms had

improved. This occurred early following the operation, i.e. immediately, to weeks, months and a few years. Some participants reported no change. In addition, 95.4% of participants would recommend the treatment to other people.

The EDSS was recorded by the participants neurologist before and after stem cell transplantation. The scores before and after treatment are tabulated in **Supplementary Table 2**, along with the differences. The average reduction in EDSS after treatment was 1.2 (95% CI: 0.97–1.41) among 197 participants ($p < 0.0001$; *t* value: 10.7, df 196) suggesting a significant difference (see Fig. 3). There were 17 participants whose EDSS scores were higher after transplantation, with 50 participants whose scores remained unchanged – 130 participants showed an increased score (see Fig. 3).

Discussion

The US Food and Drug Administration regards stem cell therapy as an experimental treatment, even though there is some promise that it might be effective in treating autoimmune diseases.[5] In addition, HSCT may improve quality of life and outcomes for patients.[5] Despite a misunderstanding that HSCT is yet to be established as a therapeutic treatment, the first transplants were successfully performed in the mid-1990s.[5] However, it is recognized that autologous HSCT can be highly effective in suppressing relapses and is cost effective when compared with other approaches.[5] The use of HSCT was reviewed in relation to quality of life following autologous HSCT.[5] Focusing on systemic sclerosis, 289 patients underwent HSCT and there were improvements noted in 275 patients who were assessed using Health Assessment Questionnaire-Disability Index.[5] This is consistent with the improvement in EDSS seen in our patients.

However, it is alleged that almost half of clinicians at stem cell clinics lack sufficient credentials to offer treatment for conditions that they claim to treat.[6] 52% of companies that advertised stem cell treatment had at least one physician with training to match the disorders they claimed to treat.[7] Sean Morrison, director of the Children's Medical Research Institute at the University of Texas Southwestern Medical Centre in Dallas claimed that "it's more evidence that companies are willing to sell unproved products to desperate patients and are just willing to ignore all kinds of best practices in terms of the medicine that they perform".[6] Clinicians that are providing treatment outside their training greatly increases risks to patients.[7]

Additionally, US Food and Drug Administration regulations regarding the safety and effectiveness of products are ignored, resulting in infections following treatment.[6] Twelve patients across three states of the USA have contracted septicaemia, joint and other infections as a result of using non-Food and Drug Administration approved stem cells.[8] Recently, a permanent injunction requiring US Stem Cell Clinic to stop marketing adipose-derived treatment was granted by a US District Court following serious complications including loss of sight in a patient.[9] This highlights that the treatment is experimental and that there are serious potential risks to patients.[8]

Although HSCT is legal, this doesn't necessarily make it ethical and it is often stated that HSCT is 'easy money' for doctors and hospitals due to the high cost of treatment.[10] Insurance companies are not generally involved, due to the treatment being largely experimental and self-funded.[10] Leigh Turner, an Associate Professor at the University of Minnesota's Centre for Bioethics, has stated that "it's an out of pocket, cash-on-the-barrel economy. Across the country, clinicians at elite medical facilities are lining their pockets by providing expensive placebos".[10] Dr James Rickert, president of the Society for Patient Centered Orthopedics, states that "it preys on people's desperation".[10] However, between 40–70% of patients have found some level of pain relief and 75 to 80% have had significant pain relief with improved function.[10] In our study, it was observed that mean EDSS decreased; one participant found that at 6 years post-transplantation, her EDSS was 1, having been 6 prior to treatment, and she was now able to run marathons — the potential benefits might outweigh the relatively unknown risks.[11]

'Medical tourism'—travelling abroad to obtain medical services—is relevant to HSCT.[12] Over 15 million US patients travel internationally for medical care.[12] In that study, 67.69% of patients who lived in the US travelled to other countries to receive HSCT. Monterrey and Puebla in Mexico were the most common destinations; Moscow, Russia was second. This probably relates to the cost: Mexican treatment, approximately US$50,000, was significantly lower than that of the United States. Chicago was the most common destination in the USA for HSCT, with a cost of about US$150,000. The fact that this procedure can be obtained for lower prices in other countries indicates a growing desire for HSCT to become more available at affordable prices in the USA and elsewhere.[12]

This study has limitations. There was high self-selection bias as data collection method was via an internet survey. In addition, there was limited access to social media platforms in diagnoses other than MS.

The correct timing of HSCT has not been investigated.[13] The therapy has been discredited for early or mild disease, and there is no evidence that HSCT will help in progressive MS.[13] Greater research is needed into this area [14] to elucidate the effectiveness and timing in order to establish it as a proven therapy as MS patients are paying with their lives.

Conclusion

Patients are overwhelmingly supportive of the treatment despite the costs. HSCT seems to be effective in reducing disability in MS. Post-treatment care seemed to be adequate. HSCT is still facing opposition from neurologists and other specialists, some of whom refuse to treat their patients following treatment. Our findings indicate that patients are prepared to travel and invest considerable amounts of time and money in HSCT. Our results suggest that this is probably justified and our study promises some stimulus towards larger randomized controlled trials.

Declarations

Availability of data

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Authors' contributions

PKP collated the data; drafted, edited and revised the manuscript; JR contributed data and helped revise the manuscript; HYC analyzed the data. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

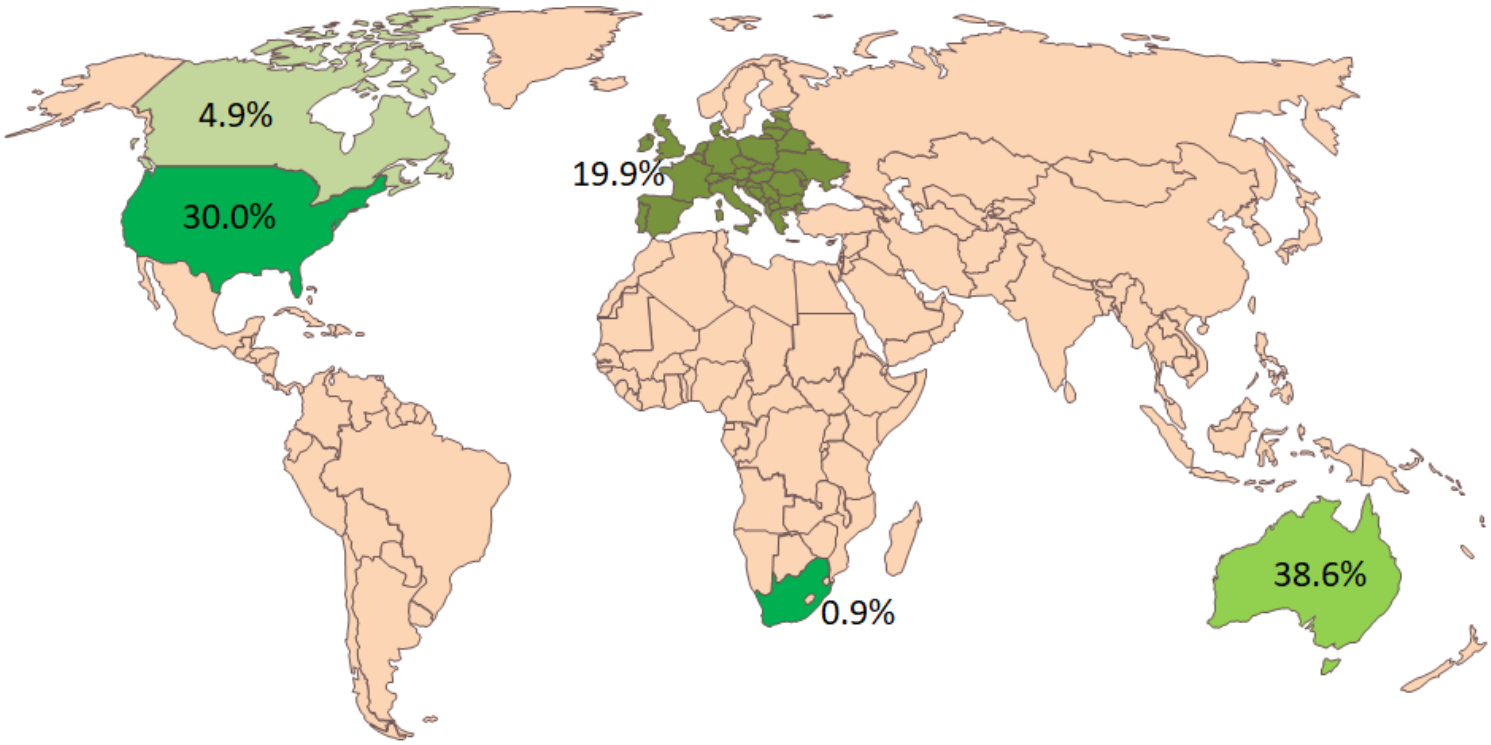

Figure 1

The country of origin of respondents (%) Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

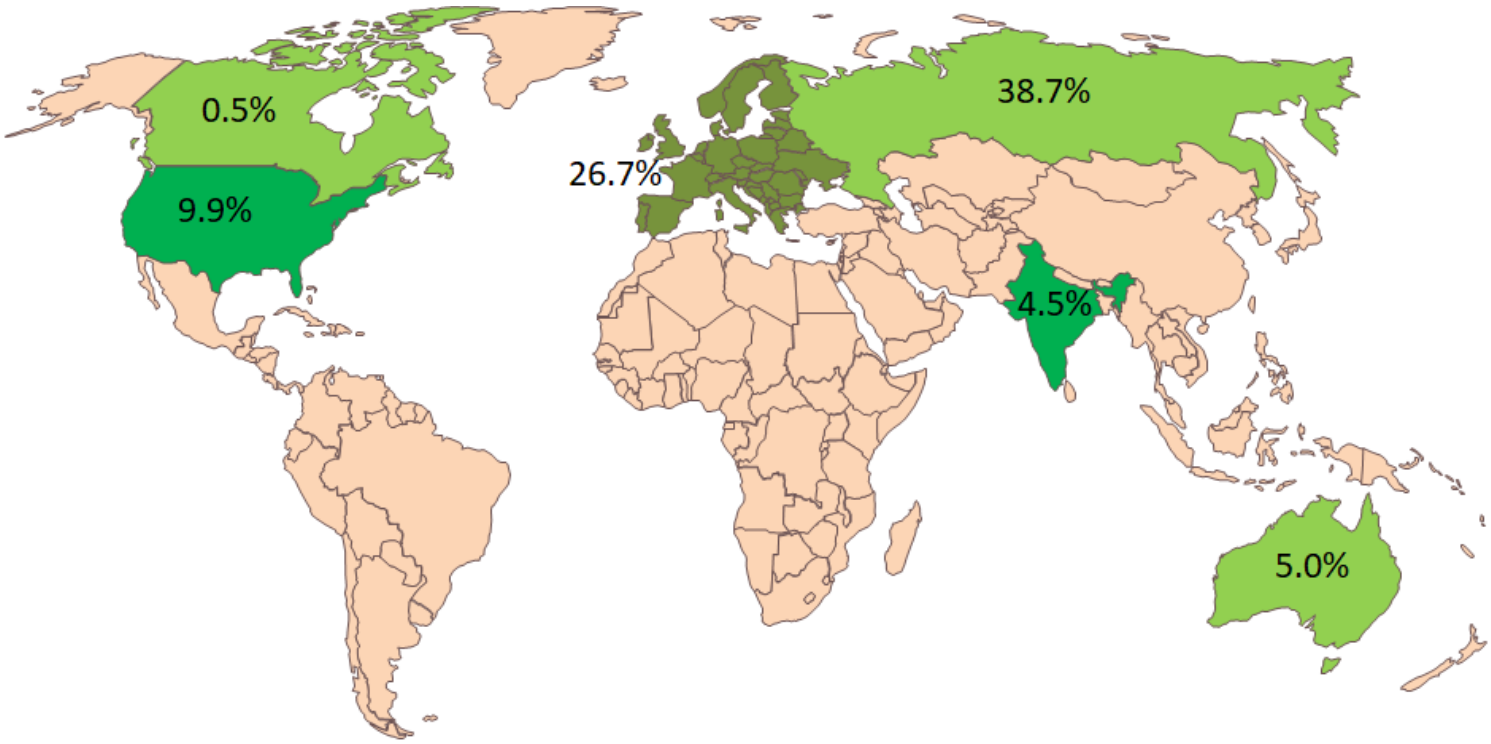

Figure 2

The country of location of stem cell treatments (%) Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

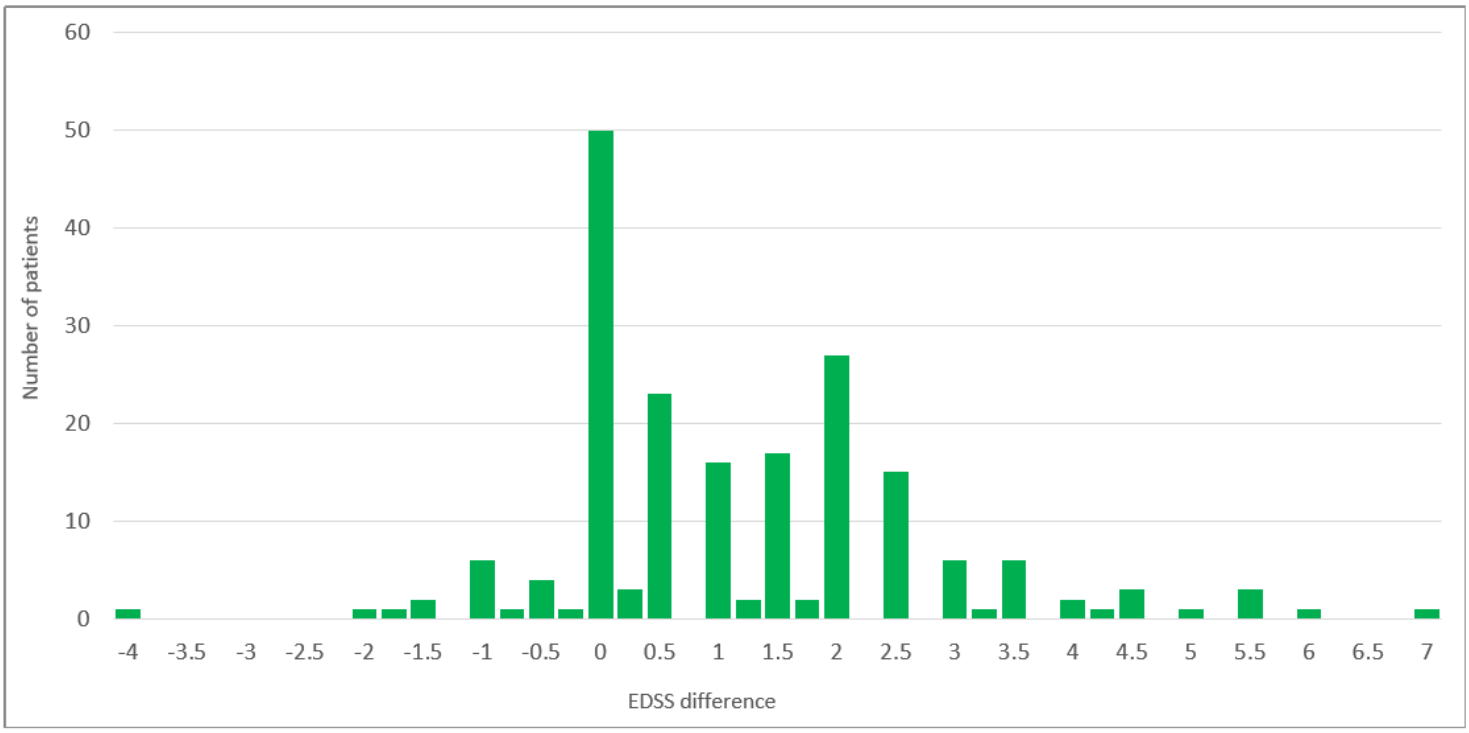

Figure 3

EDSS difference among 197 patients after stem cell transplantation

Supplementary Files

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- Supplementarytables.docx