Review Article

The Therapeutic Effect of Human Stem Cell Therapy on the Expanded Disability Status Scale Improvement in Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a central nervous system inflammatory disease in which the myelin sheaths of neurons are damaged. This impairs the ability of the neurons for signal conduction and communication and causes many neurological signs and symptoms. In this study, we evaluated stem cell therapy for multiple sclerosis. We reviewed the scientific literature focusing on stem cell therapy for multiple sclerosis available from 2003 to 2022. This narrative systematic review was performed to evaluate the effect of human stem cell therapy on expanded disability status scale (EDSS) improvement in multiple sclerosis. No time limits were set for the search and all relevant clinical trials were included. The results showed that the rate of recovery of patients with stem cell therapy depends on the rate of stem cell injection and the frequency, the volume of injected cells, and the rate of disease progression. Overall, the survival rate and quality of life increased following the treatment. The expanded disability status scale changed with stem cell injection, but this change was not significant. Most cases experienced an improvement in bladder control. Death or hospitalization after injection and severe allergies were not observed. Our results showed stem cells could increase the quality of life and survival and reduce the incidence of motor symptoms in MS patients.

Keywords: Stem cell, Multiple sclerosis, Systematic review, Improvement

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Introduction

Multiple sclerosis (MS) is a debilitating central nervous system (CNS) disease. In MS, the immune system attacks the myelin sheath and causes signal conduction abnormalities (1,2). The signs and

symptoms of MS vary widely based on the degree and location of the pathology. For instance, some patients experience a progressive course and may lose the ability to mobilize independently, while others may have a relapsing-remitting course. MS does not have a known curative treatment; however, treatment can help prevent relapses and prolong remissions (3,4). Up to 70 percent of patients experience recurrent MS. Some patients have a gradual onset and continuous progression of non-recurrent signs and symptoms, known as primary progressive MS. In contrast, others have secondary progressive MS, which is the recurrence and progression of symptoms after initial recovery (5,6). Research is currently underway to find more effective and tolerable treatments. The existing drugs for the treatment of MS are divided into three main groups in terms of application. They either target the disease attacks (intravenous immunoglobulin), control the symptoms (amantadine and baclofen), or control the course of the disease (glatiramer state, mitoxantrone) (7,8). Recently, various therapies have been developed to suppress the immune system and control the inflammatory process that causes myelin damage. Stem cell-based therapy is a new strategy for treating neurodegenerative diseases (9). In previous studies, stem cells derived from Adipose tissue have been shown to promote the process of myelination in animal models. The use of cell therapy to treat MS has raised great hopes. Studies have shown that cell therapy has anti-inflammatory and immunomodulatory effects on brain tissue (9, 10). This study aimed to examine the therapeutic effect of human stem cell therapy on expanded disability status scale (EDSS) improvement in MS.

Methods

This systematic review evaluates the therapeutic effect of human stem cell therapy on MS patient improvement. We investigated the PubMed/Medline, EMBASE, Cochrane Library, Scopus, Google Scholar, and reference lists of relevant articles from January 1, 2003, to January 1, 2022. The following keywords were selected for searching the databases: multiple sclerosis, stem cells, and mesenchymal stem cells/neural stem cells/bone marrow stem cells/hematopoietic stem cells/olfactory ensheathing stem cells/adipose stem cells. We restricted the search to English articles. We examined the title and abstract of the obtained studies for compliance with the set of inclusion criteria. We assessed the full texts of selected studies and determined the study design and result-reporting quality based on the checklist for critical appraisal of clinical trial studies.

The inclusion criteria and search strategy were as follows:

• Type of Study: Randomized clinical trial (RCT) or interventional studies
• Publication date: All published studies until 2022
• Sample size: No restrictions
• Outcomes: Effect on cell therapy in MS
• Quality: Earning a minimum acceptable score based on critical appraisal
• Language: English

Table S1 shows the details of strategies used in PubMed. Only randomized controlled trials (RCT) in which stem cells were used as a treatment for MS were included. The inclusion criteria were as follows: (1) the intervention involved any stem cells with no limitation in administration route or dose, (2) at least three months follow-up period, and (3) no stem cell in the control arm. Review articles, duplicate publications, and articles with unclear data were ruled out from the analysis.

Data extraction: We collected the following data: patient information, stem cell type, follow-up duration, outcome, and study quality. Two reviewers from the author's team independently conducted the steps of the systematic review. In case of disagreement between reviewers, an expert's opinion, as a third person, was asked to resolve disputes. We took ethical considerations into account in all stages of the study (9).

Quality assessment: To determine the included studies' quality, we utilized the main assessment checklist for RCTs provided by the Joanna Briggs Institute (JBI).

P-value < 0.05 for publication bias and funnel plots was considered significant.

Finally, we extracted the required information, including the demographic characteristics of participants and findings of the eligible studies, and recorded them in an Excel worksheet.

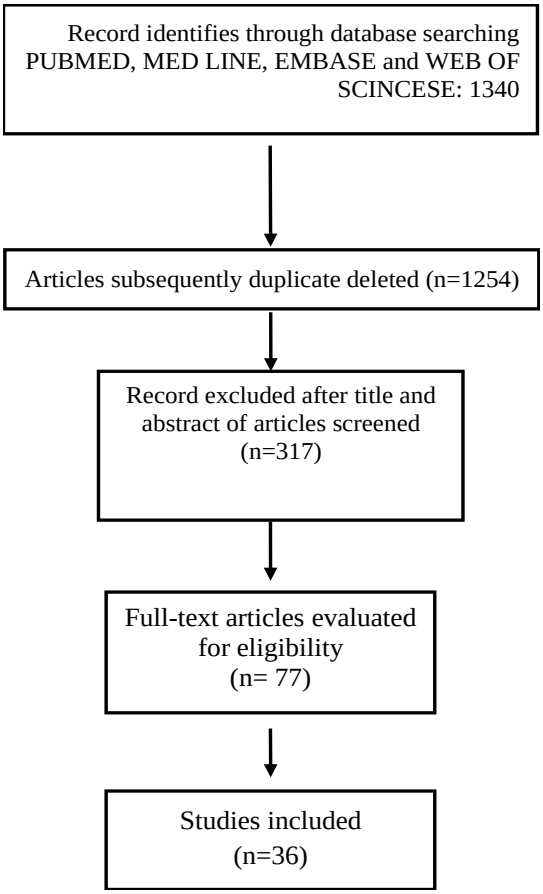

Figure 1. Diagram of study selection for inclusion in this research.

Results

Figure 1 shows the included and excluded articles. In the initial search, a total of 1340 articles were found. After deleting repetitious articles and screening the titles and abstracts of the remaining 1254 references, we selected seventy-seven papers for a full-text assessment, and thirty-six studies eventually met the inclusion criteria (figure 1). Table 1 shows the characteristics of the included studies. They were conducted from 2000 to 2021, with patients' mean age of 55 years (from 44 to 66 old) and a mean follow-up duration of 9.6 months. The sample size ranged between 12 and 116, adding up to a total number of 1617 patients. The bias risk was low in included studies according to the JBI tool, as shown in Table S2.

Discussion

In this study, we examined the effects of using stem cells in the treatment of motor recovery in MS patients. Our results showed that cell therapy can improve movement and also reduce mortality and hospitalization. Also, the rate of recovery depends on various factors, which include the type of cells, the amount of injection, and the degree of disease progression. Cell therapy is a promising approach for treating neurodegenerative disorders, such as spinal cord injury, and Parkinson's (9). Cell therapy involves the transplantation of healthy cells into the CNS to replace lost or damaged cells. This can help restore normal brain function and improve symptoms. In some cases, stem cells are used to create new neurons that can replace those that have been lost due to the disease (9). Stem cells used in cell therapy are obtained from different sources and have many capabilities. The level

Table 1: Features of involved studies.

Author	*Year*	*Type of cell*	*Country*	*Sex*
Richard K (1)	2019	HSCT	USA	73 F/36M
Violaine K (2)	2018	(MSC-NP)	USA	14F/6M
Neil H. Riordan (3)	2018	MSCUC	Panama	12F/8M
Oscar FernaÂndez (4)	2018	ADSC	Spain	21F/9M
Richard K Burt (6)	2018	HSCT	Brazil	11F/10M
G. J. Ruiz-Argüelles (7)	2019	HSCT	México	401F/216M
Mandana Mohyeddin(8)	2007	MSC	IRAN	7F/3M
Richard A. Nash (10)	2015	HSCT	USA	17F/8M
Peter Connick (12)	2012	MSC	UK	3F/7M
Richard K (13)	2003	HSCT	USA	10F/11M
Claire M. Rice (15)	2015	BMSC	UK	-
Richard A. Nash (16)	2003	HSCT	USA	12F/14M
Paolo A. Muraro (17)	2005	HSCT	USA	2F/5M
Jin-Feng Li (18)	2013	MSCUC	CHINA	9F/4F
James D. Bowen (19)	2012	HSCT	USA	12F/14M
Peter Connick (20)	2011	MSC	UK	3F/7M
M Inglese (21)	2004	HSCT	ITALY	-
Sara Llufriu (22)	2014	MSC	Spain	7F/2M
Said Dahbour (23)	2017	MSC	JORDAN	4F/6M
Fred D.Lublin (24)	2014	MSCP	USA	11F/5M
Richard A. Nash (10)	2017	HSCT	USA	
monica leon (25)	2016	HSCT	mexic	12F/7M
Simon Thebault (26)	2019	HSCT	CANADA	14F/9M
Carolyn A. Keever-Taylor (27)	2017	HSCT	USA	-
Fabian Zohren(28)	2008	HSCT	GERMANY	15F/5F
Panayiota Petrou(29)	2020	MSC	GERMANY	20F/28M
Andreas Tolf(30)	2019	HSCT	Sweden	-
Bose G (31)	2018	HSCT	CANADA	14F/9M

of access to these cells and autografts is important, although some factors can also affect the proliferation, differentiation, and migration of these cells (11). Clinical trials are currently underway to evaluate the safety and efficacy of cell therapy in treating these conditions. Cell therapy is a promising approach for treating MS. It involves the use of stem cells, which are capable of self-renewal and differentiation into various cell types, to replace damaged or lost cells in the central nervous system. Cell therapy has been used to treat MS by transplanting autologous hematopoietic stem cells (HSCs) into the patient's bone marrow. This procedure has been shown to reduce inflammation and improve neurological function in some patients with MS (12).

Table 2: Search strategy for the PubMed/Medline database.

Search	Query
#3	((((((((((((((Multiple sclerosis (MeSH Terms)) OR (Multiple sclerosis(Title/Abstract))) AND ((((((Stem Cells(MeSH Terms)) OR (Stem Cells(Title/Abstract))) OR (mesenchymal stem cell(Title/Abstract))) OR (mesenchymal stromal cell(Title/Abstract))) OR (mesenchymal progenitor cell(Title/Abstract))) OR (Mesenchymal Stem Cells(MeSH Terms))
#2	((((((((((((((Multiple sclerosis (MeSH Terms)) OR (Multiple sclerosis (Title/Abstract)))
#1	(((((Stem Cells (MeSH Terms)) OR (Stem Cells(Title/Abstract))) OR (mesenchymal stem cell(Title/Abstract))) OR (mesenchymal stromal cell(Title/Abstract))) OR (mesenchymal progenitor cell(Title/Abstract))) OR (Mesenchymal Stem Cells(MeSH Terms))

Additionally, mesenchymal stem cells (MSCs) have been used to reduce inflammation and promote remyelination in animal models of MS. Clinical trials are currently underway to evaluate the safety and efficacy of cell therapy for treating MS (13).

MS is a central nervous system autoimmune disease, and the most critical components of myelin protein that are targeted by the immune system include myelin-basic protein (MBP), myelin-associated glycoprotein (MAG), proteolipid protein (PLP), and myelin glycoprotein (MG). The role of various immune system factors in the occurrence of multiple sclerosis has been investigated in different studies. Macrophages residing in the CNS (Microglias) are involved in phagocytosis, antigen delivery, and cytokine production. Microglial cells are also involved in nerve demyelination and myelin phagocytosis through inflammatory cytokines and myeloperoxidase production (10-12). Typically, the number of mast cells in the CNS is small; But during MS, their number also increases in plaques and inflammatory lesions. Under normal circumstances, the number of dendritic cells (which act as antigen-supplying cells) in the CNS is very low. In contrast, an increase in the number of dendritic cells in the peripheral blood and CSF of MS patients has been observed (13,14). Astrocytes are the principal complement-producing cells in the brain and thus may play a role in tissue damage in some diseases. Nerve demyelination occurs not only through activation of the classical complement pathway but also through direct activation of complement after attachment to the myelin. The MOG can also bind to the C1q complement and activate it without antibodies. Activation of complement leads to lysis of oligodendrocyte cells and acts as a chemotactic agent for macrophages. Oligodendrocyte sensitivity to complement is partly due to the lack of complement inhibitors on the surface of these cells (15,16). It seems that regulating complement activity in MS can somewhat reduce inflammatory damage to the central nervous system. In MS, inappropriate immune responses can alter microglia cells from the neuroprotective phenotype to the pro-inflammatory phenotype, which promotes inflammation and further damage to oligodendrocytes. Such inappropriate immune responses in MS are likely genetic. To prove this, some mouse species are more suitable for induction of EAE, which depends on their genetics and their tendency of immune response to Th1. In transgenic mice with high GATA3 expression (which

Table 3: Quality of studies used in research.

First author	Did participant analysis take place in the groups to which they were [illegible]?	Did the authors conduct outcomes measurement for the treatment groups similarly?	Were all the treatment groups identical at the onset of the study?	Was contributors' blindness to the treatment detected?	Was blindness to treatm ent assignment observed for those delivering the treatment?	Was blindness to treatment assignment observed for outcomes assessors?	Did the authors treat treatment groups identically apart from the intervention of interest?	Did the authors complete the follow-up, and if not, did they describe and analyze the follow-up sufficiently?	Is the concealment of group allocation to treatment groups observed?	Were the participants assigned randomly to treatment groups?	Are the analyses of outcomes measured reliably?	Do we have the correct statistical analysis?	Was the right trial plan used, and were deviations from the standard RCT like [illegible] for in the conduct and analysis of the [illegible]?
Richard K.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Violaine K.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neil H. Riordan	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oscar FernaÂndez	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Richard K Burt	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
G. J. Ruiz-Argüelles	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mandana Mohyeddin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Richard A. Nash	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peter Connick	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Richard K.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Claire M. Rice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Richard A. Nash	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Paolo A. Muraro	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jin-Feng Li	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
James D. Bowen,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peter Connick	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
M Inglese	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Sara Llufriu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Said Dahbour	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fred D. Lublin	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Richard A. Nash	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monica Leon	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Simon Thebault	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carolyn A. Keever-Taylor	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fabian Zohren,	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Panayiota Petrou	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Andreas Tolf	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gauruv Bose	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

leads to a diversion of the immune response to Th2), a reduction in CNS inflammation was observed, as well as minimal clinical signs after EAE induction (16-18). Some studies have shown that in MS, although the number of Treg cells is normal, they are functionally defective, and in MS patients, Treg cells have less power to suppress IL-17 production than in healthy individuals. Other studies have shown a 2 to 3-fold decrease in the number of Treg cells in the exacerbation phase of MS and an increase in the number of these cells in the regression phase of the disease (19,20).

Conclusion

According to the results of this study, we concluded that using stem cells can improve mobility in MS patients. The disease severity is the key determinant for choosing the treatment option

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Appendix 1: A Summary of the Studies

References	type of cell	number of	country	TRNSPLAN	Sample si	IMMUNO	follow-up	SS- EXP(SD)	EDSS-CONTR	GENDER	AGE	Duration of MS	TRNSPLANT	serious	hospitaliz
Richard K.	HSCT	1×10⁶	USA	IV	110	SD: 3.2 (1.	2	)D: 3.4 (1.2)	SD: 3.3 (1.0	34 (62) F/21 (38)M	18 - 55	9.4	AUTOLOGOS	NO	NO
Violaine K.	(MSC-NP)	3×10× 10⁶	USA	rathecally	20	cyclophos	2	6.8	6.5	14F/6M	27-65	6.1 (44.8)	AUTOLOGOS	NO	NO
Neil H. Riordan	MSCUC	20×10⁶	Panama	IV	20	cyclophos	1	4.6	5.2	12F(60%)/8(40%)M	24-55	5.7	ALLOGRAFT	NO	NO
Oscar FernaÁndez	ADSC	4×10⁶	Spain	IV	34	cyclophos	1	7.78±0.44	7.64±0.98	21F/9M	31-61	6.8	AUTOLOGOS	NO	NO
												4.3 (3.1)	AUTOLOGOS	NO	NO
Richard K Burt	HSCT	11.40×10⁶	Brasil	IV	21	CYCLPHOS	1	SD:2	SD:3	11F/10M	20-53	5.9	AUTOLOGOS	NO	NO
G. J. Ruiz-Argüelles	HSCT	37×10⁶	México	IV	617	CYCLPHOS	1	4.5	5.1	401F/216M	18-73	8.6	AUTOLOGOS	NO	YES
Mandana Mohyeddin	MSC	8.73×10⁶	IRAN	IT	10	NO		6	6.4	7F/3M	22-40	7.4	AUTOLOGOS	ATTACK	YES
												5.7 (3.7)	AUTOLOGOS	NO	NO
Richard A. Nash	HSCT	2×10⁶	USA	IV	25	carmustin	5	4.5 (3.0 to 5.5)	SD:4.4 (0.6	17F/8M	18 - 60	9.6	AUTOLOGOS	NO	NO
												7.3	AUTOLOGOS	NO	NO
Peter Connick	MSC	1·6×10⁶	UK	IV	10	NO	1.5	)7 (0·3; 5·5–6·5)	SD:6·1 (0·3; 5·5–9·5	F/7M	18-65	14·4 (7·9; 5·–	AUTOLOGOS	NO	NO
Richard K.	HSCT	2×10⁶	USA	IV	21	cyclophos	5	SD:6.1	SD:3.4	10F/11M	21-52	3.5/2.5	AUTOLOGOS	YES	YES
												11.4	AUTOLOGOS	NO	NO
Claire M. Rice	BMSC	1×10⁶	UK	IV	80	NO	2	SD:5.5	SD:5.1		18-65	4.5	AUTOLOGOS	NO	NO
Richard A. Nash	HSCT	3.5×10⁶	USA	IV	26	CYCLOPH(	2	SD:8.5	SD:7.5	12F/14M	27-60	8.4(10–27MO	AUTOLOGOS	YES	YES
Paolo A. Muraro	HSCT	4×10·8	USA	IV	7	CYCLOPH(	2		2F/5M			7.3	AUTOLOGOS	NO	NO
Jin-Feng Li	MSCUC	4×10⁶	CHINA	IV	23	methylpre	1	5.8	6.98 ± 1.2	9F/4F	25-55	9.1	ALOGRAFT	NO	NO
James D. Bowen,	HSCT	3.5×10⁶	USA	IV	26	CYCLOPH(	4	.0 (5.0–8.0)	SD:6	12F/14M	27-60	8.4 (10–277 mc	AUTOLOGOS	YES	YES
Peter Connick	MSC	2×10⁶	UK	IV	10	NO	(range 3–7	SD:6.1	SD:5.5	3F/7M	18-65	7.9	AUTOLOGOS	NO	NO
M Inglese	HSCT	1×10⁶	ITALY	IV	10	CYCLOPH(	2	:3.5 (3.0–6.0)	SD:7 (3.8–1(	7F/2M	(23–48)	8.1 (2.15)	AUTOLOGOS	NO	NO
Sara Llufriu	MSC	2×10⁶	Spain	IV	9	NO	1	8	7.3	7F/2M	18-50	7.1	AUTOLOGOS	NO	NO
Saïd Dahbour	MSC	2×10⁶	JORDAN	IT	10	CYCLOPH(	1	5.1 (±1.73)	5 (±1.86)	4F/6M	18-54	9.6 (±2.91)	AUTOLOGOS	NO	NO
Fred D.Lublin	MSCP	2×10⁶	USA	IV	16	NO	1	;.0(1.5–6.5)	4.0(4.0–4.0	11F/5M	18-65	10.4	AUTOLOGOS	NO	NO
Richard A. Nash	HSCT	1×10⁶	USA	IV	25	BCNU	4	4	4.5	17F	31-42	4.9	AUTOLOGOS	YES	YES
monica leon	HSCT	2×10⁶	mexic	IV	19	CYCLOPH(	1			12F/7M	30-65	8.9	AUTOLOGOS	NO	NO
Simon Thébault	HSCT	2×10⁶	CANADA	IV	23	CYCLOPH(	6.7	4	6	14F/9M	18-50	3.5	AUTOLOGOS	YES	YES
Carolyn A. Keever-Tayl	HSCT	2×10⁶	USA	IV	57	NO	1					6.2	AUTOLOGOS	NO	NO
Fabian Zohren,	HSCT	2×10·5	GERMANY	IV	20	natalizum	3		15F/5F		21-43	Jan-00	AUTOLOGOS	NO	NO
Panayiota Petrou	MSC	1×10⁶	GERMANY	IV/IT	48	CYCLOPH(	1	5.75± 0.77	5.44±1.05	21F/27M	31-65	12.70±7.5	AUTOLOGOS	NO	NO
Andreas Tolf	HSCT	1×10⁶	Sweden	IV	10	CYCLOPH(	2.5	7.5	6.5		13-33	14.1	AUTOLOGOS	NO	NO
Gaurav Bose	HSCT	1×10⁶	CANADA	IV	23	NO	3	;.5 (3.6–6.5)	5.0 (4.0–6.(	14F/9M	(24–45)	11.5	AUTOLOGOS	NO	NO