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Feasibility and toxicity of hematopoietic stem cell transplant in multiple sclerosis

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ABSTRACT

Multiple sclerosis is a debilitating disease of the central nervous system. It affects people of all ages but is more prevalent among 20-40 year olds. Patients with MS can be presented with potentially any neurological symptom depending on the location of the lesion. A quarter of patients with MS suffer from bilateral lower limb spasticity among other symptoms. These devastating effects can be detrimental to the patient's quality of life. Hematopoietic stem cells (HSCs) have been used as a treatment for MS over the past 2 decades but their safety and efficacy has are undetermined. The objective of this study is to evaluate the feasibility and toxicity of autologous HSCs transplantation in MS. A literature search was done from 1997 to 2016 using different keywords. A total of 9 articles, which met the inclusion and exclusion criteria, were included in this review. The type of conditioning regimen and technique of stem cell mobilization are summarized and compared in this study. All studies reported high-dose immunosuppressive therapy with autologous HSCs transplantation being an effective treatment option for severe cases of multiple sclerosis. Fever, sepsis, and immunosuppression side effects were the most observed adverse effects that were reported in the selected studies. HSCs is a feasible treatment for patients with MS; nevertheless the safety is still a concern due to chemo toxicity.

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Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (1, 2). It is characterized by focal inflammation and demyelination of the brain and spinal cord nerve cells (3). This damage inhibits the ability of axons to transmit signals between nerve cells. As the disease progresses, the CNS loses its self-repair capacity, leading to permanent damage and eventually cell death, scarring, and sclerosis (4, 5). The exact etiology of MS is unknown. It is thought that genetic factors and environmental triggers such as smoking, vitamin D deficiency, and infections play a role in its development (6). Autoreactive T cells that are self-activated or cross-reactive antigens pass through the blood brain barrier (BBB) and generate inflammation that ultimately can lead to demyelination and neurodegeneration (7). In autopsy, the pathological findings are inflammatory infiltration, degeneration of myelin, reactive gliosis and degeneration of axons (8, 9). As with most autoimmune disorders, MS is more common in women than in men. It predominantly affects those between ages of 20-40 (5); however, 10% of cases occur in people less than 18 years old. There are gender-related differences in the pathophysiology of MS at the cellular level. In male patients, the estrogen pathway is predominant-ly activated, whereas in females progesterone is the foremost activated pathway (10). There are 4 types of MS, i.e. relapsing-remitting (RR-MS), secondary-progressive (SP-MS), primary-progressive (PP-MS), and progressive-relapsing (PR-MS) (11). In the majority of cases (over 80%), the disease started as RR-MS, characterized by relapses due to inflammation followed with complete or incomplete remissions (5). Finally, after 5-15 years, 50% of patients show pre-existing neurological deficits that are aggravated with frequent relapses and categorized as SP-MS. PP-MS is presented in 15% of patients in whom disabilities progressed much faster compared to RR cases. The least frequent form is PR-MS, characterized by progressive deterioration of neurological function with superimposing of acute attacks (12). About 50% of patients with MS eventually require walking aid by the 15th year (5). Life expectancy of patients with MS is on average 7-10 years less than the general population and in 50%

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of the cases, disease-related complications are the cause of death, suicide and death causes similar to the general population are other cause of death in these patients (13).

There is no individual definitive test for MS and the confirmation of this diagnosis requires multiple tests and clinical evaluation in order to demonstrate dissemination of lesion in term of space and time (14). In 2001, the first version of McDonald's criteria was developed to assist in the diagnosis of MS (15, 16). These criteria are not without criticisms and were revised twice in 2005 and 2010 (16-19). The Expanded Disability Status Score (EDSS) is used to evaluate the neurological impairment and is useful in determining the effectiveness of the treatment. The lower the EDSS score is, the better (5, 20). Study shows that there is a significant difference in term of severity between men and women and EDSS score is significantly higher in men, especially if the onset of the disease is before age 45 (21).

Currently, there is no cure for MS, the treatment is usually focused on dealing with relapses, their symptoms, and slowing the progression of the disease. The main targets for new treatments are immune activation and controlling inflammation (1). Therefore, chemotherapeutic agents, corticosteroids, and immunomodulation are used conventionally (22).

Cell therapy for different central nervous system disorders such as Parkinson's disease, cerebral palsy, and Alzheimer's disease have shown promising results (23-25). Different types of cells from a variety of sources have been used to treat MS including neural stem cells (NSCs) mesenchymal stem cells, hematopoietic stem cells (HSCs) and embryonic stem cells. However, HSCs have attracted more attention most likely due to the less invasive collection method as it is collected from peripheral blood (26). Among a variety of stem cells, differentiation of HSCs to neuron cells is still challenging even established protocols are available for using these cells in treating other disorders such as myocardial infarction, leukemia, and blood cancers (27, 28). Suppressing the human immune system with immunosuppressive therapy followed by hematopoietic stem cell therapy (HSCT) has been used in the last 2 decades for treating severe forms of MS. However, the treatment of MS with autologous stem cells is not an established method (5, 29).

The goal of HSCT in any autoimmune diseases is to remove the lymphocytes responsible for the inflammation and generating new self-tolerant lymphocytes. Hematopoietic stem cells are initially mobilized after which a conditioning regime helps to eradicate the patient's disease prior to infusion of the HSCs (4, 30). The effectiveness of HSCT on MS is still undetermined. Outcomes have been mixed with patients having a significant improvement while others seem to gain little to no benefit at all. In this study, we aimed to answer whether autologous HSCs transplantation is a feasible treatment for MS as well as review chemotoxicity of this approach. Much of criticisms are due to the transplant-associated side effects and mortality. Studies revealed fever and engraftment syndrome among the most common adverse effects of this treatment modality (29, 31).

Materials and Methods

Selection of literature

A literature search was carried out in PubMed, Google Scholar, and Cochrane using different keywords such as multiple sclerosis, MS, stem cells, HSCs transplant, autologous HSCs transplant, and HSCT.

Inclusion and exclusion criteria

To improves the specificity and conceptual breakdown of clinical problems PICO framework was utilized (32). Each paper was selected according to the elements of PICO. Table 1 summarizes the elements of PICO.

Only human studies including case-control, case study, cohort study, RCT that were published in English from 1997 till 2016 with a minimum follow-up of 12 months were included. Relevant papers in the reference lists of the viewed papers and other papers citing the viewed papers were also searched and reviewed.

Studies performed using any other treatment modalities alongside with HSCT were excluded.

Data extraction

Titles and abstracts of studies from databases searches were reviewed by two reviewers to identify relevant studies. The disagreement for inclusion or exclusion if any, was discussed with the third reviewer. Two reviewers (TLTK and MSS) independently extracted the data from eligible studies. The extracted data included author(s), year of publication, sample size, details of intervention, outcome of studies assessment method, duration of follow-up, any reported complication, and duration of symptoms in the patient at the beginning of the study.

Quality assessment

Quality assessment of the papers was done according to the subjective scoring and using answer matrix separately by authors.

Table 1. PICO Framework

P - Patients	Patients with multiple sclerosis
I - Intervention	Hematopoietic stem cell therapy
C - Comparison	Before and after treatment
O - Outcomes	Safety and Efficacy -EDSS*, treatment related toxicity

* Expanded Disability Status Scale (EDSS)

Table 2. Details of assessment scoring for selected studies

	Fassas, 1997	Nash, 2003	Carreras, 2003	Su, 2006	Shevchenko 2008	Fagius, 2009	Burman, 2014	Mancardi, 2015	Atkins, 2016
Did the study clearly focus on the issue?	√	√	√	√	√	√	√	√	√
Did the study clearly mention the treatment plan?	√	√	√	√	√	√	√	√	√
Was the study mention measurement system for the outcomes?	√	√	√	√	√	√	√	√	√
Were the outcomes accurately measured to minimize the bias?	-	-	-	-	-	-	-	-	-
Were the studies having accurate follow-up measures?	√	√	√	√	√	√	√	√	√
Total score	4	4	4	4	4	4	4	4	4

Studies with scores 0-2 were considered to have low quality and studies with scores 3-5 were considered to have high quality (Table 2).

Results

Using different keywords, a total of 840 articles were retrieved. After reviewing the titles and abstracts, only 122 articles were relevant to the objectives of this systematic review. Finally, 9 articles met all inclusion and exclusion criteria and had assessment scores of more than 3 (Table 2). There were three studies which included MS patients with both RR and SP, one study only with SP patients, one study only RR patients, two studies all types of MS patients, one study patients with PP and SP, and one study MS patients with SP, PP, and RR (Figure 1).

Patient selection

In 1997, Fassas published a paper and reported fifteen patients with PP-MS and SP-MS multiple sclerosis, aged below 55 years old were selected for their pilot study. Intervention and outcome of this study are summarized in Table 3 (29). From July 1998 to April 2001, 26 patients were enrolled at Fred Hutchinson Cancer Research Center for a pilot study of high-dose immunosuppressive therapy (HDIT) for severe MS (33). Only severe forms of MS were included and the mean EDSS at baseline was 7.0. The average age of the patients was 41 however they did not interpret it in their results. Carreras *et al.* in 2003 published the results of their study on 15 patients aged 18–60 years old, diagnosed with MS (34). They included patients with increasing EDSS during the previous year, despite conventional treatment, in their study. From September 2001 to January 2005, 15 patients, diagnosed with MS were included in another study by Su *et al* (35). Patients aged 18 to 51 years were included in this study conditional on having increment of EDSS in the past 12 months. Some details of this study are summarized in Tables 3.

From 1999 to 2006, 50 patients between ages 18 to 51 were enrolled in a study in five Russian centers by Shevchenko and his team (36). All patients had initially undergone conventional therapy but the disease still progressed.

Another study has been published in 2009 that reported the results of successful treatment of 9 patients with early

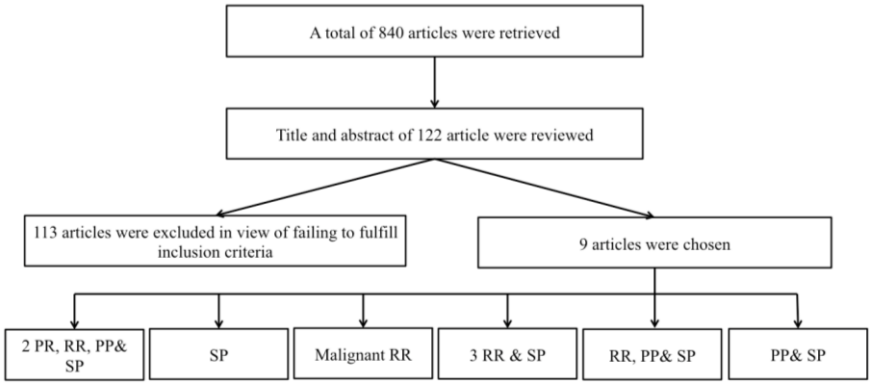

Figure 1. Article selection process

highly aggressive MS using HSCT (30). Previously, treatment of MS with HSCT was mainly given to patients with a high degree of disability. In this study, Fagius and team recruited 9 patients with malignant RRMS. Their patients were young with a median age of 27 years (9-34) and duration of MS also was short (4-100 months, median 26). The outcome of their study was incomparable with other studies and they reported median improvement in EDSS scale 3.5 (ranging from 1.0-7.0). One patient had a very mild relapse after 7 months otherwise, all patient were stable during the follow-up. Other details of this study are outlined in Table 3.

Burman and his colleagues in 2014 published the results of their study in Sweden (37). They followed up 48 patients the majority of whom (n=34, 83%) had RR-MS. In this cohort, they followed up the cases for the mean duration of 47 months. EDSS score progression survival was 77% and disease-free survival was 68%. They did not report any mortality related to transplants. Other details of this study are summarized in Table 3.

In 2015 American Academy of Neurology published the result of phase II trial of autologous hematopoietic stem cell transplantation (AHSCT) in MS, by Giovanni Mancardi and colleagues (38). It was a multicenter randomized trial and they included 21 patients with SP and RR-MS with documented increment in EDSS despite receiving conventional medication. They compared this group, with patients that received mitoxantrone (MTX) and measured MRI indexes to follow up disease activity. In their study immunosuppression followed by AHSCT reduced the number of new T2 lesions by 79%, which is significantly superior to conventional treatment with MTX. In term of EDSS, there were no significant differences, however annual relapse rate (ARR) was significantly reduced in the study group. Other details of the intervention and outcome of the study are summarized in Table 3.

Atkins and his team reported another multi-center, phase II trial in Canada in 2016 (39). They enrolled 24 patients with aggressive MS aged 18–50 years, after immunoablation and AHSCT they followed up the clinical relapses and new lesions in MRI and EDSS. Median follow-up was 6.7 years. 69.6% showed activity free at least for 3 years after transplantation. No relapse and new Gd-enhancing lesion was reported in 314 sequential MRI scans and the rate of brain atrophy was same as healthy controls. Sustained improvement in EDSS score had been reported in 35% of patients. Other details of this study are outlined in Table 3.

Conditioning and supportive treatments

Seven out of 9 studies used Cyclophosphamide with different doses (60 mg/kg, 2 g/m^2, 3 g/m^2, 4 g/m^2 and 4.5 g/m^2) followed by daily s/c injections of G-CSF (Granulocyte Colony-Stimulating Factor) or GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor) at 5-10 µg/kg body weight to mobilized stem cells, whereas Nash and his team prescribed G-CSF at 16 µg/kg per day and Su *et al.* used daily s/c G-CSF at 5 µg/kg for 4 to 6 days.

While, Nash *et al.* (33) used high dose immunosuppressive therapy included fractionated total body irradiation, cyclophosphamide 60 mg/kg and equine antithymocyte globulin 15 mg/kg per day, Carreras and his team (34) prescribed BCNU (Carmustine) 300 mg/m^2 and ATG (Anti-thymocyte globulin, Lymphoglobuline, Merieux) 15 mg/kg, and Atkins *et al.* (39) used conditioning chemotherapy with cyclophosphamide 50 mg/kg and rabbit antithymocyte globulin 1.25 mg/kg for 4 days, for transplant procedure. All the other studies used BEAM regimen (BCNU 300 mg/m^2, etoposide 200 mg/m^2, cytosine-arabinoside 200 mg/m^2, and melphalan 140 mg/m^2).

Supporting treatment was provided in each study with a different regimen.

Fassas *et al.* and Shevechenko *et al.* used IVIG$^{\mu}$ at 0.5/kg body weight, Oral ciprofloxacin, fluconazole, and acyclovir were given daily as infection prophylaxis, and patients were isolated. Nash and his team used infection prophylaxis including trimethoprim-sulfamethoxazole, fluconazole, and acyclovir. Routine prednisone was started with 1 mg/kg/day from fifth patient enrolling onward. Carreras expended a more comprehensive approach by using low microbial diets and oral ciprofloxacin, fluconazole, and acyclovir. Patients were admitted in rooms equipped with HEPA filters and laminar airflow. Immunoglobulins was administered intravenously at 100 mg/kg per week until day +90. Methylprednisolone 500 mg was given before each ATG$^{\alpha}$ dose for the last 6 patients. In the Su *et al.* study all patients were in air-filtered medical units and platelets were transfused to keep platelet counts > 20x10^9/L. Infection prophylaxis with sulfamethoxazole for *Pneumocystis carinii*, fluconazole for fungal infection, and ciprofloxacin or sultamicillin for bacterial infection were given. Intermittent use of dexamethasone during transplantation was prescribed if neurologic symptoms worsened. Fagius team only prescribed Acyclovir for 3 months and trimethoprim/sulfametoxazole for 6 months after transplant. Marcardi used almost the same combination and patients were treated only with symptomatic therapy. Burman and Atkins groups administered prophylaxis against fungal, viral, and bacterial infection during neutropenia. Prophylaxis against varicella virus *and P. carinii* continued for an additional 3 months.

Assessment

Fassas and his team (29) assessed the improvement of disability in their study by using two scoring systems:

1. EDSS

Table 3. Summary of studies

	Patients' characteristics	Type of MS	EDSS baseline	Duration of follow-up	Number of cells	Transplant related toxicity	EDSS score change	Clinical improvement
Fassas, 1997 (29)	15 patients median age 37 years, M/F=8/7	8 PP-MS and 7 SP-MS	5.0-7.5	24 months	minimum CD34+ : 4 x 10^6/kg	Allergic reaction such as fever, erythema, bronchospasm, hypotension, anaphylaxis, or a combination of the symptoms. Infection was common affecting 13/15 patients. Liver toxicity was also noted in 3 patients. Mild transient neurotoxicity in 6 patients There were no mortalities.	By Month +3, the mean EDSS change was -0.5. By Month +9, the mean EDSS change was -1.3.	MRI analysis showed less involvement however it was not statistically significant. 2 patients had relapse 3 and 5 months after transplant, however, their SNRS score remain above the respective score
Nash, 2003 (33)	26 patients, median age of patients 41 years, M/F= 14/12	17 SP-MS, 8 PP-MS and 1 RR-MS with a worsening in EDSS of 1.0 or more points over the previous year	5.0-8.0	36 months	more than 3.5 x 10^6 $CD34^+$ cells/kg	Infection was common – UTI, bacteremia, central venous catheter infection. No fungal infections were noted. Engraftment syndrome, which consisted of fever and rash, occurred in 13 patients. Flare of MS occurred in 1 patient and 1 mortality secondary to development of EBV-PTLD occurred	By Month +12, 6 people showed an improvement while 7 had a worsening of symptoms	Of the 25 patients, 6 had a confirmed treatment failure, 3 had an unconfirmed increase of EDSS 0.5 points, 2 had a decrease of 0.5 points and 14 patients remained stable throughout Enhancing lesions in MRI for 4 patients were noted. In 3 patients oligobands in the CSF turned negative during follow-up
Carreras, 2003 (34)	15 patients median age of 30 years M/F= 2/13	9 SP-MS and 6 RR-MS	Median 6.0 (4.0 to 6.5)	12 months	2.5 x 10^6 CD34+1/kg	Out of the 14 patients, 12 patients developed fever and 5 had positive bacteremia. 1 Patient developed severe persistent paraparesis that worsened her EDSS by 1.5 while 2 patients developed a reactivation of herpes zoster. No mortalities.	improvement in 3 patients and worsening in 2 patients. Other patients had a stabilization of EDSS.	Three relapses in 2 patients, which manifested as transient subjective sensory symptom, and 2 patients had relapses that need treatment with good recovery. Five patients had notable lesions pre HSCT. No enhancing lesions were noted at 12 months post HSCT even in patients with worsening EDSS. CSF – Oligoclonal band persisted in evaluated cases
Su, 2006 (35)	15 patients aged 20-51 years. M/F=5/10	SP-MS	3.0-6.5	49 months	Minimum 2.0 · 10^6 cells/kg.	Gastrointestinal tract toxicity characterized mainly by diarrhea was present in 8 of 15 patients. Otherwise, engraftment syndrome (rash, fever) was observed in 6 patients and bacteremia in 4 patients. Elevated liver enzymes (grade I toxicity) developed in a few patients	There is a general improvement or stabilization in the EDSS scores post-HSCT	2 patients had subjective complaints that recovered with resuming steroid or immunosuppressive therapy. Only 5 patients had disease progression while the rest had either an improvement or stabilization of disease. MRI assessment showed only 1 patient to have enhancing lesions at 1 year of follow-up. The same patient had progression of the disease

Shevchenko 2008 (36)	50 patients, median age of 32	27 SP-MS, 1 PR-MS, 11 PP-MS, and 11 RR-MS	5.0 (ranged1 .5 to 8.0)	Up to 6 years	Minimum 6 and 2.5 x 10^6 cells/kg	Fever occurred in 51.6% of the patients while hepatotoxicity grade I and II was also observed in almost half of the patients.	Improvement of EDSS scores in 28 patients and 27 patients had achieved stabilization.	28 patients showed objective improvement of neurological symptoms and in 17 patients disease stabilized. Only 4 patients progressed thereafter. MRI – 16 patients had active lesions at baseline and all but 2 remained active after HSCT. Of the 21 patients without active lesions at baseline, 20 remained inactive
Fagius, 2009 (30)	9 patients, median age 27 years M/F=3/6	9 "malignant" RR-MS	7.0 (3.5-8.0),	Median follow-up 29 months (23-47)	Not mentioned	Patients generally developed fever, temporary mucositis, and hair loss. 2 patients developed sepsis and 2 developed serum sickness. No CMV or EBV reactivations.	Improvement in EDSS scale 3.5 (ranged from 1.0-7.0)	One patient had very mild relapse after 7 months otherwise, all patient were stable during the follow-up MRI follow-up showed enhancing lesions at 1 and 2 months in two patients. No more enhancing lesions thereafter except for 1 patient with a relapse
Burman, 2014 (37)	48 patients, median age of 31 years, M/F= 22/26	40 patients diagnosed with RR-MS, 5 SP-MS, 2PP-MS and 1 PR-MS	Median 6 (ranged 1-8.5)	47 months	Not mentioned	Almost all patients experienced expected toxicity symptom (alopecia, anemia, thrombocytopenia, and leukopenia). Half of them had fever with bacteraemia a patient had fungal infection. There was no mortality. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%)	median change in EDSS was −0.75 (range −7 through 1.5)	After 5 years relapse-free survival and MRI event free survival were reported 87 and 85%, respectively. In MRI, five new lesions and eight new T2 lesions were detected, equating to one new T2 lesion for every 20th year of follow-up. CSF: The mean IgG index post-HSCT was significantly lower in comparison to the pre-HSCT value in those patients
Mancardi, 2015 (38)	21 patients, Median age of patients in this group is 36 years M/F 4/5.	21 patients with SP-MS RR- MS	Median 6.5 (5.5–6.5)	48 months	3 to 8 x 10^6 $CD34^+$ cells/kg	Almost all patients in AHSCT group had experience expected toxicity signs and symptoms fever with bacteremia, alopecia, anemia, thrombocytopenia, and leukopenia.	No difference in EDSS change at year 1, 2, 3, and 4 was found	AHSCT significantly reduced the number of new T2 MRI lesions counted over 4 years, compared to MTX
Atkins, 2016 (39)	24 patients, median age of 34 years, M/F =10/14	12 patient RR-MS and 12 with SP-MS	3.0-6.0	Median follow-up was 6·7 years (range 3·9–12·7)	Not mentioned	Standard supportive care and anti-infective prophylaxis had been given and treatment-related toxic effects were assessed each day during admission with the Bearman Regimen-Related Toxicity Score, however, the details are not reported in the article	EDSS score shows improvement or stabilized in 91% (n=11) , though 50% (n=12) patients with higher baseline score progress	Progression ceased in 70% of patients in this study None of the patients that had T2 lesions showed Gd-enhancing lesion after transplant, only one patient that had not had any lesion in MRI 5 months back showed 4 lesions 1 month after transplant

Worsening and relapse is defined as a gain of 1.0 or more EDSS points from baseline

a. Improvement is defined as a reduction of 1.0 or more EDSS points from baseline

2. Scripps Neurological Rating Scale

a. Worsening and relapse is defined as a loss of 10 or more SNRS points from baseline

b. Improvement is defined as a gain of 10 or more SNRS points from baseline

By end of 24 months mean EDSS scores declined gradually over time while SNRS scores gradually improved.

Nash and his team (33) used EDSS, Scripps neurologic rating scale, MRI of the brain, CSF analysis.

Carreras (34), Su *et al.* (35), Fagius (30), Burman (37), and Atkins (39) also used Change in EDSS, MRI evaluation, and adverse events as assessment tools. Meanwhile, Shevchenko did not emphasize controlling MRI for all participants and mainly used EDSS score and adverse events as the assessment tool, Mancardi and his team assessed disease activity by using MRI.

Nash and his team did not report any side effects but expected immunosuppression-related side effects.

Discussion

The selected papers in this study are case series, clinical trials, and one RCT, with sample sizes ranging from 9 to 50 patients and follow-up duration of 1–7 years. Alongside comparison of clinical characteristics in baseline and post autologous hematopoietic stem cell transplant (AHSCT) treatment, results of MRI (if was available), intervention, and procedural side effects are discussed. Gender distribution is not following normal gender distribution, that can be due to including severe cases in these studies and sex-specified severity of MS (40).

The median age of cases was 27 to 41 years (range 9–75) and median duration of disease prior to AHSCT are 26 months to 8 years, which reflected inclusion criteria in almost all of studies that included severe or malignant MS cases.

There are wide differences in basal EDSS scores in these studies as this score was not the criteria in recruiting cases and only deterioration of this score was considered in these studies. Therefore, based on this review basal disability score cannot be considered as an effective factor for predicting treatment response and prognosis, however, based on neural history studies we know that conversion to the SP-MS course is the most important factor in long-term prognosis (41).

In general, reviewing the outcome of these studies reveals that there were improvement or stabilization in neurological signs and symptoms after AHSCT. The oldest study that was reviewed was published in 1997 by Fassas and was among the early series of studies that treated multiple sclerosis with HSCT and their results showed that HSCT can be used with relative safety without causing exacerbations of the disease.

Despite very promising results achieved in this study in term of EDSS score reduction, Nash *et al.* and Carreras *et al.* had mixed results regarding disability score, however based on these studies still AHSCT is an efficient treatment for stabilizing the symptoms with acceptable related toxicity. The mixed results in these two studies can be due to recruiting severe cases. Other studies in this review showed a general improvement of clinical neurological outcome measured by the EDSS score, excluding the study reported by Mancardi in 2015. Mancardi and his team found out that, AHSCT can stabilize MRI lesions and reduce the annual relapse rate (ARR) in comparison with conventional MTX treatment, however this modality of treatment did not make a significant change in the EDSS score. On the contrary Fagiuse and his team in 2009 had a very promising outcome in terms of reduction of EDSS score and clinical disability improvement in their patients, which can be attributed to choosing young (median age of 27 years) patients with short duration of disease before transplant (median duration 26 months). This finding is in line with other studies' results that showed in general younger patients (<40 years) with a shorter history of multiple sclerosis (<5 years) tend to respond better to HSCT (42).

All of the patients in reviewed studies received stem cell mobilization with a basis of cyclophosphamide (2-4.5 g/m^2) together with G-CSF or GM-CSF and immune ablation consequently. Harvested HSC had been transplanted following this conditioning preparation in order to engraft hemostatic expansion of new mature T cells and B cells (43). It is likely due to the fact that in these patients, T-cells play a significant role in the ongoing disease pathogenesis. By providing high dose immunosuppressive therapy, these autoreactive T-cells are eradicated. Subsequently, a new immune system can be reconstituted with the use of HSCT.

It is more difficult to treat MS when the disease has progressed and irreversible damage to the CNS has already occurred. Advanced stage of disease can result in significant and permanent loss in neurological function. By understanding this, treatment for MS with HSCT should target patients with active inflammation such as in RR-MS or PR-MS (22, 42).

As the majority of patients in these studies showed substantial recovery it could be assumed that repair mechanisms in MS are still active, but suppressed with ongoing inflammation. Constant improvement in EDSS score up to 50% is reported in patients after AHSCT (44-46).

It is also important to note that the papers in this study were published between years 1997 and 2016. This meant that the stem cell treatment procedure was allowed to evolve over the span of 19 years. Even so, stem cell mobilization and the transplantation procedure was vastly the same. Cyclophosphamide or G-CSF was used for stem cell mobilization while BEAM regimen, modified BEAM regimen, or ATG was used for stem cell transplantation. Even the dosages of the drugs were relatively the same.

Transplant-related toxicity was very common during the process. Undoubtedly, the degree of toxicity observed was greater than the conventional therapy for MS. However, most of these side effects were transient and reversible. Nash *et al.* in their study had reported a transplant-related mortality with the development of EBV –PTLD in one of the patients (33). The most common side effects were allergic reactions, which included fever and rash. Only one mortality related to this treatment modality was reported in all of the reviewed studies, which is concordant with, not negligible mortality rate of 1-2% that is estimated for this treatment (31). In these reviewed studies, main important side effects were chemotoxicity and its consequences. This finding is very similar to 93- 97% survival rate among patients that received chemotherapy before bone marrow transplant in other studies (47, 48). Therefore wise patient selection to reduce the procedural risk and better outcome are crucial.

Burman *et al.* reported thyroid disease in 8.4% of their patients as one of long-term side effects of their treatment which is similar to autoimmune side effects such as thyroiditis reported in other studies (44).

Conclusion

Multiple sclerosis is an incurable disease of the CNS and whilst conventional therapy has shown to provide a level of relief of its symptoms, it is far from satisfactory. This review can conclude that hematopoietic stem cell transplantation is a feasible treatment for patients with multiple sclerosis; nevertheless, safety is still the area of concern due to chemo toxicity side effects as the greatest risk of transplant. It has been shown that HDIT + autologous HSCT can be utilized as a safe treatment for multiple sclerosis, conditional to wise selection of candidates. Therefore, practical criteria for selecting patients for this treatment should be defined. It can also be concluded that it is best to perform hematopoietic stem cell transplant after high-dose immune suppressive therapy in patients with active or early MS whereby inflammation and T-cells play a pivotal role. This is to obtain maximal effect from the treatment.

Most of the studies conducted consist of a relatively small sample size. A larger sample size and a longer follow-up duration are required to understand better the efficacy and safety of HSCT in MS.

Conflict of interest

The authors declare that no conflict of interest exists.

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