MEDDOCS Open Access Publisher

Annals of Oncology Case Reports

Open Access | Research Article

Emerging Role of Autologous Hematopoietic Stem Cell Transplantation (ASCT) as Compared to Disease Modifying Therapies (DMT's) for Multiple Sclerosis

Furqan Ul Haq[1]; Madeeha Subhan Waleed[2]; Brooke Peters[3]; Fatima Hassan[4]; Maimona Bano[5]; Salman Abdul Basit[6]; Nadia Jamil[7]; Fazila Khan[8]; Rafiullah Khan[9]

[1]Hayatabad Medical Complex, Peshawar, KP, Pakistan.

[2]Ayub Medical College, Abbottabad, KP, Pakistan.

[3]Regional Clinical Pharmacist, Pharmacy Operations, American Oncology Network, LLC.

4Fatima Jinnah Medical University Lahore, Pakistan.

[5]Deccan College of Medical Sciences Hyderabad, India.

[6]Shalamar Medical & Dental College, Lahore, Pakistan.

[7]Sargodha Medical College, Sargodha, Pakistan.

[8]Khyber Teaching Hospital, Peshawar, KP, Pakistan.

[9]Consultant Hematologist and Oncologist, Division of Hematology and Oncology The Christ Hospital, Cincinnati, Ohio, USA.

***Corresponding Author(s): Furqan Ul Haq**
Hayatabad Medical Complex, Peshawar, KP, Pakistan.
Email: furqanulhaq459@gmail.com

Received: Jun 07, 2022

Accepted: Jul 08, 2022

Published Online: Jul 11, 2022

Journal: Annals of Oncology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Multiple Sclerosis; Stem cell transplantation; DMT's; Autoimmune diseases; Immunotherapies.

Abstract

The treatment of Multiple Sclerosis comprises two types of Regimens, those are Disease Modifying Drugs and Autologous Hematopoietic Stem Cell Transplantation (ASCT). ASCT has been studied in MS for more than two decades. It is a process in which normal/healthy blood stem cells of your own body replace your disease stem cells in bone marrow by using Granulocyte colony stimulating factors for stem cell mobilization, CD34 for stem cell depletion, and CY, Busulfan and Antithymocyte Globulins for ablation at the time of cell infusion. It has successfully treated over 1400 patients. The indication for treatment is age less than 45 years, short duration (less than 10 years), Expanded Disability Status Scale (EDSS) >5.5 not very disabled, highly active relapsing-remitting MS (RRMS), malignant and in progressive MS. Nonmyelo ablative ASCT for relapsing-remitting MS found improved neurologic disability and a 5-year disease-free remission of 80% and decreased the relapse in RRMS from 80-97%. It has proved to be the most effective treatment by showing no progression in disease after compared to Disease-Modifying Therapy (DMT), where relapsing and disability continue. The marked improvement in safety has shown its way from appropriate patient selection, the choice of conditioning regimen, increasing experience, and accreditation of transplant centers. In contrast to ASCT therapy, treatment with DMT's has low efficacy and due

Cite this article: Ul Haq F, Waleed MS, Peters B, Hassan F, Bano M, et al. Emerging Role of Autologous Hematopoietic Stem Cell Transplantation (ASCT) as Compared to Disease Modifying Therapies (DMT's) for Multiple Sclerosis. Ann Oncol Case Rep. 2022; 5(1): 1002.

to its high costs and low efficacy after 5 years even with a trio of standardized therapy of Ocrelizumab, Cladribine & Alemtuzumab the disease progression occurs and relapse of symptoms occur with in few months. The efficacy drops to 15% and relapse of symptoms occur in about 80% of patients within 3 to 4 years.

Introduction

Multiple sclerosis is a chronic immune-mediated, neurodegenerative disorder of the central nervous system (brain, spinal cord, and optic nerves). In MS, the immune system destroys the oligodendrocytes, which myelinate axons of neurons in the CNS, resulting in life-long disability. The individuals affected with MS usually present various symptoms, including fatigue, motor weakness, ocular and brainstem/cerebellar symptoms, spinal cord syndromes (Lhermitte phenomenon), neurogenic bladder, mobility limitations, and cognitive impairments. Being an autoimmune disease, it is more prevalent in females in their 20's and 30's than males. In most cases, the most common clinical course is relapsing and remitting type (RRMS). Secondary progression occurs in a lot of patients.

MS has two types of therapies mainly these days.

1. Disease modifying drugs (DMD's)-an older concept.
2. Autologous hematopoietic stem cell transplantation (ASCT).

DMDS has been approved for relapsing and remitting MS. It has been approved in many Countries worldwide such as in European countries (EMA), first line therapies are (Interferon Beta, Glatiramer Acetate, Teriflunomide, Dimethyl Fumarate) while if first line doesn't work we add second-line drugs such as (Cladribine, Fingolimod, Natalizumab, Ocrelizumab, and Alemtuzumab) [1]. The second set of therapy is AHSCT, a well-known procedure primarily used to manage hematologic malignant disorders. Since the last few decades, it has been aggressively used for the management of autoimmune disorders in which one of the diseases high on the list is MS. It works for resetting the immune system so that the body's immune system will not attack the body's own nervous system. Compared to DMDs, and is a one-time procedure after which most of the patients do not require additional therapies.

Epidemiology and historical perspective of it's treatments

Approximately 3 million people in the world have Multiple Sclerosis (MS). MS usually presents in early adulthood and can cause significant neurological deficits. The disease affects 2.3 million people globally and has a prevalence of approximately 100 /100,000 or 1 in 700 adults [2]. The condition is so disabling that 5 years after diagnosis, only 25% of people are still working. The existence of the disease varies in different populations. MS is more common in females; the exact cause of gender difference is still unknown but females to males ratio is almost 2.3:1, affecting more predominantly people of Cold areas because of less sun exposure and low Vitamin D production especially in Northern Europe, Northern America, Australia and New Zealand etc. Although MS generally affects females, it has an earlier onset in the male population. The progression of the disease seems to be slower in females.

Early on, it was believed that the genotype of the bone marrow generally dictated the propensity of acquiring an autoimmune disease. However, in the early 1990s, rats with adjuvant arthritis responded similarly to autologous /syngeneic bone marrow transplants and allogeneic bone marrow. The first trial of ASCT was performed in April 1995 in patients with progressive MS. Studies on 15 patients were published in 1997 having secondary progressive MS. For MS both in primary and secondary progressive type several trials of ASCT were published and reported [3]. In 2009, the turning point and independent groups concluded that hematopoietic stem cell transplant could stop the disease in the majority of relapsing-remitting MS patients. The European Group of Blood and Marrow Transplantation (EBMT) multicenter study suggested positive early results in their trials. Long-term follow-up studies showed a progression-free survival rate (PFSR) of 44% in patients with active central nervous system disease vs.10% without the active disease [4]. In 2012 based on the results of various trials, consensus recommended using this as a treatment modality for severe deteriorating MS despite standard therapy. Finally, AHSCT was approved for the treatment of RRMS on the national level by the Swedish Board of Health and Welfare in the year 2016.

Since the last recommendation, there has been increased interest by small-scale case series, case studies, meta-analyses and multicenter studies in patients with MS responding favorably to this. The American Society for Transplantation and cellular Therapy (ASTCT), Task Force recommends this as "standard of care, clinical evidence available," for patients with relapsing-remitting or progressive MS. The results of the MIST study concluded the same [5].

Procedure of AHCT and it's review

Autologous Hematopoietic Stem Cell Transplant (ASCT) has been highly efficacious for severe, treatment-resistant Relapsing-Remitting type of Multiple Sclerosis (RRMS). It works by resetting the body's immune system through apoptotic pathways by removing the auto-reactive T-cells and replacing them with new clones, observed post-infusion. As evidenced by clinical trials and long-term data entries, it occurred that this has shown long-term safety and efficacy. The European Bone Marrow and Transplant (EBMT) has successfully treated over 1400 patients with this. The marked improvement in the safety of has seen its way from appropriate patient selection, the choice of conditioning regimen, increasing experience, and accreditation of transplant centers by the FACT in the US. The criteria for patient selection include age less than 45 years, short duration (less than 10 years), EDSS >5.5 not very disabled, plus highly active RRMS (at least one relapse in the last 12 months with evidence of Magnetic Resonance Imaging (MRI)-disease activity regardless of the use of DMT [6]. Many conditioning regimens have been put to trial. Although able to achieve increasing high NEDA, high conditioning regimens switched to intermediate and low-intensity conditioning regimens due to high mortality rates. The two most widely used conditioning regimens in EMBT are the 'intermediate' regimens - the myeloablative BEAM-ATG and the non myeloablative Cyclophosphamide-ATG. With no data showing superiority, these have been shown to induce high rates of sustained NEDA (absence of clinical relapse, disability progression, and any evidence of radiological disease activity on Magnetic Resonance Imaging (MRI)) and no TRM. In 2019 the European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Disease Working Party (ADWP) and The American Society for Transplantation and Cellular Therapy (ASTCT) made this "the standard of care" for highly active RRMS, failing at least one DMD. During the transplant and long-term follow-up, BMT Physicians must collaborate closely with Neurologists and

other multidisciplinary team members for a better outcome. The follow-up period should focus on the early and late post-transplant complications. Over the years, there has been much improvement in the treatment-related mortality (TRM) using AHSCT. Those patients who were treated by DMD's suffered a lot due to high costs from lifelong treatments, had low quality of life, unemployment and dependency ratio was several folds raised in them. On the contrary, though not cheap, is a one-time procedure that provides therapeutic benefits leading to better health economics.

Various steps are necessary for the ASCT in patients with MS.

i). Generation of HSCs and HPCs:

The hematopoietic stem cells and hematopoietic progenitor cells are mobilized; for doing this step, we need stimulating agents like granulocyte colony-stimulating factor (G-CSF) to proliferate HSCs/HPCs.

ii). Administration of the conditioning regimen:

After collecting the required cells, the next step is administering the conditioning regimen followed by infusion of the HSCs and HPCs. In the conditioning regimen, the chemotherapy agent is used to remove the auto-reactive lymphocytes. This process enhanced the efficacy in the management of MS patients. Immunosuppression before AHSCT removed the auto reactive lymphocytes. The removal of the auto reactive lymphocytes has been demonstrated to improve the recovery rate and reduce complications associated with this.

iii). Pre and post-transplant care

Prior to the transplantation, patients with MS should be evaluated entirely for infectious diseases. Post-transplantation care needs to support the patients from possible complications

iv). Candidate for transplant

The results obtained in MS patients were very favorable. ASCT was best for RR MS because of –increased extended disability surviving scale was reported in RRMS patients treated with immunosuppressive and ASCT.

-Decreased mortality rate was observed into less than 5% in the RRMS after treatment with immunosuppressive drugs and ASCT - Relapse free survival rate was increased and was reported to be more than 80% in MS patients if treated with ASCT and respective conditioning regimen.

Efficacy

The efficacy is explained based on three parameters.

1) Progression-free survival (PFS)

2) Long term prognosis

3) Quality of life

Two meta-analyses have previously established the effectiveness of this in MS. The first meta-analyses consisted of 15 studies. It included 764 patients; with the majority suffering from progressive MS and advanced disease (median EDSS score of 5.6). The results showed progression of disease post-transplant of 17.1% and 23.3% at 2 and 5 years follow up. However, in patients with RRMS, the prognosis was better, and the progression rate was much lower at 2 years follow up. Another study also reported NED (no evidence of disease) status i-e, absence of relapses, progression, and new signs of disease activity on MRI scan. It showed NED reached 83% (70-92%) in 2 years and 67% (59-70%) in 5 years. The second meta-analysis contains 18 studies on 732 patients. It has shown PFS among RRMS patients of about 85% and 80% in the post-transplant patients on low and intermediate therapies [7].

The worth of any therapeutic procedure also depends upon long-term prognosis, particularly in chronic diseases like MS. It was demonstrated in a multi-centric study from 1995 till 2006 on 281 patients from 13 countries, with 77% suffering from progressive MS treated with ASCT. They were followed up for an average of 6.6 years (range 0.2-16 years). At 5 years post-transplant, 46% were disease-free, and the overall survival was 93%. Patients with old age, progressive MS, and who underwent more than 2 previous disease-modifying therapies had neurological progression after transplant [8].

Costs of treatment

Although there is limited information available about the cost of transplant, the data still favors it, and the expenses are calculated indirectly. As this is a one-time investment with no direct cost post-transplant, its average expenses with high-intensity regimens have been estimated to be 140,000 USD in 2017. On the other hand, Hartung and colleagues calculated the yearly cost of MS patients treated with immunosuppressive medications around 80,000 (± 20,000$). But this cost enhances forever and has been discussed scientifically in table no. 1 and table no. 2 below.

Table 1: Estimated Costs (USD) of Drugs used for MS: (Avg. wholesale pricing):

Serial no.	Medication	Dose	Cost per unit in USD	Cost per dose	Cost per 4 weeks (USD)	Cost per year
1	Fingolimod (Gilenya)	0.5 mg daily	363.81 per capsule	363.81	10,186.68	132,426.84
2	Beta Interferons (Avonex)	30 mcg IM once a week	8646.65 each	8,646.65	34,586.60	449,625.80
3	Glatiramer (Copaxone)	20 mg daily SQ	284.56 per mL (20 mg/mL)	284.56	7,967.68	103,579.84
4	Teriflunomide(AUBAGIO)	14 mg daily	322.36 per tab	322.36	9,026.08	117,339.04
5	Cladribine (Mevenclad)	1.75 mg/kg/year	52.2 per mL (1 mg/mL)	913.50 (80 kg)	3654	7308
6	Natalizumab (Tysabri)	300 mg every 4 weeks	597.11 per mL (20 mg/mL)	8956.65	8956.65	116,436.45
7	Ocrelizumab (Ocrevus)	600 mg every 6 months	2,043.64 per mL (30 mg/mL)	40,872.80	40,872.8	81,745.60
8	Alemtuzumab	12 mg daily for 5 days year 1 then 3 days year 2	31,058.00 per 1.2 mL (10 mg/mL)	31,058.00	155,290	155,290
9	Dimethyl Fumarate (Tecifedra)	240 mg twice daily	165.51 per capsule	165.51	9,268.56	120,491.28

Table 2: Estimated costs (USD) of Drugs used in AHCT (Avg. wholesale pricing):

Serial no.	Drug	Dose per AHCT	Costs per unit in USD	Costs per therapy in USD (80 kg, 1.7 m^2)
1	Rabbit ATG	6 mg/kg	1103.65 per 25 mg	20,969.35
2	Cyclophosphamide	200 mg/kg	395.56 per 500 mg	1,265.79
3	Carmustine (BiCNU)	300 mg/m2	4481.09 per 100 mg	22,853.56
4	Etoposide	800 mg/m2	2.99 per 20 mg	203.32
5	Cytarabine arabinoside	800 mg/m2	1.25 per 100 mg	17
6	Melphalan	140 mg/m2	1378.32 per 50 mg	6,560.80

Table 3: Studies done on ASCT for MS.

Serial no.	Author	Journal/Year of publication	No. of patients	Study design	Methods/Interventions	Results and Post-Transplant Complications
1	Fassas A.	PubMed, 1997	15	Pilot study	BEAM followed by ASCT and ATG therapy	Median follow-up time is 6 months (6-18). Durable neurologic improvements have been detected on both the EDSS (7/15) and SNRS (15/15) systems. One patient worsened at 3 months and two have relapsed. Allergy (93%) and infections (87%) were the principal toxic complications with Mild neurotoxicity.
2	Openshaw H	PubMed, 2000	05	Prospective Cohort	G-CSF for stem cell mobilization, CD34 for stem cell depletion, and Cyclophosphamide, Busulfan and ATG at the time of cell infusion.	Neurologic progression of 1 point on EDSS occurred in one patient after 17 months; one patient died on day 22 due to Influenza pneumonia. One died in 19 th month due to overwhelming Staph A pneumonia sepsis. At 18 and 30 th month patients were having stable MS.
3	Fassas A	Neurology PubMed 2002	85	Retrospective cohort study	Chemotherapy e anti Lymphocyte antibodies with or not total body irradiation.	Progression free survival rate was 73% (+-12%). At 3 years. Patients experience neurologic complications while moving stem cells to peripheral blood. 7 patients died, 5 due to toxicity and 2 due to infections, 2 suffered from neurologic damage.
4	Prof. Dr Xiu-Shi Ni	The Journal of Clinical and Translational Research, 2006	21	cohort	Cyclophosphamide and Beam followed by stem cell reinfusion and ATG therapy	Median follows up time 42 (6-65) months. Progression free survival of 75% and disease activity free survival 33.3%. Two patients died of pneumonia and VZV hepatitis at 4.5 and 15 months post transplant, ASCT seems beneficial to Progressive type of MS.
5	Krasulova E	SAGE Neurology J, 2010	26	Prospective Cohort	Stem cells were mobilized; G-CSF plus Cyclophosphamide, BEAM, and ATG were used for ablation.	Progression free survival after 3 and 6 years was 71% and 29% respectively. Patients with RRMS having age less than 35 were having more favorable outcomes. No patient between the first 100 days after transplantation.
6	Snowden J.	BMT,2012	21	Review Article guidelines	Literature Review study of Articles Published	Recommended ASCT for patients of RRMS, malignant MS with severe disability from previous year, progressive MS with secondary inflammatory evidence and MS in which the patient has EDSS OF 6.5 upper limit with inability to walk.
7	Mancardi G	PubMed Neurology J,2015	Multi centers	Randomized control trial	Patients received CY with Filgrastim , ATG and BEAM with ASCT or 20mg Methotrexate every month for 6 months.	79% reduction occurred in T2 lesions with ASCT as compared to Methotrexate. It also reduced Gd + lesions with decrease in relapse rate annually.
8	Sormani M P	American academy of Neurology J, 2017	764	Meta-analysis	Meta-analysis	Out of 764 patients the Disease free survival was 83% and 77% and disease progression rate was 17.1% at 2years(95%CI 9.7%–24.5%) and 23.3%(95%CI16.3%–31.8%) at 5 years and treatment related mortality was 2.1 %.
9	Muraro PA	JAMA Neurology, 2017	281	Multicentre Prospective Cohort study from 1995 to 2006.	Literature Review study of Articles Published, meta-analysis.	Overall survival after 5 years of follow up was 93% (95% CI, 89%-96%). Almost half of the patients survived free of disease for 5 years. Young age ,relapsing form of MS , fewer prior immunotherapies, and lower baseline EDSS score were factors associated with better outcomes.

10	Sharrack B	Bone Marrow Transplantation Journal 2019	21 in peads for multiple Sclerosis	Meta Analysis	ASCT studies for MS as well as other diseases such as Myasthenia Gravis, Chronic Inflammatory Polyneuropathy, Stiff Person Syndrome etc. For MS they have used both types of studies of ASCT procedures like BEAM based ASCT and Cyclophosphamide based therapies.	EMBT is the largest database for ASCT even for other diseases like 0.5 Million people are registered for ASCT and more than 3000 people were successfully treated with ASCT. RRMS and Progressive type MS has been treated very frequently with ASCT, But very rarely used for Aggressive type of MS. Cohort of 21 patients under 18 were treated for MS EDSS scores were 81% and PFS was 100% in 3 to 5 years. Chronic Inflammatory Polyneuropathy has been successfully treated with ASCT, 90 % OF patients have been improved and after 04 to 05 years follow up only 35 % of patients got relapsed.
11	Ge F.	Springer Neurology, 2019	732	Metaanalysis and systematic review	Literature Review study of Articles Published, Meta Analysis	PFS was 75% and Disease FS rate was 61% after 48 months. Relapsing and Remitting type of MS patients were relatively more benefitted with 80% PFS. TRM was 1.38 % but overall Mortality rate was 3.58. Treatment related Mortality with high intensity regimen is 4% and in older studies done before 2006 is 2%.
12	Boffa G.	PubMed/Neurology, 2020	215	Prospective Cohort	BEAM plus ATG with ASCT.	Disability worsening-free survival (95%CI) was 85.5 %(76.9-94.1%) at 5 years and 71.3 %(57.8-84.8%) at 10 years. In case of progressive MS the disability worsening-free survival was 71.0 %(59.4-82.6%) and 57.2 %(41.8-72.7%) at 5 and 10 years, respectively. Numbers of deaths within 100 days after ASCT were 3 (1.4%).
13	Miller AE	JAMA neurology ,2020	-	Literature Review study	ASCT supporting study for MS .	Mainly they have explained that ASCT is successful for RRMS, for patients younger than 50 years of age, for people having MS less than 10 years of duration.
14	Bose G	Multiple Sclerosis Journal , SAGE 2020	-	Perspective Study	Study on different Regimen on ASCT.	According to this article ASCT efficacy has been improved because of better immune ablating drugs, followed by ASCT. Selection of patient and better conditioning Regimen has also decreased the morbidities and mortalities related to ASCT.
15	Nicholous RS	American J of neurology ,2021	120	Retrospective Cohort study in UK	Study of patients from 2012 to 2019 at 06 months interval time.	DFS was 98% and 93% at 2 and 4 years respectively. No MRI lesions were detected in 90% and 85 % at 2 and 4 years of follow ups. EBV reactivation was detected and monoclonal paraproteinemia was associated in patients with worse PFS. Within the 1st 100 days 3 deaths occurred (2.5%) from fluid overload and cardiopulmonary failure.

Abbreviations: EMBT: European Society for Blood and Marrow Transplantation; SNRS: Scripps Neurological Rating Scale; BEAM: Carmustine, Etoposide, Cytarabine, Melphalan; EDSS: Extended disability Scoring Scale; PFS: Progression Free Survival; DAFS: Disease Activity Free Survival; TRM: Treatment Related Mortality; G-CSF: Granulocytes Colony Stimulating Factor; ATG: Anti thymocyte Globulins. [9-23].

6.Comparative graphs of AHSCT to DMD's conventional treatment for MS

Some patients with MS still have relapses of symptoms even after having therapy with first-line, the most standard and efficacious drugs even if the therapy period is for years, as compared to the drugs used in MS autologous hematopoietic stem cell transplant therapy guarantees the treatment of a relapsing and remitting type of MS for years. This is likely saving a lot of money as compared to the disease-modifying drugs (DMDs). In 2019 The European Group for Blood and Marrow Transplantation (EMBT) and the American Society for Transplantation and cellular Therapy (ASTCT) recommends standard therapy choice for the relapsing-remitting type of MS. Comparison of DMD's Therapy with Standardized therapy Table number (3) below:

Results of the above studies on ASCT in term of increase in Progression Free Survival from 2002 to 2021 shown in Graph no.01:

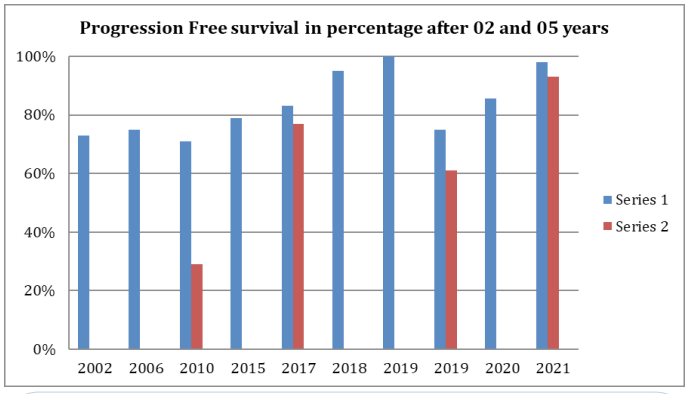

Figure 1: Progression Free Survival (PFS) comparison at follow-up of 02 years and 05 years after doing Autologous Hematopoietic Stem Cell Transplantation for MS. Series 1 (blue bars) shows PFS at 02 years and series 2 (red bars) shows PFS at 5 years. In 2019 the PFS was 100% in Patients of Pediatrics having 100% PFS (Most effective in Pediatric patients having MS).

Table 4: Comparative table on ASCT and DMT's for MS.

	Autologous Hematopoietic Stem Cell Transplant Therapy	Disease Modifying Drugs(DMDs)
Method	• Transplant therapy in which healthy hematopoietic stem cells are collected, stored and given back to the same person after treating the MS patients with a high dose of conditioning chemotherapy.	• Drugs that halt the progression relieve the symptoms acutely and prevent the relapses of MS without curing the disease permanently.
Medication used are:	• Rabbit-ATG and Cyclophosphamide, methotrexate, Busulfan once to ablate the bone marrow. Then for years no use of autoimmune drugs is needed.	• 1st line: Steroids in acute flares, Beta Interferon, Glatiramer ,Teriflunamide,Dimethyl Fumarate. • 2nd line:Cladribine, Natalizumab,Ocrelizumab, Alemtezumab and Fingolimod etc used if 1st line therapy fails to treat the acute flares.
Treatment related Mortality and Morbidities	• After 5 years 46% people showed no disease or completely disease free with 93% survival rate. • Mortality was initially high up to 3.6% but after 2005 the studies has shown that mortality has reduced to 0.3% due to improvement due to improvement in conditioning regimen and supportive care, greater experience and appropriate patient selection.	2.9 times higher mortalities are associated with MS patients.
Advantages and Disadvantages	• It is available for most of the patients with no risk of Graft vs Host reaction, lowers risk of other autoimmune diseases. • In female patients menstrual periods return to normal and have good pregnancy outcomes [24]. Though it is still considered as the most effective procedure.	• Easily available and easy to take the drug • Steroids are cost effective but the rest of the drugs are very expensive. • Causes a lot of side effects like immune suppression, obesity. Hypertension. • Johnco Nigam (JC) virus infections with Natalizumab / Interferons causing leukoencephalopathy.
Costs	• As this is a one-time investment with no direct cost post-transplant, its average expenses with high-intensity regimens have been estimated to be 140,000 USD in 2017. • This corresponds to 57% of the pharmaceutical spending expected for continuous treatment with DMT's for all patients throughout the same follow-up period.	• Hartung and colleagues calculated the yearly cost of MS patients treated with immunosuppressive medications around 50,000 to 70,000 USD.
Limitations	• Costs vary from center to center, selection of patients, regimen selection, accreditations, center experience and regional variations.	• The three licensed drugs for DMT's Alemtuzumab, Ocrelizumab, & Cladribine , there is clinical evidence of net huge gains in these procedures as compared to DMT , which costs 50,000 to 70,000 $ per year.
Futuristic perspective	• 80 to 98% of relieving the symptoms of RRMS once it has been done, due to its high efficacy . So this method is the most sophisticated and advanced approach. Since its treating the RR MS symptoms upto 85% even after 5 years no relapse and remittance occur in majority of patients.	• Due to its high costs and low efficacy after 5 years even with a trio of standardized therapy of Ocrelizumab, Cladribine & Alemtuzumab. The efficacy drops to 15% and relapse of symptoms occur in about 80% of patients.

iii).Comparative Graph showing the efficacy and Costs of therapies for MS:

By comparing the three different approaches to treat MS , such as treatment with placebo, DMT's and ASCT we got this graph. Actually explains the efficacy and costs of treatment once therapy is given in Graph no.2 and Graph no.3 . We measure the No evidence of Disease activity percentage (NEDA%) annually up to five years. NED or NEDA% means no evidence of disease, i.e. no relapses, no progression, no new or enlarging or enhancing lesions on magnetic resonance imaging.

- ASCT showed almost 95-98% NEDA after one year, meaning no symptoms of relapse observed in above 95% of patients in one year. After following the patients for 5 years, studies showed that more than 80-85% people showed no relapse of symptoms with NEDA % above 80%. Only 20 % or even less than 20 % of people with ASCT got a relapse of MS after treating them with ASCT.
- Studies show that after treating with DMT's NEDA% was 50%. It means 50% of patients have relapse of symptoms of MS in one year after therapy and after receiving the high doses of 1st line therapy for five years, relapse of symptoms occurred in 80% of patients with only 20 % people with NEDA%.
- Placebo has only 20% effects for one year with NEDA 20% or even less, after 5 years almost all of the patients get relapses of the symptoms.

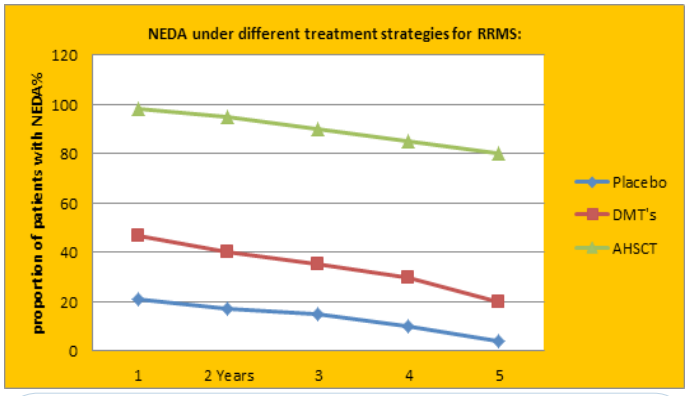

Figure 2: AHSCT, DMD's and placebo comparison and placebo by observing NED% (No evidence of Disease percentage). AHSCT (Autologous hematopoietic stem cell transplant), DMT's (Disease modifying therapies), NEDA (No evidence of disease).

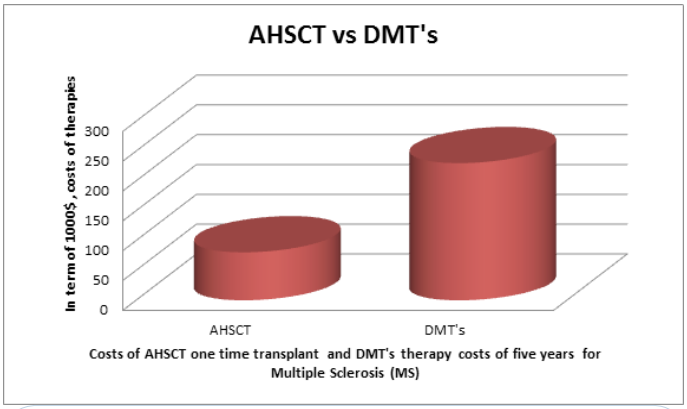

Figure 3: Comparison of costs of Autologous Hematopoietic Stem Cell Transplant (ASCT) done to a patient and another patient treated with Disease Modifying therapies (DMT's) for 5 years costs in terms of American Dollars.

Discussion

Despite a soaring annual cost of disease-modifying therapy, the proportion of patients with no evidence of disease activity (NEDA) is 30-50% after two years of treatment and 18% after four years of treatment. Some studies expect their cost to rise to the point that they will be beyond the healthcare system tolerance or generally accepted cost-effectiveness thresholds. Some DMDs are proven to be effective at the cost of potentially life-threatening side effects, e.g., (PML) progressive multifocal leukoencephalopathy for Natalizumab, lymphopenia for Cladribine, ocular disorders for Fingolimod, and the increased risk of strokes, heart attacks, pulmonary hemorrhages and cervical-cephalic arterial dissection for Alemtuzumab.

The prior case series of nonmyeloablative ASCT for relapsing-remitting MS demonstrated improved neurologic disability and a 4-year disease-free remission of 70%. Earlier clinical trials of high-dose immunosuppressive therapy (HDIT)/HCT were performed in advanced disease patients and progressive MS forms. The extensive, careful analysis demonstrated a far better outcome in patients with active CNS inflammation before HDIT/HCT than those without active inflammatory processes before the HDIT/HCT therapy [25]. Thus, this treatment may be more beneficial if administered earlier in the inflammatory stages of MS. This procedure such as ASCT has long lasting therapeutic effects and is cost effective overall than the treatment with DMD's. An emerging corpus of data and two prospective comparative trials have proven the efficacy of ASCT in suppressing inflammatory MS activity. Meta-analyses of studies performed on patients undergoing transplants since 1995 demonstrate a long-term remission in RRMS patients, induced by ASCT.

Mortality is the main concerning limiting factor in using ASCT. The advancement and enhancements in transplant techniques, accreditation of centers, and optimization of patient selection have improved the treatment-related mortality (TRM) from 3.6% to 0.3% as per the studies post-2005. Many complications of ASCT are secondary to immunosuppression, including febrile neutropenia, sepsis, urinary infections, and viral reactivations. Late adverse events described include infertility, malignancies, and secondary autoimmune conditions. However, studies have reported recuperation of menstruation and good pregnancy outcomes in women after ASCT for autoimmune diseases.

The long-term follow-up studies have illustrated a significantly lower incidence of secondary malignancies and secondary autoimmune conditions than some DMDs, such as Alemtuzumab. No cases of Progressive multifocal Leuckoencephalopathy were seen even in patients treated with Natalizumab and while having high titers of JC Virus antibodies. The NEDA rates 2-years post-ASCT exceed 70%, considerably higher than DMDs, suggesting the extensive effect of ASCT on disease activity in patients with the aggressive disease compared to other clinical trials participants. ASCT provides the most effective benefit/risk ratio to the patients with a low level of disability, the RR form, and clinical and MRI signs of disease activity.

Multidisciplinary guidelines have been published to select and manage patients based on clinical evidence. The recently updated and revised EBMT-ADWP & ASTCT guidelines recommend ASCT as the standard of care for highly active RRMS with failing with minimum of one type of DMD's fails and symptoms relapse occur even on MRI activities are seen on different times with in the past 12 months. ASCT is considered a clinical option for patients with aggressive RRMS developing severe disability in the last 12 months before failing an entire course of DMD. ASCT procedure shall be used in patients of active RRMS, young aged having short disease course and low Expanded Disability Status Scale (EDSS) score.

The consent protocol should incorporate a comprehensive discussion of the risk-benefit of ASCT and alternative treatments with both neurologists and BMT physicians.

Future trials

Although much improvement has been made in the biologic therapies for MS, we still need treatment for aggressive and refractory MS patients. In patients when DMD's therapy fails the ASCT is having highly successful and efficient results , presently occurring in nonmalignant settings such as Italy, Germany, Sweden, The United Kingdom (UK), The Netherlands, Spain, France and Australia. Randomized controlled trial, and auto graft for MS should continue to be performed in clinical trial settings. There are multiple trials working on the same platform, and development of such is underway [26]. In the USA, a national institute of health "BEAT-MS" trial will randomize patients to ASCT or best available approved treatment.

Similarly, other trials like the "NET-MS" trial, "RAM-MS" trial, and "STAR-MS work'' work in the same way. It is hoped that these trials, along with the use of real-world databases such as EBMT and MS Base, may better explain or describe which patients are most appropriately referred for ASCT vs. alternate IR therapy. Further investigation is still required to find the best treatment protocol for ASCT. Stem Cell transplantation has been used for many other diseases like Myasthenia Gravis, Stiff person Syndrome, Chronic Autoimmune Polyneuropathy. EMBT has registered more than half Millions of people for Autologous Stem Cell Transplantation and more than 3000 have undergone successful stem Cell transplantation.

Conclusion

The literature review concludes ASCT to be the most effective therapeutic intervention for patients suffering from diseases with disabling nature like MS as compared to Disease modifying therapies (DMT's). The advent of ASCT has revolutionized and modified the treatment of MS. ASCT has evolved over the last 2 decades and now has improved the quality of life and has better outcomes with PFS .It is reported that 80-98% of symptoms are relieved, especially in the patients with RRMS with no relapse of symptoms even after 5 years in the majority of patients, in Malignant MS and in severely progressive MS. The

cost of AHSCT has been estimated at $80,000 to $130,000 once in lifetime expenditure varies in different centers while the expenses of DMDs pile up indefinitely (three to five times of ASCT costs) in just five years of treatment for the patient. Because of good prognosis, cost-effectiveness, and marked safety, ASCT has been accepted and practiced in many parts of the world. ASCT shall be done in patients of age less than 45 year old with a short duration of onset such as less than 10 years , EDSS >5.5 not very disabled, and highly active RRMS. This article also depicts that the success of ASCT lies in supportive care during the peri and post-transplant period with early and long-term follow-ups.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

Abbreviations: ASCT: Autologous Hematopoietic Stem Cell Transplantation; BEAM: Carmustine, Etoposide, Cytarabine, Melphalan; DAFS: Disease Activity Free Survival; DFS : Disease Free Survival; DMT's: Disease modifying therapies; EDSS: Expanded Disability Status Scale (EDSS) score; EMBT: European Group for Blood and Marrow Transplantation; NEDA: No evidence of disease activity; PFS: Progression free survival; RRMS: Relapsing and Remitting type of Multiple Sclerosis; SNRS: Scripps Neurological Rating scale; TRM: treatment-related mortality.

References

1. Dörr J, Paul F. The transition from first-line to second-line therapy in multiple sclerosis. Curr Treat Options Neurol. 2015; 17: 354-10.
2. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J: Incidence and prevalence of multiple sclerosis in the UK 1990-2010: A descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry. 2014; 85: 76-84.
3. Openshaw H, Lund BT, Kashyap A, et al. Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: Report of toxicity and immunological monitoring. Biology of Blood and Marrow Transplantation. 2000; 6: 563-575.
4. Fassas A, Kimiskidis VK, Sakellari I, et al. Long-term results of stem cell transplantation for MS: a single-center experience. Neurology. 2011; 76: 1066-1070.
5. Snowden J, Badoglio M. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. PubMed. 2017; 20: 2742-2755.
6. Sharrack B, Saccardi R, Alexander T, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: Updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). Bone Marrow Transplant. 2019; 10.1038/s41409-019-0684-0.
7. Hartung DM, Bourdette DN, Ahmed SM. The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: Too big to fail?. Neurology. 2015: 2185-2192.
8. Bertolotto A, Martire S, Mirabile L. Autologous Hematopoietic Stem Cell Transplantation (AHSCT): Standard of Care for Relapsing-Remitting Multiple Sclerosis Patients. Neurology. 2020; 9: 197-203.
9. Fassas A, Anagnostopoulos A, Kazis A, Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: First results of a pilot study. Bone Marrow Transplant. 1997; 20: 6318.
10. Openshaw H, Lund BT: Kashyap A, Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: Report of toxicity and immunological monitoring. Biol Blood Marrow Transplant. 200065; 563-75.
11. Fassas A, Passweg JR, Anagnostopoulos A, Autoimmune Disease Working Party of the EBMT (European Group for Blood and Marrow Transplantation: Hematopoietic stem cell transplantation for multiple sclerosis. A retrospective multicenter study. J Neurol. 2002; 249: 1088-97.
12. Ni X, Ouyang J, Zhu W: Autologous hematopoietic stem cell transplantation for progressive multiple sclerosis: report of efficacy and safety at three yr of follow up in 21 patients. Transplantation Journal. 2006; 20: 485-489.
13. Krasulova E, Trneny M, Kozák T. High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a single centre 10-year experience. Multiple Sclerosis Journal. 2010; 16: 685-93.
14. Snowden J, Saccardi R, Allez M. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2012; 47: 770-790.
15. Mancardi GL, Sormani MP, Gualandi F, et al. ASTIMS Haemato-Neurological Collaborative Group, On behalf of the Autoimmune Disease Working Party (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT); ASTIMS Haemato-Neurological Collaborative Group On behalf of the Autoimmune Disease Working Party ADWP of the European Group for Blood and Marrow Transplantation EBMT: Autologous hematopoietic stem cell transplantation in multiple sclerosis: A phase II trial. Neurology. 2015; 10: 981-8.
16. Maria Pia Sormani, Paolo A. Muraro, Irene Schiavetti, Alessio Signori, Alice Laroni, Riccardo Saccardi, Gian Luigi Mancardi , Neurology May. 2017; 88: 2115-2122.
17. Muraro PA, Pasquini M, Atkins HL, et al. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. JAMA Neurol. 2017, 74:459-469.
18. Sharrack B, Saccardi R, AlexanderT. Autologous hematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: Updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). Bone Marrow Transplant. 2020, 55: 283-306.
19. Ge F, Lin H, Li Z, et al. Efficacy and safety of autologous hematopoietic stem-cell transplantation in multiple sclerosis: a systematic review and meta-analysis. Neurol Sci. 40: 479-487.
20. Boffa G, Massacesi L, Inglese M. Long-Term Clinical Outcomes of Hematopoietic Stem Cell Transplantation in Multiple Sclerosis. Neurology. 2021; 20: 10-1212.
21. Miller AE, Chitnis T, Cohen BA, et al. Autologous Hematopoietic Stem Cell Transplant in Multiple Sclerosis: Recommendations of the National Multiple Sclerosis Society. JAMA Neurol. 2021; 78: 241-246.
22. Bose G, Thebault S, Rush CA. Autologous hematopoietic stem cell transplantation for multiple sclerosis: A current perspective. Multiple Sclerosis Journal. 2021; 27: 167-173.

23. Richard S. Nicholas, Elijah E: Rhone et al, on. Hematopoietic Stem Cell Transplantation for Multiple Sclerosis:10.1212/WNL.0000000000012449

24. Maciejewska M, Snarski E, Wiktor-Jędrzejczak W. A preliminary online study on menstruation recovery in women after autologous hematopoietic stem cell transplant for autoimmune diseases. Exp Clin Transplant. 2016; 14: 665-9.

25. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv. 2017; 1: 2742-55.

26. Tanaka T, Watanabe S, Takahashi M, et al. Transfer of in vitro-expanded naive T cells after lymphodepletion enhances antitumor immunity through the induction of polyclonal antitumor effector T cells. PLoS One. 2017; 12: 0183976.