Autologous hematopoietic stem cell transplantation in progressive severe multiple sclerosis

Awadh Kishor Pandit, Kameshwar Prasad, Tulika Seth[1]

Departments of Neurology, and [1]Hematology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of central nervous system (CNS), which is disabling and majorly involves younger population. Various available treatments in forms of immunomodulation are not very effective; however, stem cell transplantation seems to be promising in recent literature. The current case report is a novel evidence for autologous hematopoietic stem cell transplantation (HSCT) in progressive MS. Case Summary: A 33 year old male with secondary progressive MS (SPMS), after being failed and/or intolerance to standard approved interferon (IFN) and mitoxantrone therapy, autologous HSCT was administered. At 2years of post-stem cell transplantation follow-up, he has remained stable with some improvement in functional status (Expanded Disability Status Scale (EDSS) reduced by 1.5), with no relapse, no treatment related complications, and no fresh magnetic resonance imaging (MRI) lesions. Conclusion: Autologous stem cell transplantation may be beneficial in progressive forms of MS, but needs to be tested in well-designed randomized trial.

Key Words

Autologous hematopoietic stem cell transplantation, HSCT in MS, multiple sclerosis, stem cell transplantation

For correspondence:
Dr. Kameshwar Prasad, Professor and Head, Department of Neurology, Neuroscience Centre, Room No. 704, 7th Floor, New Delhi, India.
E-mail: kp0704@gmail.com

Ann Indian Acad Neurol 2015;18:459-463

Introduction

One of the leading inflammatory diseases of central nervous system (CNS) in young adults is multiple sclerosis (MS), which is disabling in nature.[1] Majorities are relapsing-remitting (RRMS) form, about 85% and they gradually progress subsequently with accumulating disability what is known as secondary progressive form (SPMS).[2] Hence, almost 90% of RRMS turn into SPMS. A very less common form is PPMS, which is a slowly progressive disease (5%).[3]

The exact pathophysiology is not clear in MS, perhaps the genetic susceptibility, environmental trigger, and abnormal immunological reactions seems to mediate autoreactive T-cell that invade and seeks CNS, resulting in oligodendrocytes damage, focal myelin destruction, and axonal loss.

Access this article online

Quick Response Code:

Website: www.annalsofian.org

DOI: 10.4103/0972-2327.165482

Various treatment modalities available currently in the form of immunomodulation and immunosuppressive are approved and are recommended for MS. However, the stem cell therapy aiming neuronal and glial cell replacement or neuroprotection could be promising[4] in severe and nonresponders to the approved therapies. Since 1995, more than 1,000 cases suffering from severe autoimmune disease including MS have been treated worldwide with autologous hematopoietic stem cell transplantation (HSCT); based on the principle of complete ablation of an aberrant immune system followed by reconstruction of a new immune system.[5] Also efficacious in MS relapse suppression.[6,7] The aim of the present paper is to present a case of progressive MS and discuss the use of autologous HSCT in it.

Case Report

Patient history

Mr. AA, a 33-year-old right-handed, Asian male, a software engineer by profession, was apparently well before May 1998 (at the age of 18 years), when he had first episode of neurodeficit in the form of abrupt onset blurring of vision involving right eye associated with binocular diplopia on looking towards the right. About 2-3 days later, there was spontaneous recovery of vision, but diplopia recovered over next 5-6 months. About 14 months later, he had another (second) episode that was in July 1999 in the form of acute onset gradually progressive imbalance while walking with a tendency to fall on either

side, but more towards the left, also, felt mild weakness of left lower limb. At the onset, his symptoms were very subtle which progressed over next 6 months when there was also change in speech. The speech was slurred with intermittent scanning and abrupt loudness of voice. At this time, the patient was admitted and was diagnosed to have RRMS and was given pulse injection methylprednisolone (1 gm intravenous once daily for 5 days) at another hospital. He completely recovered within 3-4 months. He remained asymptomatic for the next 2 years (January 2000-December 2002). By the end of December 2002, he developed (third episode) subacute onset and progressive gait instability, which progressed over next 6months. He was admitted and underwent relevant and extensive investigations. During this period of progression, injection Rebiff was initiated, but the patient could tolerate only four doses and was discontinued due to intolerable fever and myalgia. His symptom was progressive and was admitted under our care in May 2003. During the hospital course, detailed work-up was done and his MS was of secondary progressive type (SPMS). Expanded Disability Status Scale (EDSS) documented at that time was 3.5. After detailed discussion and understanding the benefits and harms, the patient was initiated on injection mitoxantrone (each 3 months apart), which he discontinued on his own after 1 year, because there was no improvement. Subsequently, he was also prescribed tablet methotrexate after discussion with him and monitoring of adverse events, which was again discontinued by the patient in 6 months. By the end of 2004, patient became dependent for activities of daily living. After another 4 years of gradual progression of disease, he had another acute episode (fourth episode) in September 2008 in the form of worsening of symptoms, he developed increased imbalance while walking and tremulousness of both upper and lower limbs (right more than left limbs); he was again infused pulse injection methylprednisolone (1 g intravenous once daily for five days), but showed no improvement. He also had associated urinary frequency and hesitancy. Between the years 2008 and 2010 (i.e., for 2 years), the patient did not have any relapse, but neurological disability continued to progress. In February 2010, for the first time he was admitted under hematology services for stem cell transplantation, but was not considered eligible in view of the absence of any relapse for last 2 years. However, he again had an episode (fifth episode) in January 2012 with worsening both clinically as well as radiological. After this episode patient was readmitted in hematology services in February 2012 for autologous HSCT (see below under autologous HSCT methodology), which was done on 13th March 2012 (at EDSS of 6.5). Post transplantation he noticed gradual improvement in speech and walking and has been ambulatory without the support till date. The patient underwent reevaluation recently in July 2014 and noted having stabilization in his symptoms without any fresh episode in the last 2 years with an improvement in EDSS from 6.5 (in March 2012) to 5.0 (with Functional Systems Score (FSS) >5 in cerebellar examination, disability severe enough to impair activities of daily living (ADL), but ambulatory without aid for about 200 m). No history of persistent headache, seizures, encephalopathy, meningism, movement disorders, stroke-like events, and peripheral neuropathy. No other systemic symptoms (fever/night sweats, weight loss, arthropathy, rash, ulcers, dry mouth and eyes, and redness of eyes) were observed. Moreover, patient was born of nonconsanguineous marriage without any significant family history and also had no other comorbidities; had no addiction to tobacco chewing, smoking, or alcohol ingestion; no history of any chronic infectious disease; and no exposure to toxins as well.

Clinical findings

He is conscious, oriented, with normal vital parameters (blood pressure of 124/70 mmHg in right arm supine position and heart rate of 84/min regular). His Mini-Mental Status Examination is 28 of 28 (copying and writing are not possible due to tremulousness). Scanning speech with intermittent loud voice is noted suggestive of cerebellar dysarthria. All the cranial nerves are normal except his visual activity of 6/9 and after pinhole 6/6 in both the eyes. Fundus examination is normal on both sides. Motor examination is showing normal bulk and power; but grade 1.5 spasticity in both the lower limbs, also brisk deep tendon reflexes at all sites. Plantar reflex is extensor on both sides. There is asymmetric (right more severe than left) abnormal cerebellar examination in the form of impaired finger nose test (dysmetria, intention tremor, and in coordination), dysdiadokinesia, knee-heel test (dysmetria, incoordination, intention tremor), and gait ataxia (impaired tandem walk).

Investigations

His routine investigations of complete blood count, liver function test, kidney function tests, and thyroid stimulating hormone were normal. Erythrocyte sedimentation rate, C-reactive protein and other vasculitis markers (antinuclear antibody, rheumatoid factor, perinuclear antineutrophil cytoplasmic antibody (pANCA), cytoplasmic ANCA (cANCA), double-stranded deoxyribonucleic acid (DNA), anti-Ro antibody, anti-La antibody, C3 and C4-complement, immunoglobulin levels (IgG, IgM, and IgA), and cryoglobulinemia were negative. Viral markers tested were negative human immunodeficiency virus (HIV) I and II, hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg). Cerebrospinal fluid (CSF) examination is normal having normal cell count, protein, glucose, and negative for infections (Cryptococcal antigen, India ink, Gram stain, Ziehl-Neelsen (ZN) stain, negative cultures, including tuberculosis (TB) and fungus, TB-polymerase chain reaction (TB PCR), herpes simplex virus (HSV) DNA, and Venereal Disease Research Laboratory (VDRL)), and positive for oligoclonal bands (OCBs). Visual-evoked potential showed asymmetric bilateral prolonged p100 latency (right more than left) suggestive of anterior visual pathway dysfunction. Neuroimaging done at various stages of disease [see Figure 1], the description is made simultaneously in the figure.

Diagnosis and differential diagnosis

The clinical diagnoses for recurrent focal neurodeficit in the described form are: MS as per revised Mc Donald 2010 criteria,[8] differential diagnosis includes: Secondary inflammatory disease of CNS: Vasculitis secondary to rheumatoid disease, systemic lupus erythematosus, Sjögren's syndrome, drugs, infection (e.g., HIV and HCV), anticardiolipin syndromes, Behçet's, sarcoidosis, other connective tissue diseases, paraneoplastic and other specific autoimmune disease (celiac disease, Hashimoto's disease, etc.). With the clinical possibilities and exclusion of various secondary and other mimics of MS, there was not much diagnostic dilemma, but challenging treatment, since young patient, aggressive and severe disabling disease.

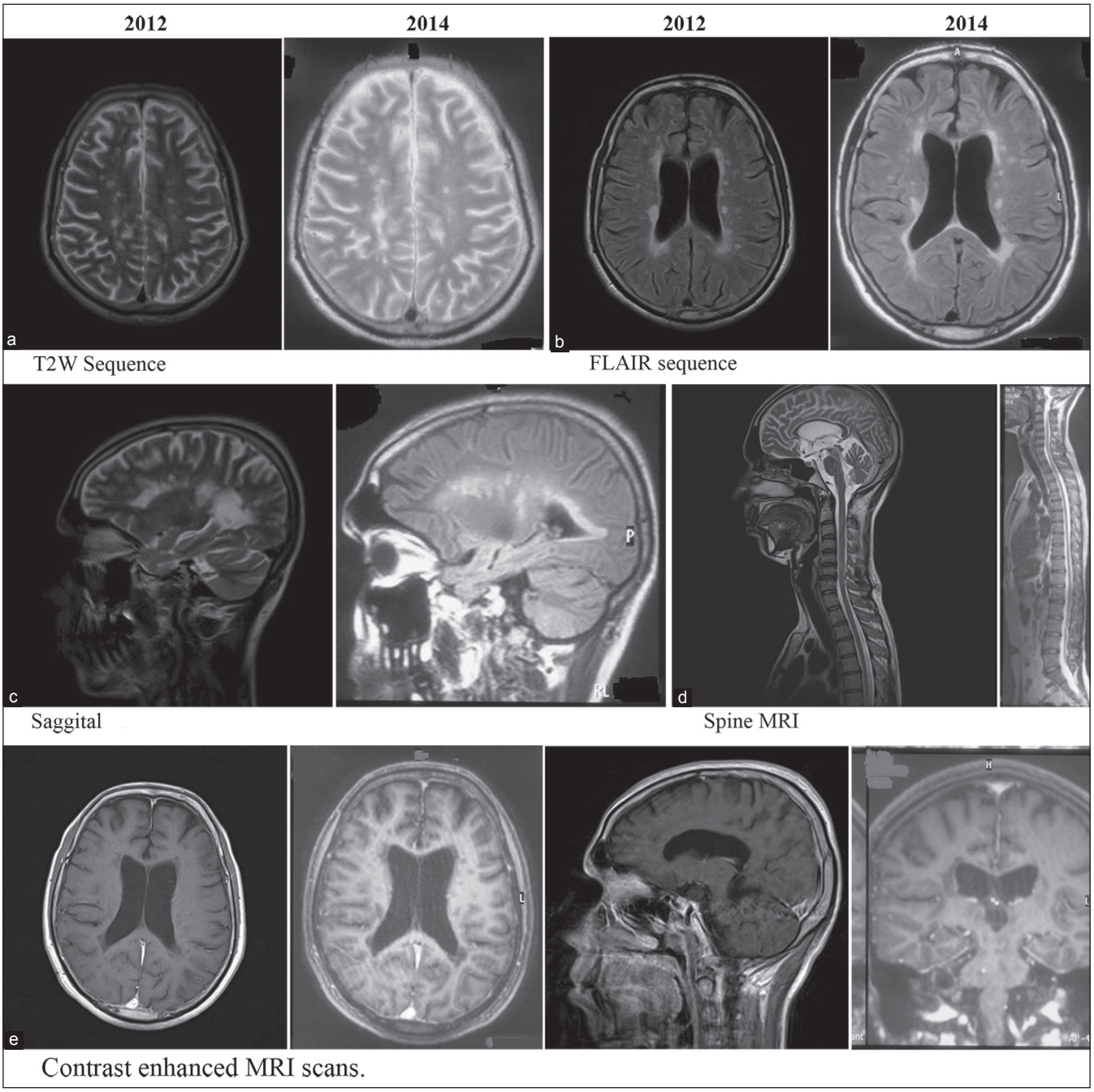

Figure 1: Multiple T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) hyperintensity (demylination plaques) noted in periventricular, subcortical, callosal, and spinal cord regions with no progression or fresh lesion in year 2014 images as compared to pre-stem cell transplantation images in year 2012 including the contrast enhanced magnetic resonance imaging (MRI) scans (a-e)

Autologous HSCT methodology[9]

After a consent (an off-labeled single patient consented intervention), initial clinical and laboratory evaluation, first stem cell mobilization was done on Day 1 with injection cyclophosphamide 2 g/m^2 adding injection 2-mercaptoethane sulfonate sodium (MESNA) dose of 2 g/m^2 to it. Intravenous fluid (0.9% normal saline) and MESNA alternate given on day 5, total of 3L/m^{2}with MESNA 2 g/m^{2}in them (at 6 AM). Injection furosemide 20 intravenous given at 6 PM. Day 2 onwards injection nupogen 10 μg/kg (= 300 μg twice daily) till absolute neutrophil count (ANC) count of 1,000/μL along with injection methylprednisolone 1mg/kg/day (50 mg intravenously daily) given. The next step of collection of stem cells done on the day, ANC crossed 1,000/μL. The collection was done on an apheresis machine (P1TA apheresis kit). A total of 2-2.5 times of blood volume (70 ml/kg body weight) processed and autologous hematopoietic stem cells collected. CD 34 + and CD 3 + enumeration done in the harvest bag by standard flowcytometry and subsequently stem cells are stored in the stem cell laboratory for cryopreservation with standard protocol. Conditioning done with high dose immunosuppressive therapy (injection cyclophosphamide

50 mg/kg body weight intravenously for 5 days, injection rabbit antithymocyte globulin 0.5 mg/kg body weight intravenously on day 6 and 1mg/kg body weight for another 5 days. Injection methylprednisolone 2 mg/kg body weight was given intravenously for 5 days). At this point, stem cell infusion was done with 3-8 × 10^6CD34 + cells/kg body weight with standard protocol and precautions. Post-stem cell infusion, all precaution was taken to reduce infections in view of the neutropenic state patient. Injection granulocyte colony stimulating factor (GCSF) 5 μg/kg body weight was given till his ANC was >500/μL. Subsequently, the patient followed-up by repeated clinical and laboratory evaluations.

Follow-up and outcomes

The patient was comfortable and adherent to the treatment option of autologous HSCT and follow-up. He was monitored on regular interval and no adverse events were noted till now in 2 years of follow-up. He was reevaluated and at 2 years follow-up of autologous HSCT his EDSS was 5.0 (reduced by 1.5), no relapse, and there was no fresh lesion load on magnetic resonance imaging (MRI) brain [Figure 1].

Discussion

Despite so many advances and persistent optimism in treatment of MS, there is no definite answer. Our case report enhances the evidence towards conducting optimum sample size randomized control trial, testing the efficacy and safety parameters of cell-based therapy in MS. There are various disease modifying therapies in MS,[10] most challenging situation for patient to accept these modalities are unpredictable relapse, repeated injections or tablets, adverse effects with every dose to almost everyone, and most important the recurring expenses. Autologous HSCT could be promising, as observed in various studies. Factors that predict to respond better with HSCT are presence of gadolinium-enhancing lesions at baseline,[11,12] short disease duration,[13,14] and diagnosis of RRMS.[13] In a recent study from Sweden, noted benefits in patients with pre-HSCT high inflammatory activity, wherein post-HSCT no relapse, no progression, and no new lesions on MRI noted in first 3 years of therapy (79%).[15] If failed, all activity got noted in the first 2 years in the same study. Freedom from disease during the first 3 years after HSCT infers an excellent prognosis.[11,13,15] Disease-free survival of 62-66% at 5 years are noted in two studies.[15,16] The median improvement of EDSS 0.75 (range −7 through 1.5) overall, but excluding progressive types of MS it was 1.5 (range −7 through 1.5) in a study,[15] while in Italian study[11] improvement was >1 only in 31%. EDSS improvement maintained till the end of 2 years, except one patient, which improved even beyond 2 years in a study.[15] Progression-free survival has been reported in the range of 32-100% in 3-5 years[11,13-17] and 25% at 15 years after HSCT.[12] As far as MRI lesions, patients undergoing HSCT as noted in a study, noted only a total of only eight new T2 lesions in overall patients over 3years, that is much better than trial of interferon (IFN)-beta, wherein there were six new T2 lesion per year in the placebo arm.[15,18]

Safety concerns: Autologous HSCT needs very expert hematologist, periprocedural care, and extreme care against infections. The safety of the procedure has been a major concern. In 2006, it was reported that treatment-related mortality (TRM) in Europe was 5.3% (busulfan inferred a greater risk of death); [7] and in 74 Italian patients treated with BEAM (Carmustine, etoposide, cytarabine, and melphalan), TRM was 2.7%.[11] No TRMs are noted in certain studies: Czech study of 25 patients treated with BEAM,[13] 95 Russian patients,[14] and Swedish study.[15] In a systematic review of 83 studies; the 48 studies of human and animal model using autologous HSCT were included, also promises benefits from autologous HSCT.[19]

"In conclusion, a 33-year old young male with recurrent focal neurological deficit involving various neural axes (optic nerves, cerebellum and its connections, subcortical white matter, brainstem, and spinal cord), subsequent disease progression with initial complete recovery with methylprednisolone, and subsequent unresponsive/intolerable to approved standard immunomodulation, showed some response to autologous hematopoietic stem cells therapy. The patient has better EDSS (reduced by 1.5), no relapse, and no treatment-related adverse events 2 years of post-stem cell therapy. Hence, autologous HSCT may be beneficial as in our patient, having a progressive form of MS, but needs to be tested in well-designed randomized trial to understand more about its indications, benefits, harms, and safety concerns."

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938-52.
2. Confavreux C, Vukusic S. Natural history of multiple sclerosis: A unifying concept. Brain 2006;129:606-16.
3. Kremenchutzky M, Cottrell D, Rice G, Hader W, Baskerville J, Koopman W, *et al*. The natural history of multiple sclerosis: A geographically based study. 7. Progressive-relapsing and relapsing-progressive multiple sclerosis: A re-evaluation. Brain J Neurol 1999;122:1941-50.
4. Silani V, Cova L. Stem cell transplantation in multiple sclerosis: Safety and ethics. J Neurol Sci 2008;265:116-21.
5. Mahevas M, Vaida I, Le Page L, Sid-Idris S, Royer B, Garedi R, *et al*. Haematopoietic stem cell transplantation in the treatment of autoimmune diseases. Rev Méd Interne 2008;29:115-21.
6. Saccardi R, Freedman MS, Sormani MP, Atkins H, Farge D, Griffith LM, *et al*. A prospective, randomized, controlled trial of autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: A position paper. Mult Scler 2012;18:825-34.
7. Saccardi R, Kozak T, Bocelli-Tyndall C, Fassas A, Kazis A, Havrdova E, *et al*. Autologous stem cell transplantation for progressive multiple sclerosis: Update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. Mult Scler 2006;12:814-23.
8. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
9. Hamerschlak N, Rodrigues M, Moraes DA, Oliveira MC, Stracieri AB, Pieroni F, *et al*. Brazilian experience with two conditioning regimens in patients with multiple sclerosis: BEAM/horse ATG and CY/rabbit ATG. Bone Marrow Transplant 2010;45:239-48.
10. Wingerchuk DM, Carter JL. Multiple sclerosis: Current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc 2014;89:225-40.
11. Mancardi GL, Sormani MP, Di Gioia M, Vuolo L, Gualandi F, Amato MP, *et al*. Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: The Italian multi-centre experience. Mult Scler 2012;18:835-42.

12. Fassas A, Kimiskidis VK, Sakellari I, Kapinas K, Anagnostopoulos A, Tsimourtou V, *et al*. Long-term results of stem cell transplantation for MS: A single-center experience. Neurology 2011;76:1066-70.
13. Krasulová E, Trneny M, Kozák T, Vacková B, Pohlreich D, Kemlink D, *et al*. High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: A single centre 10-year experience. Mult Scler 2010;16:685-93.
14. Shevchenko JL, Kuznetsov AN, Ionova TI, Melnichenko VY, Fedorenko DA, Kartashov AV, *et al*. Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis. Exp Hematol 2012;40:892-8.
15. Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, *et al*. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: The Swedish experience. J Neurol Neurosurg Psychiatry 2014;85:1116-21.
16. Burt RK, Loh Y, Cohen B, Stefoski D, Stefosky D, Balabanov R, *et al*. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: A phase I/II study. Lancet Neurol 2009;8:244-53.
17. Fassas A, Nash R. Stem cell transplantation for autoimmune disorders. Multiple sclerosis. Best Pract Res Clin Haematol 2004;17:247-62.
18. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1995;45:1277-85.
19. Ardeshiry Lajimi A, Hagh MF, Saki N, Mortaz E, Soleimani M, Rahim F. Feasibility of cell therapy in multiple sclerosis: A systematic review of 83 studies. Int J Hematol-Oncol Stem Cell Res 2013;7:15-33.

How to cite this article: Pandit AK, Prasad K, Seth T. Autologous hematopoietic stem cell transplantation in progressive severe multiple sclerosis. Ann Indian Acad Neurol 2015;18:459-63.
Received: 03-12-14, **Revised:** 04-01-15, **Accepted:** 02-02-15
Source of Support: Nil, **Conflicts of Interest:** None declared.