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Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis

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Abstract Aggressive forms of multiple sclerosis (MS) represent a limited group of demyelinating diseases that rapidly progress to severe disability. Currently available therapies are poorly effective against these clinical entities. Recently, it has been demonstrated that intense immunosuppression followed by autologous haematopoietic stem cell transplantation (AHSCT) can affect the clinical course of individuals with severe MS and completely abrogate the inflammatory activity detected by MRI. We report the result of the Italian phase 2 GITMO study, a multicentre study in which 21 MS patients, who were rapidly deteriorating and not responding to the usual therapeutic strategies, were treated with this procedure. The clinical effect of the treatment is long lasting, with a striking abrogation of inflammation detected by MRI findings. These results support a role for intense immunosuppression followed by ASCT as treatment in rapidly evolving MS cases unresponsive to conventional therapies.

Key words Multiple sclerosis • Autologous haematopoietic stem cell transplantation • Immunosuppression

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Introduction

In multiple sclerosis (MS), clinical course is unpredictable, ranging between single self-limiting episodes and extremely aggressive and hyperacute forms with a poor prognosis. The immunopathogenesis of MS has been elucidated in recent years, indicating the role of autoreactive T cells actively crossing the blood-brain barrier with the subsequent activation of the immune cascade causing typical white matter lesions [1]. Immunomodulating and immunosuppressive treatments are currently the only recognised strategies. Interferon β, glatiramer acetate and azathioprine are utilised in the relapsing-remitting phase of the disease, while mitoxantrone or cyclophosphamide are employed in secondary progressive clinical course or in severe cases [2]. Following experimental treatment in animals [3] and experience on single MS cases treated for haematologic malignancies [4], autologous haematopoietic stem cells transplantation (AHSCT) in the late 1990s was adopted for the treatment of severe MS cases. Data on the MS cases treated with ASCT have been reported as single centre studies [5, 6], multicentre trials [7, 8] and as a collective European Group for Blood and Marrow Transplantation (EBMT) retrospective study [9]. Our personal data come from a prospective phase 2 multicentre trial started in 1998 involving 7 Italian centres. The protocol was promoted by the Italian Group for Bone Marrow Transplantation (GITMO), focusing on clinical and magnetic resonance (MRI) follow-up.

The two crucial steps of AHSCT in the treatment of autoimmune diseases are first the mobilisation of peripheral blood cells with cyclophosphamide (4 g/m^2) followed by harvesting and cryopreservation of CD34+ cells, and the reinfusion of the graft after a conditioning regimen. BEAM (BCNU, cytosine arabinoside, etoposide and melphalan) followed by antithymocyte globulin (ATG) adapted from the pivotal experience of Fassas et al. [10] is frequently utilised. The protocol was planned by the Italian GITMO-Neuro Intergroup to treat at least 20 patients with a follow-up of 2 years or more. Data on the first 10 patients treated have already been reported [7], and very recently an update of a larger group of patients with a median follow-up of 36 months has been published [11].

Patients, materials and methods

Starting from July 1998, 21 patients were enrolled in the GITMO study. The three major end-points were, respectively, changes in the number of triple-dose gadolinium (Gd)-enhancing lesions on brain MRI, changes in the Expanded Disability Status Scale (EDSS) and AHSCT toxicity. Changes in evaluation of quality of life were quantified in nine patients.

Inclusion criteria

Eligibility criteria were: age between 18 and 55; clinically defined MS either secondary progressive (SP) or relapsing–remitting (RR); EDSS score between 5 and 6.5; rapid clinical deterioration in the previous 12 months, despite conventional treatment (i.e., increase of 1 point or more on the EDSS in the range of 5–6 or 0.5 point where EDSS was between 6.0 and 6.5); presence of at least 1 Gd+ area on brain MRI using a triple dose (TD) of Gd; absence of cognitive disturbances measured with Mini-Mental Status Examination and neuropsychological set of tests; absence of concomitant diseases; no treatment with interferon in the previous three months and immunosuppressive agents within 6 months from enrolment.

Stem cell mobilisation and conditioning regimen

Peripheral blood stem cells were mobilised with cyclophosphamide (Cy) 4 g/m^2 in 1 day followed by daily nonglycosylated granulocyte colony-stimulating factor (G-CSF) 5 mg/kg subcutaneously from day +2 after Cy until harvesting. Prednisone (5 mg/kg) was utilised to prevent cytokine release during Cy administration. An efficient CD34+ cell collection varied between 3 and 8x10^6/kg. Harvested cells were then cryopreserved according to standard techniques. The chemotherapy was started after 30/40 days from mobilisation with BCNU at day –7, cytosine arabinoside and etoposide from day –6 to day –3 and melphalan at day –2. On day 0 CD34+ cells were infused together with rabbit ATG (5 mg/kg/day for two days) and prednisone (5 mg/kg). Infectious prophylaxis was carried out with acyclovir for at least 3 months, trimethoprimsulphamethoxazole for 6 months and intravenous immunoglobulin weekly during hospitalisation until discharge.

Neurologic evaluation

Neurological assessment was performed at screening visit, baseline, at 30 days from mobilisation, after the conditioning regimen, then monthly for the first six months after transplantation and then every six months. Cerebrospinal fluid was also performed at baseline, and months 6 and 12 in three cases. Clinical improvement or deterioration was assessed as 0.5 variation of EDSS score, confirmed after six months.

MRI evaluation

TD Gd brain MRI scans were performed monthly for a pretreatment period of 3 months and compared with serial scans obtained monthly in the following 6 months and then every 3 months until month 24, and every 6 months afterwards. Images were evaluated at the Neuroimaging Research Unit of S. Raffaele Hospital, Milan in a masked way for the first two years of the study. Then the MRI activity was locally evaluated by the neuroradiologist. In ten patients analysis of brain volume

changes was also performed comparing baseline with month 12 and then month 12 with month 24.

Quality of life assessment

The first nine patients enrolled in the study were evaluated with the 54-item MS quality of life (MSQoL-54) questionnaire at baseline, 6, 12 and 24 months.

Results

Twenty-one patients have been enrolled with a median age of 36 years. Only 4 patients had a RR clinical course, the majority having a secondary severe and rapid progression of disability. The median age at the onset of the disease was 24 years and the median duration 12 years. All the patients were previously treated either with interferons or immunosuppressors. At the screening the median EDSS was 6.5. At baseline, immediately before stem cell mobilisation, the neurological conditions deteriorated even more in 11 patients.

Transplantation effects

Mobilisation was successful in all cases with a median number of 8.69×10^6/kg collected CD34+ cells. Mobilisation toxicity was quite acceptable, with, apart from fever, only one case of haemorrhagic cystitis, one case of subclavian phlebitis and one patient with a transient inappropriate secretion of antidiuretic hormone. The postconditioning phase was heavier for our patients. Median days with polymorphonuclear leukocytes below 0.5×10^9/l and platelets below 50×10^9/l were 8 and 10, respectively. Fever was present in the majority of them and receded after a median of 12 days of intravenous combined antibiotics. In 6 cases a cytomegalovirus (CMV) reactivation was detected by p65 antigenemia or PCR. In 5 cases CMV reactivation was symptomatic, requiring specific treatment. During and after the conditioning regimen neither clinical relapses nor transplantation-related adverse events were observed.

Clinical course

In the pretreatment period, from baseline to mobilisation, 11 patients worsened in their EDSS score. After treatment 20 patients were stable or improved. Two patients showed an improvement of 0.5 points for 36 and 48 months, and then worsened at the baseline EDSS score (6.5), remaining stable until now. Only one patient, after a nine-month improvement, progressed from the baseline EDSS of 6.5 to 7, reached at month 30. After ASCT all patients were only treated with symptomatic therapy. In one case a relapse was observed 4.5 years after treatment. Sixty months after ASCT this patient reported dyplopia due to fourth nerve palsy. MRI detected a single Gd+ area localised in the pons. Before relapse, an improvement of EDSS was observed (from 6.5 to 6). Now, at month 66, after the relapse, EDSS is stable (EDSS=6) and she is followed with monthly MRI.

Quality of life evaluation

Median values in MSQoL-54, comparing baseline to months 6, 12 and 24, show significant improvement of physical function, change in health and health distress.

MRI results

At enrolment, the mean number of lesions per month per patient was 10.8, increasing to 11.9 during the screening period. After induction with Cy a relevant drop of enhancing areas was already observed. In all the cases but two, an abrogation of MRI activity was observed in the first months. One single Gd+ lesion reappeared at month 60 in the patient already described (see Clinical course). A 1.9% reduction of brain volume was present in ten cases, 12 and 24 months after transplantation [12].

Cerebrospinal fluid examination

AHSCT does not change the pre-existing oligoclonal banding, suggesting the permanence in CNS of the autoreactive B lineage, in spite of intense immunosuppression.

Conclusions

Our clinical and MRI data suggest that AHSCT can be considered as a possible treatment in selected cases of severe MS forms. More clinical information about efficacy will come from the ASTIMS trial, a two-arm randomised multicentre European study comparing this procedure with monthly mitoxantrone infusion at the dosage of 20 mg for six months. The trial has already started.

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