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Inefficacy of Rituximab Post- Autologous Hematopoietic Stem Cell Transplant to Prevent Relapses in Persons with Multiple Sclerosis

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Abstract

Background: Individuals with Multiple Sclerosis (MS) have undergone autologous hematopoietic stem cell transplant; this approach has produced promising results. The role of post-transplant adjuvant therapeutic agents needs to be further clarified.

Methods: Consecutive patients autographed using the "Mexican method" to graft persons with MS were prospectively accrued in the study. Autografts were carried out on an outpatient basis, using cyclophosphamide and filgrastim as mobilization regimen. After granulocyte recovery, all individuals received a rituximab infusion and at discharge, patients were recommended to continue a follow-up period with additional rituximab infusions.

Results: Eighty-four subjects were prospectively enrolled between June 2015 and November 2016. Median EDSS score was 5.5. After recovering hematopoiesis and receiving the initial dose of rituximab, 42 patients were given rituximab in their residence countries every two months during one year, whilst 42 did not. The EDSS values prior to and 12 mo. after the HSCT were compared in the groups with and without additional rituximab; the median change in the EDSS score in the rituximab group was 0.25 and in the no rituximab group was 0.00; accordingly. The change in the EDSS score between patients receiving or not rituximab was not statistically significant. We neither found short-term difference in MS-Relapse Free Survival (RFS).

Conclusion: The 12-month period therapy with rituximab in patients with MS who underwent autologous transplant was not effective to prevent relapses nor to cause further reduction in the EDSS score.

Keywords: Hematopoietic transplants; Multiple sclerosis; Rituximab; Treatment

Introduction

Persons with Multiple Sclerosis (MS) have been treated with high-dose immune suppressive or cytotoxic drugs and an auto transplant [1-2]. More than 1000 auto transplants have been reported worldwide in MS [2-4]. Some data suggest outcomes are better in persons with relapsing-remitting MS compared with other MS variants [1]. Therapy-Related Mortality (TRM) has decreased to <2% because of less intensive pretransplant regimens and better subject selection [2-4]. We have previously reported that auto transplants for several diseases can be done in an outpatient setting using non-frozen refrigerated blood cells [2,5-7]. The role of post-transplant immunosuppressive therapy in patients with MS has not been fully analyzed. We report here the analysis of the efficacy of the delivery of low doses of rituximab after the transplant.

Materials and Methods

Subjects

We studied consecutive subjects with MS referred to our centre between June 2015 and November 2016 including those with: (1) Relapsing-Remitting (RRMS); Secondary Progressive (SPMS); and (3) Primary Progressive Multiple Sclerosis (PPMS). Eligibility criteria included all the following: (1) Karnofsky performance score (8) >70%; (2) Extended Disability Status Scale (EDSS; 1) ≤7 2 w pretransplant; (3) CNS Magnetic Resonance Image (MRI) ≤3 mo pretransplant, (4) no prior bone marrow toxic drugs; (5) normal heart, liver, lung and kidney function; and ≥6 mo since exposure to immune suppressive drugs (6). The study was approved by the Ethics Committee of the Clinica RUIZ (Conbioetica 21CEI00120130605, Registry N. 13 CEI 21 114 126) and participants gave written informed consent. A neurologist who assigned the pretransplant EDSS score assessed subjects. Primary co-endpoints were recovery of granulocyte and platelet counts and TRM. Secondary endpoints were Overall Survival (OS) and overall response (improvement and stabilization of the EDSS score). Subjects were instructed to provide data of their neurologic evolution every three months post-transplant on special forms and were sent e-mail reminders every 3 mo. Compliance was 70 percent at 3 mo. The protocol is registered in ClinicalTrials.gov identifier NCT02674217.

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Blood cell collection

Hematopoietic stem cells were mobilized by cyclophosphamide, 50 mg/Kg, given intravenously over 2 h on d -11 and -10 (Figures 1 and 2). Filgrastim, 10 µg/kg, was given twice daily on d -9 to -1 subcutaneously. Apheresis was done on d -2 using an Amicus® device (Fresenius Kabi, Deerfield, IL, USA) or a Spectra Optia® device (Terumo BCT, Lakewood, CO, USA) using the Spin-Nebraska® protocol [9] either by vein or *via* Mahurkar™.

Conditioning and transplant

The procedures were conducted fully on an outpatient basis [2,5]. Cyclophosphamide, 50 mg/kg intravenously, was given over 2 h on d -2 and -1 followed by 2-mercaptoethane sulfonate Na (mesna), 1g/mE+2 over 3 h (Figure 1). Ondansetron, 8 mg, dexamethasone, 4 mg and pantoprazole were given to all subjects. Filgrastim (10 µg/kg, once daily) cotrimoxazole, fluconazole and acyclovir were given until granulocytes >0.5 x 10E+9/L and cotrimoxazole and acyclovir continued for 6 mo. Total cumulative dose of cyclophosphamide along the procedure was 200 mg/Kg.

Graft storage

The apheresis product and 1 ml aliquots there of were kept in ACD-A (Baxter Healthcare, Deerfield IL) at 4ºC in 1 L transfer packs (Baxter Healthcare) composed of gas impermeable, polyvinyl chloride plastic film for up to 96 h. Enumeration of Mononuclear (MNC) and CD34-positive cells was done by flow-cytometry in a Gallios® device (Coulter Electronics, Hialeah FL, USA), using phycoerythrin labelled anti-CD34 HPCA-2 monoclonal antibody (Becton Dickinson, San Jose CA, USA) and a fluorescence isothiocyanate tagged anti-CD45 monoclonal antibody (Beckman Coulter, Hialeah, FLA, USA), gating on 7' amino-actinomycin-D-excluding cells. Viability studies of the stored apheresis product used propidium iodide exclusion and evaluated by flow cytometry. The apheresis product obtained on d –2 was infused on d 0 after storing in a conventional blood bank refrigerator (Thermoforma, Marietta OH, USA).

Posttransplant rituximab

Patients described in this study were part of a larger group of 168 subjects, which periodically responded a follow up questionnaire for at least 12 months. Forty-two of such patients received rituximab, 100 mg, every 2 m for 1 y, while the remaining 126 did not. A subgroup of 42 patients out of the 126 not getting rituximab was selected for comparison, primarily to match the numbers of CD34+ cells that they were infused, followed by sex and age. The purpose of this selection was to make both groups as most comparable as possible.

Statistical analysis

Comparisons were performed with the aid of the MedCalc® statistical package. Chi-squared and Mann-Whitney tests were used for the analysis of non-parametric data, while Student's T test or the Welch modification were used to compare parametric variables.

Results

Subjects

Eighty-four subjects were prospectively enrolled between June 2015 and November 2016. Twenty-eight were male (33%). Median age was 47 y (range, 28-66). Twenty subjects (24%) had primary progressive MS, 33 (39%) relapsing remitting MS and 31 (37%) secondary progressive MS. Median EDSS score was 5.5 (range, 0.5 – 7.5). After recovering hematopoiesis and receiving the initial dose of rituximab, 42 patients were given rituximab in their residence countries every two months for one year, whilst 42 did not. As shown in (Table 1), there were not significant differences in clinical and demographic data among both groups. The only significant difference was observed in the proportion of smokers amongst those receiving and those not receiving rituximab.

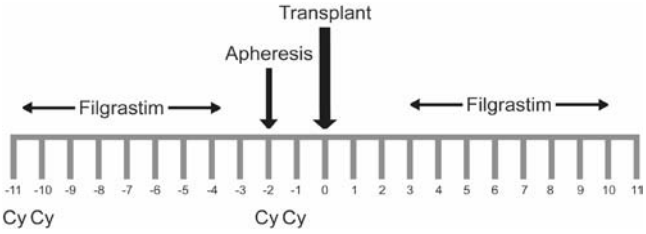

Figure 1: Scheme of the transplant procedure. Cy, cyclophosphamide, 50 mg/Kg each dose.

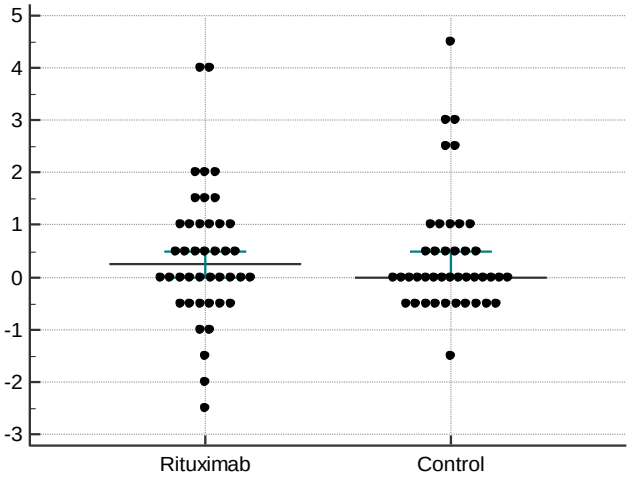

Figure 2: Change in the EDSS score before and 12 months after the hematopoietic stem cell transplant, the median change in the EDSS score in the rituximab group was 0.25 (95% CI for the median 0.00 to 0.81), and in the no rituximab group it was 0.00 (95% CI for the median -0.04 to 0.77); accordingly, the change in the EDSS score between patients receiving or not rituximab was not statistically significant (P=1.00, 95% CI of difference -0.531 to 0.531). Large horizontal lines depict the median values, while short lines represent 95% CI for mean.

Apheresis

Subjects in both groups needed a median of 1 apheresis procedure (range, 1-2) to collect the necessary number of CD34-positive cells. A mean of 4.2 x10E+6/kg viable CD34-positve cells was infused to the first group, while a mean of 4.6 x10E+6/kg viable CD34-positive cells were infused in the control group.

Hematopoietic recovery and TRM

Median intervals to granulocytes >0.5 x10E+9/L were 8 days for the rituximab group and 8 days for the control group (ranges 6 to 10 and 5 to 10 d); to platelets >20 x109E+9/L were 4 days for both, the rituximab and control groups (ranges 1 to 8 and 1 to 17 d). Only 3 subjects -1 from the Rituximab group and 2 from the control group-

Table 1: Clinical and demographic data of both groups of MS patients.

		Rituximab group	Control group	p
Gender	Male	12	16	0.354
	Female	30	26	
Age median (range)		45 (30 to 66)	46 (28 to 62)	0.959
BMI (kg/m^2) mean (SEM)		25.24 (0.683)	24.1 (0.753)	0.274
MS type	RRMS	21	12	0.103
	PPMS	7	13	
	SPMS	14	17	
Disease duration years median (95% CI for the median)		8 y (7.2-11.7)	13 y (10.4 – 15.4)	0.479
Previous disease modifying therapy		33	33	1.0
Number of apheresis median (range)		1 (1 to 2)	1 (1 to 2)	1.0
Collected CD34+ cells media (SEM)		4.196 (0.510)	4.602 (0.475)	0.561
Smoking status	Never	25	42	<0.0001
	Ever	17	0	

were hospitalized within 28 d of their auto transplant with durations typically <2 d. There were no events of hemorrhagic cystitis nor transplant-related deaths.

Efficacy

The OS is 100% in both groups. In the rituximab group, the overall response rate (stabilization or improvement of the EDSS score) was 73.8%, whereas in the non-rituximab group was also 73.8%. In order to analyze data comparatively, the EDSS values prior to and 12 mo. after the HSCT were compared in the groups with and without additional rituximab; the median change in the EDSS score in the rituximab group was 0.25 (95% CI for the median 0.00 to 0.81), and in the no rituximab group was 0.00 (95% CI for the median -0.04 to 0.77); accordingly, the change in the EDSS score between patients receiving or not rituximab was not statistically significant (P=1.000, 95% CI of difference -0.5311 to 0.5311). We neither found short-term difference in MS-Relapse Free Survival (RFS).

Discussion

Immunosuppression has been shown to be useful in persons with MS [11-15]. Up to now, no immunosuppressive drug has been shown to be better than autologous HSCT in the treatment of the disease [15]. Around 70-80% of patients with MS have a response to HSCT, either stabilization or improvement of the neurological condition [2-5,11-15]. In addition to T cells, which are mainly depleted during HSCT, B cells play a central role in the pathogenesis of MS: they are involved in the activation of pro-inflammatory T cells, secretion of pro-inflammatory cytokines and production of autoantibodies directed against myelin. Hence, the use of B cell-depleting monoclonal antibodies as therapy for autoimmune diseases, including MS, has increased in recent years; accordingly, both anti-CD20 monoclonal antibodies (rituximab and ocrelizumab) have been used in the treatment of patients with MS [16-18]. Despite the fact that HSCT followed by immunosuppression has been used in the treatment of autoimmune conditions for more than 15 years [18,19], the combination has not been widely explored. The rationale behind the combination of HSCT and after transplant B-cell depleting monoclonal antibodies relies on the pathophysiology of the disease, with the main goal of fully depleting both T as well as B cells.

We have employed rituximab after HSCT and were unable to show a decrease in the relapse rate of the activity of MS in those patients given the anti-CD20 monoclonal antibody. The response rate (both stabilization and improvement of the neurological condition as assessed by the EDSS score) in the patients given and HSCT employing our method was 73.8% in the whole group of 84 patients, a figure similar to those informed in previous HSCT trials in MS [2-3,5,11-15]; in the rituximab group (n=42), the overall response rate was 73.8%, whereas in the control group (n=42) it was exactly the same: 73.8%, (Difference 0%, 95% CI -18.65% to 18,65%. p= 1.00)

We are aware that a serious limitation of our study is the fact that the EDSS was recorded by different physicians across the planet, patients' carers or even by the patients themselves; however, we believe that any bias induced by this fact should affect both groups similarly; hence, over or underestimation of the disability score is expected to be equal in patients receiving or not rituximab.

In summary, we have not been able to prove a positive effect of rituximab after HSCT as continuation therapy for one year; accordingly, we have changed our protocol and are delivering now a single 1000 mg. dose after the transplant, once the granulocyte counts recover to normal levels. Additional studies are needed to explore the role of other immunosuppressive drugs in the post-HSCT setting, with the aim of preventing MS relapses.

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