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Research Article

Early Outcomes of Autologous Hematopoietic Stem Cell Transplantation in Patients with Relapsing-Remitting type of Multiple Sclerosis

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Abstract

Background of the study: For more than 20 years, high-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (autoHSCT) has been successfully used in the world to stop the progression of multiple sclerosis (MS). The effectiveness of this therapy has been proven in many multicenter randomized trials. However, data on the outcomes of such treatment in the early post-transplant period (up to three months) in the world literature is not enough.

Objective: To evaluate the early neurological outcomes of HIST followed by autoHSCT in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: The study included 20 patients with significant RRMS (McDonald 2017). Among them, 6 men and 14 women aged 19 to 51 years (median 34.2 ± 9.6 years) who underwent HDIT (R-Cph 200) followed by autoHSCT. The follow-up period ranged from 31 to 34 days (median 31.45 days). At both points of the study, the neurological status was assessed according to the Scripps neurologic rating scale (SNRS), the score on the extended Kurtzke disability scale (EDSS), MRI of the brain and spinal cord with contrast, the presence of spasticity in the paretic limbs according to the modified Ashworth scale (MAS).

Results: After treatment, significant differences were obtained for both EDSS (p = 0.0001) and SNRS (p = 0.00004). Improvement on the EDSS scale averaged 0.5 points [0; 1] in 13 patients (65%). According to the SNRS scale - 5 points [3; 9] in 19 patients (95%). The disappearance of contrast accumulation was noted in three patients (30%), however, in one (10%), an accumulation of a contrast agent was detected, which was not previously observed. The presence of negative dynamics according to the EDSS and SNRS scales was not observed in this patient. In 6 (75%) patients, a decrease in the severity of the increase in pyramidal tone according to MAS was revealed by at least 1 point.

Conclusion: HDIT with autoHSCT can improve the performance of the neurological rating scale and the extended disability scale even in the early post-transplant period. For a more accurate assessment of the effectiveness of treatment, it is preferable to evaluate the dynamics on the SNRS scale due to its complexity and completeness of the indicators used. Absence of accumulation of a contrast agent during MRI in the early stages after treatment was detected in 30% of cases. In 75% of patients, a decrease in spasticity by 1 point on the MAS scale was noted 2 weeks after VIST with autoHSCT.

Keywords: Relapsing-Remitting Multiple Sclerosis; RRMS; HDIT + AUTOHSCT; Autologous Hematopoietic Stem Cell Transplantation; HSCT

Introduction

Multiple sclerosis is a chronic, demyelinating, factorial disease, which is based on a complex of autoimmune-inflammatory and neurodegenerative processes leading to multiple focal and diffuse lesions of the nervous system, leading to disability and a significant indicator of quality of life [1]. The factors that cause MS are currently unknown. The average age of onset of MS in various manifestations ranges from 28 to 31 years. The general clinical picture debuts at the age of 15 to 45 years [2]. Remitting type of MS has an earlier onset and a course of 15 years with a probability of 60%, which can lead to secondary progression [3]. According to multicenter studies disease modification therapy (DMT) of multiple sclerosis reducing the incidence of the disease to 68% compared with placebo, the risk of disease progression is up to 42% within 2 years, depending on the type of MS course [4]. However, the therapeutic picture is leading in evaluating the effectiveness. Traditional methods of pathogenetic therapy in more than 30% of cases [5] do not have the possibility of stable control over recovery, except for the presence of a number of side effects. The first data on the effectiveness HDIT with auto-HSCT in MS was shown by Fassas., *et al*. in 1997. Long-term neurological manifestations were detected by the Kurzke Extended Validation Scale (EDSS) as well as the Scripps Neurological Rating Scale (SNRS) [6]. The study suggested that the use of HDIT + autoHSCT showed that it is possible in MS patients and gives a positive effect.

In Russia, the first transplantation of hematopoietic cells in MS was carried out in 1999 on the basis of the Clinic of Hematology and Clinical Immunology of the Military Medical Academy under the health care of Academician of the Russian Academy of Sciences Yu.L. Shevchenko, prof. A.A. Novik, Corresponding Member of the Russian Academy of Sciences M.M. Odinak [7,8].

Using a number of successful studies over the past 5-7 years, autoHSCT is increasingly being used as an alternative treatment for MS when patients refuse standard therapy or its ineffectiveness [8-10].

According to historical authors, in patients with RRMS, the lymphablative protocol resulted in later progression of the disease, an increase in neurological parameters, and a decrease in the number of new lesions on MRI. These indicators were evaluated for 5 years [11-13]. According to the literature data, the effect of HDIT + autoHSCT deficiency is currently observed, which was the reason for this study.

The aim of the study was to evaluate the early neurological outcomes of HDIT with autoHSCT in patients with RRMS.

Materials and Methods

The study included 20 patients (34.2 ± 9.6 years, 6 men and 14 women) with presumptive RRMS, established according to the McDonald criteria from 2017 (mean duration of the disease - 4.7 ± 2.5 years), who underwent HDIT according to non-myeloablative protocol (R-Cph 200) with the autoHSCT version. The conclusion

criteria in the study were: a confirmed diagnosis of relapsing-remitting MS, age over 18 years, no absolute contraindications to the appointment (the presence of acute somatic use, infectious diseases, immunodeficiency, abnormal platelet or leukocyte counts before treatment). Exclusion Criteria - patient refusal to participate in the examination, serious treatment, age under 18 years, the presence of HIV infection, primary or secondary progressive multiple sclerosis, hereditary neurological diseases, pregnancy, pulmonary, cardiac, renal or hepatic insufficiency, abnormal platelet or white blood cell counts before treatment, active infection, previous treatment with alemtuzumab or mitoxantrone within 1 year prior to HDIT with autoHSCT.

The follow-up period was 31 to 34 days (median 31.45 days). The initial examination was carried out upon admission to the clinic. Hematopoietic stem cell (HSC) infusion was performed 7-19 days after the first examination (median 14.6 days). Re-examination was carried out on days 11-20 (median 13.1 days) after transplant growth. At both points of observation, the patient's neurological status was assessed using the SNRS scale [14] and EDSS [15] scales, MRI of the brain and spinal cord with contrast was performed. An MRI study of the brain was performed on a Siemens MAGNETOM Verio magnetic resonance tomograph with a magnetic value of 3 T using a 12-channel head coil (Siemens AG, Erlangen, Germany), a contrast study (CS) "Ultravist" 0.2 ml/kg body weight. Axial, coronal and sagittal sections were evaluated. Foci of pathological accumulation of contrast agent in the white matter were considered active [16,17]. The assessment took into account the presence/absence of activity in the foci of demyelination. Also, at the initial detection, the effect of previous DMT therapy and the dynamics of EDSS indicators for 12 months were recorded. All patients have disease progression on the ongoing therapy of DMT. Muscle tone was assessed in order to achieve paretic limbs. This parameter was assessed using the modified Ashworth scale (MAS) [18] before and after treatment.

Characteristics of the transplant program

20 patients were exposed to hematopoietic stem cell mobilization with granulocyte colony-stimulating disease (G-CSF) at a dose of 10 μg/kg/day for 4 days. On the 5th day, leukocytapheresis was performed with the sampling of CD34+ cells in the amount of 2–4 x 106/kg of the patient's body weight. The resulting material was subjected to cryopreservation using dimethyl sulfoxide 10% and liquid nitrogen at a temperature of -1800C, where it was stored until use. High-dose immunosuppression is carried out using cyclophosphamide at a dose of 200 mg/kg and rituximab 500 mg/m2 at a dose of 200 mg/m2 with normalization of hemogram parameters, once. At the end of chemotherapy, thawing and infusion of HSCs were performed. The frozen graft was thawed in a water bath at 370C, especially before infusion. The introduction of HSC was carried out intravenously through a central catheter against the background of infusion-corrective therapy and premedication.

Statistical data processing

Statistical analysis was performed using SPSS Statistics 23.0 (IBM) software. The main descriptive statistics for categorical and ordinal variables were frequency and percentage; for quantitative variables, mean and standard deviation or median and quartiles. In all cases, two-sided versions of statistical tests were used. The null hypothesis was rejected at $p < 0.05$. Given the sample size of less than 30, in controversial cases, preference was given to analysis by non-parametric methods.

To assess the condition of patients before and after treatment according to the studied scales, Student's t-test was used for related samples, since counting indicators were quantitative. To simultaneously clarify the relationship of many features, the method of multivariate statistical analysis, i.e., linear regression analysis, was used. Binary logistic regression was used to assess the predictive ability of individual indicators in the development of expected outcomes.

Results

All patients included in the study group had a relapsing course of MS and the duration of the disease was not more than 10 years (Table 1).

After treatment, significant differences were obtained for both EDSS ($p = 0.0001$) and SNRS ($p = 0.00004$) (Figure 1).

The patients tolerated the procedure satisfactorily. There were no life-threatening complications or deaths.

Improvement on the EDSS scale was 0.5 points [0; 1], an improvement in functional activity when using the assessment of this treatment scale was observed in 13 patients (65%). While when

Index	RRMS patients n = 20
Middle age (mean ± SD)	34,2 ± 9,6, min. 18, max 51
Male / female ratio (n, %)	6 (30%) /14 (70%)
Disease duration (Me [Q25%; Q75%])	4,7 ± 2,5, min. 1, max 10
EDSS 12 months before starting treatment (Me [Q25%; Q75%])	3 [1,5; 4,5]
EDSS 6 months before starting treatment (Me [Q25%; Q75%])	3,5 [3,0; 4,0]
EDSS at the start of treatment (Me [Q25%; Q75%])	4,5 [3,5; 4,5]
SNRS at the start of treatment (Me [Q25%; Q75%])	83 [76; 92]
MPT brain and spinal cord with contrast ("Ultravist" 0.2 ml/kg m of body) -Gd+ -Gd-	20 (100%) 10 (50%) 10 (50%)
Spastic paresis (type) Hemiparesis Paraparesis Triparesis Monoparesis	8 (40%) 3 (37,5%) 5 (62,5%) 0 0
Spasticity (MAS) 0 1 1+ 2 3 4	8 (40%) 2 (25%) 3 (37,5%) 2 (25%) 1 (12,5%) 0

Table 1: General characteristics of the group.

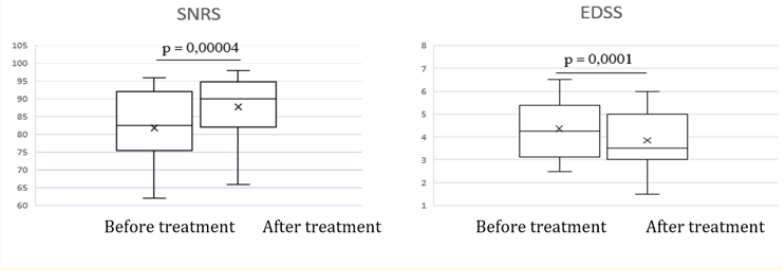

Figure 1: Comparison of EDSS and SNRS scales before and after treatment.

using SNRS, the improvement was 5 points [3; 9] and was shown to some extent in 19 patients (95%).

Using multiple linear regression, it was shown that the EDSS score 2 weeks after treatment depended only on the baseline score just before treatment. There was no dependence of the degree of improvement of patients after treatment on the baseline EDSS score for 12 months and 6 months, the duration of the disease and the age of the patients. SNRS at 2 weeks post-treatment also depended only on baseline just before treatment, but not on disease duration and patient age. At inclusion in the study, in 10 patients, accumulation of contrast was detected in foci of demyelination.

After treatment, the absence of contrast accumulation was noted in three patients (30%). However, one (10%) showed an accumulation of a contrast agent that had not previously been observed. The presence of negative dynamics according to the EDSS and SNRS scales was not observed in this patient.

Of the 20 patients included in the study, 8 (40%) had spasticity. In 5 patients, a change in muscle tone in the lower extremities was revealed, and in 3 patients, according to the hemitype. On re-examination, 4 patients from the spastic paraparesis group and 2 patients from the hemiparesis group showed a decrease in muscle tone by 1 point on the MAS scale. Thus, 6 (75%) patients showed a decrease in the severity of the increase in pyramidal tone on the Ashworth scale by at least 1 point. The use of logistic regression did not reveal a significant relationship of this phenomenon either with the duration of the disease, or with age, or with EDSS or SNRS indicators before and after treatment.

Conclusions

HDIT with autoHSCT can improve the Neurological Rating Scale and Extended Kurzke Disability Scale scores even in the early post-transplant period. However, in our study, it was noted that for a more accurate assessment of the effectiveness of treatment, it is preferable to evaluate the dynamics on the SNRS scale due to its complexity and completeness of the indicators used.

The dynamics of EDSS and SNRS 2 weeks after treatment depended only on the baseline immediately before treatment. There was no dependence on the duration of the disease, age and functional state of patients during the previous year. The lack of relationship between the effectiveness of treatment and the duration of the disease can be explained by the fact that in this sample the average duration of the disease was less than 5 years, which is a favorable predictor of such treatment [19].

The absence of accumulation of a contrast agent during MRI in the early stages after treatment was noted in 30% of cases, which is not indicative at this stage of evaluating the effectiveness of such treatment. In 1 patient, fixation of the paramagnet was noted after treatment, although no MR activity was recorded earlier. However, the MR picture did not correlate with negative dynamics on the SNRS and EDSS scales.

The value of this study is to assess the dynamics of spasticity in the early stages after HDIT with autoHSCT in RRMS, which is currently not covered in the literature. In an open, uncontrolled clinical study, positive dynamics of regression of spasticity in cerebral palsy in children aged 2–15 years after autologous transplantation of bone marrow mononuclear cells was noted, but the results are presented for 3–6 months of observation [20]. Our study showed a decrease in spasticity by 1 point on the MAS scale in 75% of cases in patients with RMS 2 weeks after HDIT with autoHSCT.

The limitation of the study is a small sample of patients, but it has already provided evidence of the effect of HDIT with autoHSCT on neurological deficit, spasticity, and the degree of invalidization.

Thus, the assessment of early outcomes of HDIT with autoHSCT in patients with RRMS allows us to draw preliminary conclusions about the effectiveness and safety of this procedure, however, further studies of this therapy program are needed.

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