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Autologous hematopoietic stem cell transplantation in multiple sclerosis

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Summary

Background Although there is no effective cure for this disease, high-dose chemotherapy (HDCT), together with autologous hematopoietic stem cell transplantation (auto-HSCT) offers promising results in the treatment of multiple sclerosis (MS) patients.
Methods In this paper we present results of a prospective clinical study of safety and efficacy of HDCT+auto-HSCT in MS patients. One hundred and nine patients with various types of MS were included in this study. The patients underwent early, conventional, or salvage/late transplantation.
Results The transplantation procedure was well tolerated by MS patients, with no transplant-related deaths at all. The efficacy analysis was performed in 79 patients. Forty-two achieved an objective improvement of neurological symptoms (defined as a ≥0.5 point decrease in EDSS score as compared to the baseline and confirmed over 6 months), and 37 patients had disease stabilization (steady EDSS level as compared to the baseline and confirmed over 6 months). Quality of life (QoL) was assessed in 44 patients. Thirty-nine patients exhibited a QoL response 1 year after transplantation.
Conclusions This study provides ample evidence in support of HDCT+auto-HSCT efficacy in MS patients. The results obtained show that transplantation appears to be effective in patients with various types of MS.

Keywords: auto-HSCT, multiple sclerosis, quality of life, early, conventional and salvage transplantation

Introduction

Multiple sclerosis is a chronic inflammatory disorder of the central nervous system (CNS) caused by autoimmune reactivity of T cells towards CNS myelin components. MS progression inevitably leads to the loss of motor function, sensitive disturbances and cognitive impairment because of the immune-mediated demyelination and axon degeneration [1].

MS is one of the most common neurological disorders, which mainly affects young adults, and causes gradual decrease of their quality of life (QoL). The clinical course of the disease is very heterogeneous. However, it typically presents with a relapsing-remitting course (RRMS; 80% of patients), which is followed after 5–15 years in about 70% of patients by a so-called secondary progressive phase (SPMS) [2]. 10–20% of patients have a primary progressive course, which is characterized by a steady progression from the onset with or without any acute exacerbations (progressive relapsing MS or PRMS, and primary progressive MS or PPMS, respectively).

Conventional therapies do not provide satisfactory control of MS due to their inability to eradicate self-specific T cell clones. Recently, HDCT+auto-HSCT was proposed as a new and

promising therapy for MS patients [3,4]. HDCT+auto-HSCT leads to the elimination of autoreactive T cells and, subsequently, to the restoration of a normal immune system.

Since 1995, several clinical studies have addressed the issue of feasibility and efficacy of HDCT+auto-HSCT in MS [3-15]. However, the information about long-term effects of HDCT+auto-HSCT in this patient population is scanty. In addition, the majority of patients included in the above-mentioned studies had SPMS, and were severely disabled with an average EDSS score of 6.5. Unfortunately, even complete suppression of autoimmune inflammation does not lead to a significant improvement of QoL in these patients. Therefore, the patient selection criteria for HDCT+auto-HSCT are still unclear and the proper selection of patients for transplantation remains the key issue.

Another important consideration is the selection of appropriate criteria for the assessment of treatment outcomes for MS patients. Both disease-free period and improvement of patient's QoL are recognized as important outcome parameters. With this in mind, evaluation of both clinical and patient-reported outcomes in MS patients after HDCT+auto-HSCT is worthwhile. However, neurologists traditionally evaluate the clinical response only and rarely use QoL data in the outcome analysis. This may be partly explained by the fact that QoL questionnaires used for MS patients—both generic and specific—are multidimensional, and the interpretation of changes in several QoL scales/domains might be difficult for physicians. Recently, we have developed an approach to obtain an Integral QoL Index (IQLI) for profile questionnaires (both generic and specific). IQLI is a standardized value based on the properties of a geometric profile formed by the scales of a questionnaire, which is assessed by the method of integral profiles; the index has been validated in different patients' populations [16]. The advantages of IQLI are its ease of use and the possibility of obtaining one index based on several QoL scales. The use of IQLI makes it possible to overcome the difficulties in the interpretation of QoL data and allows the assessment of patient-reported outcomes, namely the QoL response.

To date, some limited information exists on the clinical response of MS patients to HDCT+auto-SCT at long-term follow-up, whereas the data on QoL response is lacking. In addition, the clinical experience in the application of HDCT+auto-HSCT to various types and stages of MS is very limited. Moreover, the timing for transplantation is still unclear.

Table 1. Demographic and clinical profile of the patient population. All patients were refractory to conventional therapy, which included IFNβ and mitoxantrone, as well as steroids, azathiopine, intravenous immunoglobulin and plasmapheresis in some patients. The mean follow-up was 19 months (range, 6–108 months).

Number of patients	109 (49 males)
Median age (range)	33 years (17–54)
Type of disease:	
SPMS	51 (46.8%)
PRMS	8 (7.3%)
PPMS	19 (17.5%)
RRMS	31 (28.4%)
Median disease duration	7.5 years (1–14 years)
Median disability score (EDSS)	5.0 (1.5–8.0)

We report the follow-up results of a prospective Phase II multicenter trial, which was started in 1999 and has since then been conducted by the Russian Cooperative Group for Cellular Therapy. This study is focused on the efficacy of HDCT+auto-HSCT in terms of clinical and quality of life responses in patients with different types and stages of MS.

Patients and Methods

One hundred and nine patients were enrolled in the study. Patient characteristics are shown in Table 1.

The trial was conducted according to the principles of the Helsinki Declaration, and approved by the IRB and Ethics Committees of all of the participating centers before initiation. All patients gave written informed consent.

The neurological disability of MS patients is quantified according to the Expanded disability status scale (EDSS) [17]. The EDSS scores range from 0 (no disability) to 10 (death related to neurological progression) in 0.5-step increments. EDSS scores from 1.0 to 4.5 refer to the fully ambulatory MS patients, while patients with EDSS scores of 7.0 are essentially restricted to a wheelchair.

Patient Eligibility

Criteria for patient selection were: age between 18 and 55 years; diagnosis of multiple sclerosis verified by clinical and laboratory findings; EDSS score 1.5–8.0; normal mental status; absence of severe concomitant diseases.

The disease activity was determined either by magnetic resonance imaging scans displaying active lesions in the CNS (i.e., gadolinium-enhancing lesions, new or enlarging lesions on serial scans) or by clinical assessment showing rapid neurological deterioration, e.g., 0.5-point increase on the EDSS during the 6-months preceding enrollment.

According to our concept there are 3 strategies of HDCT+auto-HSCT [18]. Early HSCT (in MS patients with EDSS 1.5–3.0) is performed soon after diagnosis in case of primary refractory disease or poor prognosis. Conventional HSCT (EDSS 3.5–6.5) is performed in patients with secondary refractory disease. Salvage HSCT (EDSS 7.0–8.0) is an option in case of high disease activity and rapid neurological deterioration in late stages of the disease. All three strategies were applied in this study (Table 2).

Table 2. HSCT timing in the studied patient population

HSCT strategy	Enrolled patients	Analyzed patients
Early HSCT (EDSS 1.5–3.0)	32 patients (30%)	24 patients (30.3%)
Conventional HSCT (EDSS 3.5–6.5)	70 patients (64%)	48 patients (60.7%)
Salvage/late HSCT (EDSS 7.0–8.0)	7 patients (6%)	7 patients (9.0%)

Stem Cell Mobilization and Transplant Procedure

Hematopoietic stem cells were mobilized with G-CSF at 10 μg/kg +/- cyclophosphamide at 4 g/m2 according to EBMT/EULAR guidelines [19]. The grafts were not manipulated. BEAM or BEAM-modified conditioning was used. The BEAM conditioning regimen included BCNU (300 mg/m2) on day -6, etoposide (200 mg/m2) from day -5 to day -2, cytarabine (200 mg/m2 bd) from day -5 to day -2 and melphalan (140 mg/m2) on day -1. It was followed by autologous hematopoietic stem cell transplantation (day 0). In vivo T cell-depletion was achieved through infusion of 30 mg/kg of horse anti-thymocyte globulin (ATG) on days 1 and 2. Five μg/kg s.c. of G-CSF were administered from day 3 post-infusion until granulocyte recovery. For infection prophylaxis oral ciprofloxacin, fluconazole, acyclovir, and IV human Ig were given.

Neurological and QoL assessments

Clinical and QoL assessments were performed at baseline, at discharge, at 3, 6, 9, and 12 months after transplantation, every 6 months thereafter up to 48 months, and then at yearly intervals. Neurological assessment included EDSS score and MRI examinations. QoL was assessed by the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) questionnaire and the Functional Assessment of Multiple Sclerosis (FAMS) questionnaire. The FACT-BMT is a self-administered instrument designed to assess multidimensional aspects of QoL in BMT patients [20]. It consists of the 27-item FACT-General and the 23-item Bone Marrow Transplantation Subscale (BMTS). The FAMS is a disease-specific questionnaire for QoL assessment in MS patients [21]. It consists of 58 questions and contains 7 scales: mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, and additional concerns.

Definition of response to treatment

According to the EBMT criteria of response, patients with either steady EDSS scores representing a halt of disease progression, or with improved EDSS scores representing subsidence of inflammation in the CNS were regarded as responding to treatment [4,8]. Clinical improvement was defined as a ≥0.5 point decrease in EDSS score as compared to the baseline. Progression was defined as an increase of at least 0.5 points. Both had to be confirmed after 6 months. Clinical relapse was defined as the appearance of new symptoms or worsening of old symptoms of at least 24-hour duration, in the absence of fever in a previously (4 weeks) stable patient.

QoL was assessed by calculating the Integral QoL Index (IQLI) value at different time points on the basis of FACT-BMT questionnaire scores, as described previously [14]. Less than 25% improvement in IQLI compared to the baseline value was considered a minimal QoL response; 25–50% improvement a moderate QoL response; 51–75% improvement a good QoL response; and more than 75% improvement a maximal QoL response.

Table 3. Efficacy of HDCT+auto-HSCT in MS patients studied patient population

Characteristics of response	Number of patients (%)
Patients with a response	79/79 (100%)
SPMS	39/79
PRMS	6/79
PPMS	15/79
RRMS	19/79
Improvement after HDCT+auto-HSCT	42/79 (53%)
Progression after improvement	2
Stabilization	37/79 (47%)
Progression* after stabilization	3

* 1 patient died of acute leukemia in 3 years after HDCT+auto-HSCT

Results

Adverse events

No toxic deaths were reported among the 109 MS patients, irrespective of their clinical condition at the time of transplant. The transplantation procedure was well tolerated by the patients. Mobilization was successful in all cases, with a median number of 2.1 x106/kg (range 1.5–5.5 x106/kg) collected CD34+ cells. and no major clinical adverse events were observed during this phase. Unmanipulated grafts were infused without complications. Engraftment was uneventful, and no signs of an engraftment syndrome were reported. Median days with PMN< 0.5x109 and Plt < 50x109 were 8 (range from 5 to 11) and 10 days (from 2 to 26), respectively.

Common adverse effects following the immunoablative regimen were thrombocytopenia (100%), neutropenia (100%), fatigue (100%), anemia (80%), alopecia (80%), neutropenic fever (51.6%), hepatic toxicity grade I and II (48.1%), transient neurological dysfunction (22.2%), enteropathy (18.5%). Documented sepsis was registered in one patient.

Clinical outcomes

Seventy-nine patients with the follow-up period of at least 9 months or longer were included in the clinical outcome analysis (Table 3).

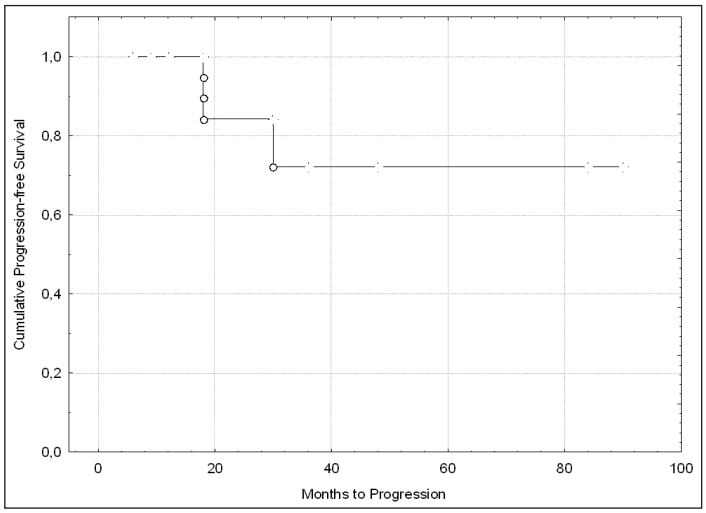
All patients responded to the treatment. At 6 months post-transplant the following distribution of patients according to clinical response was observed: 42 patients (53%) achieved an objective improvement of neurological symptoms (defined as a ≥0.5 point decrease in the EDSS score as compared to the baseline and confirmed over 3 months): 20 SPMS; 11 RRMS; 4 PRMS, and 7 PPMS. Thirty-seven patients (47%) had disease stabilization (steady EDSS level as compared to the baseline and confirmed over 3 months): 19 SPMS; 8 RRMS; 2 PRMS, and 8 PPMS. Among the patients with improvement there were 25 patients after conventional HDCT+auto-HSCT, 15 after early HDCT+auto-HSCT, and 2 after salvage HDCT+auto-HSCT. Among the patients with stabilization there were 23 patients after conventional HDCT+auto-HSCT, 9 after early HDCT+auto-HSCT, and 5 after salvage HDCT+auto-HSCT. At long-term follow-up, the clinical response in 40 patients (50.6%) was classified as an improvement; 34 patients (43.1%) remained stable. Two patients deteriorated to a worse score after 18 months of stabilization (SPMS and PPMS; conventional auto-HSCT), and one patient

after 6 months of stabilization (SPMS, conventional auto-HSCT); 2 others progressed after 12 and 30 months of improvement (RRMS, early auto-HSCT and SPMM, conventional auto-HSCT, respectively). No active, new or enlarging lesions were registered in patients without disease progression.

Remarkably, nine patients improved dramatically (≥1.5 point by EDSS). Patients with different types of MS were observed in this group. As an illustration, in a SPMS patient with the baseline EDSS value of 6.0 we observed a 2.0 point decrease on the EDSS scale at 1 month post-transplant, an additional 1.5 point decrease at 6 months and stabilization with EDSS score of 1.5 at 18 months post-transplant. In another case, a RRMS patient with a base-line EDSS score of 4.5 experienced a decrease in EDSS to 2.0 at 1 month post-transplant with a further decrease to 1.0 at 3 months. The latter EDSS level remained stable throughout the entire follow-up period of 1.5 years. The PRMS patient with baseline EDSS value of 6.0 improved at 3 months to EDSS of 4.5, and then showed further improvement at 30 months post-transplant to the EDSS score of 4.0. The EDSS score at the end of follow-up (6.5 years post-transplant) was 3.5. Finally, the PPMS patient with severe disease (EDSS score of 7.5) had a 1.5-point EDSS decrease and maintained this score during the 3.5 years of follow-up.

The progression-free survival at 6 years after HDCT+auto-HSCT was 72% (Figure 1). Remarkably, all patients who did not have disease progression were off therapy throughout the post-transplant period.

Figure 1. Progression-free survival after HDCT+auto-HSCT. Probability of progression-free survival in 42 MS patients. Estimated progression-free survival is 72% at 6 years.



QoL outcomes

QoL monitoring and assessment of QoL response were performed in 44 patients. Forty patients exhibited improved QoL at 6 months post-transplant. An increase in QoL parameters was observed according to both FACT-BMT and FAMS questionnaires. Notably, the patient who progressed 18 months after transplantation (SPMS) exhibited no QoL response. Despite clinical disease stabilization, his QoL gradually deteriorated.

In another case, a QoL deterioration was observed in a PPMS patient at 6 months post-transplant in spite of clinical stabilization during the 18 months after transplantation. It is worth mentioning that the patient (RRMS) who experienced relapse at 2.5 years post-transplant experienced a significant QoL decrease 2 years after transplantation.

The distribution of patients according to the grades of QoL response one year after HDCT+auto-HSCT is presented in Table 4.

Figure 2 demonstrates the QoL profiles of two MS patients (patient A, a 21-year-old female, PRMS, base-line EDSS 6.0; patient B, a 35-year-old female, SPMS, base-line EDSS 5.0) with the long-term follow-up after HDCT+auto-HSCT.

Discussion

Since 1995, HDCT+auto-HSCT has been performed in more than 600 MS patients all over the world. Published clinical results demonstrate that this approach can stop the disease progression in a majority of patients. A comprehensive analysis of the EBMT registry data of 85 patients from 20 centers published by EBMT ADWP in 2002, showed no disease progression for 3 years in 74% of patients [4]. Similar results were obtained in five US studies that included 66 patients in total [6,11]. Remarkably, transplant-related mortality in MS patients does not exceed transplant-related mortality in hematological patients (0–4%).

The results of our study have also demonstrated the benefits of HDCT+auto-HSCT in MS. We have included 109 patients with various types of MS from 6 centers affiliated with the Russian Cooperative Group for Cellular Therapy. The transplantation procedure was well tolerated by patients with no transplant-related deaths at all. The efficacy analysis was performed in 79 patients monitored for more than 1 year. All the patients responded to treatment: in 42 patients the EDSS score decreased after HDCT+auto-HSCT as compared to the base-line and was confirmed over 6 months, while disease stabilization (stable EDSS

Table 4. Distribution of MS patients according to the grades of QoL response at 1 year after HDCT+auto-HSCT(n=44). As is seen in the table, 3 patients exhibited a maximal QoL response, 12 patients a good QoL response, 11 patients a moderate QoL response, 13 patients a minimal QoL response, and 5 patients no QoL response. Remarkably, patients with a longer follow-up experienced further QoL improvement.

QoL response grade	Number of patients (n)	Type of MS (n)
No response	5	SPMS - 3 PPMS - 1 RRMS -1
Minimal	13	PPMS - 4 SPMS - 4 PRMS -1 RRMS -4
Moderate	11	SPMS - 6 RRMS -5
Good	12	PPMS - 1 SPMS - 7 RRMS - 4
Maximal	3	PPMS -1 RRMS -2

Figure 2. Quality of life profiles of patient A(a) and patient B (b) at different time points after HDCT+auto-HSCT.

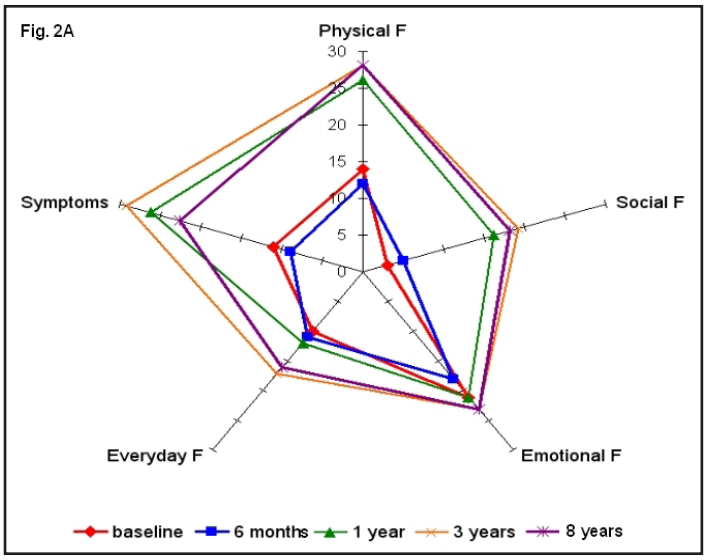
In both patients the QoL parameters improved dramatically at 1 year after HDCT+auto-HSCT.

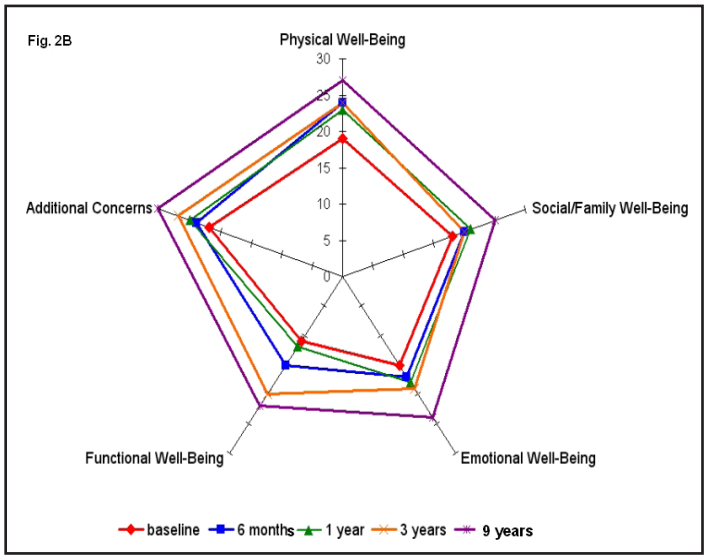
Improved QoL profiles were preserved throughout the 8-year QoL monitoring of patient A, and the 9-year QoL monitoring of patient B.

Of special interest is the dynamics of QoL profiles of patient A (Figure 2a).

Six months after transplantation an improvement was observed in this patient, which led to the formation of a significantly less compressed and less deformed QoL profile as compared to the baseline.

Further QoL improvement took place at different time points during the 8-year follow-up.





after transplantation confirmed over 6 months) was registered in 37 patients. The majority of patients had either moderate or good QoL responses as well. This data strongly supports the use of HDCT+auto-HSCT as the therapy of choice in autoimmune diseases with imminent patient debilitation, such as MS.

It is worth mentioning that the issues surrounding the patient selection criteria for HDCT+auto-HSCT are still unclear. The advantage of our study is that we included patients with different types of MS. In spite of some evidence that PPMS patients are less responsive to HDCT+auto-HSCT as compared to both SPMS and RRMS [8], the information about the outcomes of HSCT in patients with various types of MS is limited. The results of our study confirm that transplantation is effective in PPMS patients, and patients with different types of MS might benefit from HDCT+auto-HSCT.

Another advantage of our study is the performance of early, conventional or salvage transplantation, while most patients in the previous studies had late stages of MS.

Our data supports the idea that HDCT+auto-HSCT is more effective in young patients with early stages of rapidly progressing disease. In these patients, autoreactive T cells play a pivotal role in MS pathogenesis. HDCT ablates the patient‘s immune system and eradicates autoimmune T cells. It is followed by HSCT to restore the immune system, which is expected to become tolerant to autoantigens. Such „resetting“ of the immune system is only effective at early stages of MS, particularly in relapsing-remitting MS. Later in the clinical course of the disease, processes of axonal degeneration prevail, and the damage to CNS tissue is too significant to expect a neurological recovery after HDCT+auto-HSCT. Indeed, the failure of HDCT+auto-HSCT to prevent progression of the disease when performed in the late stages has been demonstrated in both animal models [22] and in clinical studies [1,11]. Considering the clinical heterogeneity of MS patients, we propose a classification of transplantation approaches based on the concept of HDCT+auto-HSCT in MS (Table 5). The concept focuses on the goals of MS treatment. There are two goals

Table 5. Classification of HDCT+auto-HSCT in MS patients

Type of transplantation	Pathogenetic goal	Overall goal	Timing
Early transplantation	To prevent the irreversible damage of the CNS by immunopathological process	To stop the disease progression and to prevent the patient’s disability	On early stages of the disease in case of poor prognosis
Conventional transplantation	To prevent the disease progression in a patient with a neural damage and partial loss of functions	To prevent exacerbation of disability and to improve or stop the decline in patient’s QoL	In case of refractory disease
Salvage transplantation	To stop the disease progression in a patient with irreversible neural damage and a significant loss of functions	To save a patient from complete disability and to improve severely declined patient’s QoL	On late stages of the disease in case of rapid progression of patient’s disability

in the treatment of MS patients. The first is pathogenetic, which is to stop the disease progression and prevent the appearance of new lesions in the nervous tissue. The second is to improve or maintain a patient's QoL. Since MS is incurable and does not shorten the patient's life span, the QoL improvement should be considered the ultimate goal of MS treatment. Therefore, QoL assessment is the key criterion for the assessment of efficacy of MS treatment in addition to traditional diagnostic tests, which describe the dynamics of the immunopathological process. It is of special importance in patients with late stages of MS.

In conclusion, our study has demonstrated that HDCT+auto-HSCT may be an effective treatment for various types of MS in terms of clinical and patient-reported outcomes at long-term follow-up. The data obtained points to the feasibility of early, conventional, and salvage HDCT+auto-HSCT in MS patients. Further studies should be done to investigate clinical and QoL response in MS patients receiving early, conventional, and salvage transplantation to better define treatment success. The concept of HDCT+auto-HSCT opens a new window of opportunities for MS treatment.

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Трансплантация кроветворных стволовых клеток при рассеянном склерозе

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Резюме

Введение: Рассеянный склероз (РС) – хроническое прогрессирующее заболевание центральной нервной системы, которое клинически проявляется мультисистемной неврологической симптоматикой, а патоморфологически характеризуется образованием множественных очагов демиелинизации в белом веществе головного и спинного мозга. Основным механизмом, приводящим к повреждению миелина, является опосредованная Т-лимфоцитами реакция гиперчувствительности замедленного типа, а непосредственными клетками-эффекторами иммунопатологического процесса - макрофаги.

Существующие методы лечения не позволяют достичь устойчивого терапевтического эффекта при рассеянном склерозе. Выдвигалась гипотеза, основанная на доклинических данных, о высокой эффективности аллогенной транплантации стволовых кроветворных клеток (ТСКК). Однако высокая посттрансплантационная летальность не позволила приступить к клиническим исследованиям данного вида терапии РС. По мнению большинства экспертов одним из наиболее перспективных методов лечения РС на сегодняшний день является высокодозная химиотерапия (ВДТ) с аутологичной трансплантацией стволовых кроветворных клеток (АуТСКК). Начиная с 1995 года, безопасность ВДТ+АуТКСК при РС была изучена в ряде клинических исследований. Тем не менее, объем информации о клинической эффективности данного метода и, особенно, о его влиянии на качество жизни больных РС, остается недостаточным. Кроме того, большинство пациентов, включенных в вышеупомянутые исследования, имели вторично-прогрессирующую форму РС и значительную степень инвалидизации со значением шкалы EDSS 4.5-8.5 баллов. К сожалению, даже полное прекращение активности иммунопатологического процесса у таких больных не может привести к значительному улучшению качества жизни. Поэтому вопрос об оптимальных сроках проведения трансплантации по-прежнему остается открытым.

В статье приведены результаты проспективного многоцентрового исследования безопасности и эффективности ВДТ+АуТКСК при РС, которое было начато в 1999 году и в настоящее время объединяет 5 крупных российских медицинских центров. Изучали влияние ВДТ+АуТКСК на клиническое течение и показатели качества жизни больных с разными формами и стадиями РС.

Материалы и методы: В исследование было включено 109 больных РС (49 мужчин, 60 женщин; средний возраст – 33 года; диапазон – 17-54): 51 с вторично-прогрессирующим течением, 19 с первично-прогрессирующим, 8 с прогрессирующе-рецидивирующим и 31 с рецидивирующе-ремиттирующим течением. Значение индекса EDSS до трансплантации колебалось от 1.5 до 8.0 баллов (в среднем было равно 5.0 баллам). Длительность наблюдения составила в среднем 19 месяцев (от 6 до 108 месяцев). Активность заболевания определяли с помощью неврологического осмотра и данных магнитно-резонансной томографии.

Больным были выполнены следующие виды ВДТ+АуТКСК:
- **Ранняя трансплантация** проводилась в дебюте заболевания при наличии неблагоприятных прогностических факторов в отношении химиорезистентности или возможности тяжелой инвалидизации больного.
- **Этапная трансплантация** проводилась при выходе заболевания из-под контроля традиционных методов лечения и формировании вторичной химиорезистентности.
- **Трансплантация спасения** проводилась в далеко зашедшей стадии заболевания при высокой активности иммунопатологического процесса и быстром прогрессировании инвалидизации больного.

Тридцати двум больным была выполнена ранняя трансплантация (EDSS 1.5-3.0); 70 больным - этапная трансплантация (EDSS 3.5-6.5) и 7 больным - трансплантация спасения (EDSS 7.0-8.0).

Оценку клинического ответа и ответа, связанного с качеством жизни, проводили до трансплантации, при выписке из стационара, через 3, 6, 9 и 12 месяцев после трансплантации, затем – каждые 6 месяцев в течение первых 4 лет и ежегодно впоследствии. Изучение неврологического статуса включало определение выраженности неврологического дефицита по шкале EDSS и магнитно-резонансную томографию. Качество жизни больных

оценивали с использованием опросников FACT-BMT (функциональная оценка состояния больных после трансплантации костного мозга) и FAMS (функциональная оценка больных с рассеянным склерозом).

Клиническим улучшением считали уменьшение выраженности неврологической симптоматики, по меньшей мере, на 0.5 балла по шкале EDSS по сравнению с исходным уровнем, при условии, что это улучшение было подтверждено через 6 месяцев на следующем визите. Любое увеличение выраженности неврологической симптоматики по шкале EDSS считали прогрессированием заболевания. Рецидив констатировали при появлении новых симптомов или нарастании выраженности прежних симптомов, по меньшей мере, в течение 24 часов в отсутствие лихорадки у пациента, который был стабилен в течение 4 предшествующих недель.

Ответ, связанный с качеством жизни, характеризовался как минимальный, умеренный, хороший или максимальный. Для определения ответа, связанного с качеством жизни, рассчитывали различия в значении интегрального показателя качества жизни до проведения трансплантации и в различные периоды времени после нее.

Результаты: У всех 79 больных со сроком наблюдения ≥9 месяцев отмечено клиническое улучшение или стабилизация в течении заболевания. Во время проведения трансплантации не было зарегистрировано ни одного смертельного исхода и тяжелых неконтролируемых побочных эффектов. Через 6 месяцев после трансплантации распределение пациентов согласно клиническому ответу было следующим: улучшение – 42 (53%) больных, стабилизация – 37 (47%) больных. Среди больных с улучшением у 20 было вторично-прогрессирующее течение, у 7 – первично-прогрессирующее, у 4 – прогрессирующе-рецидивирующее и у 11 – рецидивирующе-ремиттирующее течение. В этой группе 25 больных проведена этапная трансплантация, 15 – ранняя и 2 – трансплантация спасения. Из 37 больных, у которых зарегистрирована стабилизация заболевания, у 19 было вторично-прогрессирующее течение, у 8 – первично-прогрессирующее, у 2 – прогрессирующе-рецидивирующее и у 8 – рецидивирующе-ремиттирующее течение. В этой группе 23 больным проведена этапная трансплантация, 9 – ранняя и 5 – трансплантация спасения.

В более длительные сроки наблюдения у 40 больных (50.6%) сохранялось улучшение, у 34 (43.1%) – стабилизация. У одного больного после 6 месяцев и двух больных после 18 месяцев стабилизации произошло повышение индекса инвалидизации. У двух пациентов прогрессирование заболевания наступило после 12 и 30 месяцев клинического улучшения.

По данным МРТ у всех больных без прогрессирования заболевания после трансплантации отсутствовали активные или новые очаги поражения. В целом, 6-летняя выживаемость без прогрессии после ВДТ+АуТКСК составила 72%. Больные, у которых не было зарегистрировано признаков прогрессирования заболевания, не получали иммуномодулирующую или иммуносупрессивную терапию после трансплантации.
Мониторинг качества жизни проводился у 44 пациентов, включенных в исследование. У 40 из них наблюдали улучшение показателей качества жизни через 6 месяцев после трансплантации. Улучшение параметров качества жизни установлено с помощью опросников – FACT-BMT и FAMS. Через 1 год после ВДТ+АуТКСК зарегистрировано следующее распределение пациентов в соответствии со степенью ответа, связанного с качеством жизни: у 3 больных наблюдали максимальный ответ (более чем 75% улучшение интегрального показателя качества жизни в сравнении с исходным уровнем); у 12 больных – хороший ответ (улучшение на 50-75%); у 11 больных – умеренный ответ (на 25-50%); у 13 – минимальный ответ (улучшение менее чем на 25%) и у 5 больных ответ, связанный с качеством жизни, отсутствовал. Следует отметить, что у пациентов с более длительным сроком наблюдения было отмечено дальнейшее улучшение показателей качества жизни.

В статье представлена классификация типов трансплантации при рассеянном склерозе, основанная на концепции ВДТ+ТКСК при аутоиммунных заболеваниях.

Заключение: Высокодозная иммуносупрессивная терапия с аутологичной трансплантацией кроветворных стволовых клеток является эффективным методом лечения больных рассеянным склерозом: у большинства больных после ВДТ+АуТКСК зарегистрировано клиническое улучшение или стабилизация заболевания; ВДТ+АуТКСК сопровождается существенным улучшением качества жизни больных. Результаты свидетельствуют о целесообразности изучения результатов ранней трансплантации, этапной трансплантации и трансплантации спасения. Необходимы дальнейшие исследования для определения оптимальных сроков проведения трансплантации и уточнения режимов кондиционирования.

Ключевые слова: трансплантация стволовых кроветворных клеток, рассеянный склероз, качество жизни, ранняя трансплантация, этапная трансплантация, трансплантация спасения