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High-dose immunosuppressive therapy with autologous hematopoietic stem cells transplantation for multiple sclerosis: Current view

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Summary

Autologous hematopoietic stem cells transplantation (aHSCT) followed by high-dose immunosuppressive therapy is a promising and effective method of treating autoimmune diseases, including multiple sclerosis (MS). Over the past 15-20 years, frequency and severity of adverse events in aHSCT were decreased after reducing the intensity of conditioning regimens. Both better understanding of the immunological mechanisms of immune reconstitution and better approach to the selection of patients for this procedure also led to improved results. In view of increased incidence of multiple sclerosis worldwide, as well as insufficient effectiveness of standard therapy, the introduction of autologous transplantation into clinical guidelines for the MS treatment could maintain quality of life in the workforce population.

Keywords

Multiple sclerosis, mobilization, apheresis, high-dose immunosuppressive therapy, autologous hematopoietic stem cells, transplantation, immunotherapy.

Introduction

Over recent decades, an increase in the incidence of multiple sclerosis (MS) was recorded worldwide [1-3]. Unfortunately, current medicamental treatment of MS is very expensive and is not efficient enough: it allows for relapse-free course only in a half of the cases. In this regard, European countries are already developing programs to include high-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (HDIT-AHSCT) into the standards of active MS treatment [4, 5]. In the Russian Federation, HDIT-AHSCT has been used for severe autoimmune diseases since the mid-1990s [6, 7] like as in the European transplant clinics [8; 9]. Hence, the purpose of this review is to analyze the scientific publications on the selection of optimal conditions and criteria for HDIT-AHSCT for multiple sclerosis.

Methods of data searching

The search for scientific publications in the databases "Pubmed", "Scopus" was carried out by the keywords "HDIT-AHSCT", "stem cells" and "multiple sclerosis".

Analysis and systematization of the data from scientific literature was based on the following issues: 1) algorithms and stages of the HDIT-AHSCT methodology; 2) immunopathgenic rationale for the HDIT-AHSCT in MS patients; 3) results of HDIT-AHSCT clinical trials (CT) in MS; 4) conditioning regimens in HSCT; 5) selection of MS patients according to the criteria for HDIT-AHSCT. Our analysis included publications with high levels of evidence: publication of the results of randomized and controlled experimental and clinical laboratory studies. The international consensus recommendations of expert groups were also considered.

The main stages of HDIT-AHSCT:

1. **Mobilization** of hematopoietic stem cells – the stimulation of the CD34+ hematopoietic stem cells (HSC) output from the bone marrow to peripheral blood aiming for subsequent apheresis and mononuclear cell collection. The granulocyte colony-stimulating factor (G-CSF) is used for CD34+ cell mobilization, either as a single drug, or in combination with cyclophosphamide (Fig. 1). The available studies have not been identified statistically significant differences between such approaches in terms of relapse-free clinical course [10]. There are also no significant differences when comparing the groups with or without CD34+ cells immunoselection, the latter technology has led to lower treatment costs [11]. Patient's age, individual features of bone marrow functioning, previous treatment modaliities are the factors that may affect efficiency of hematopoietic stem cell mobilization.

2. **Apheresis** means removal of CD34+ cells from peripheral blood for subsequent cryopreservation. The HSC apheresis may take 1-2 days for sufficient cell collection. The optimal number of CD34+ cells in the transplant should be 2-5×10^6/kg of recipient weight.

3. **Cryopreservation** of the transplant, i.e., storage of the transplant in liquid nitrogen with a cryoprotector (dimethylsulfoxide) is required for the time period of treatment and pre-transplant conditioning therapy.

4. **Conditioning regimen** (CR) includes high-dose immunosuppressive therapy (HDIT) in order to deplete autoreactive T- and B- lymphocytes. The AHSCT conditioning regimens are heterogeneous for their intensity, being 4 to 7 days long. Atkins H. et al. showed the effectiveness of high-intensity, i.e., myeloablative regimens which include cyclophosphamide and busulfan, even in the patients with progressive forms of MS [12]. However, the use of high-intensity conditioning has an adverse toxicity profile and may lead to increased therapy-associated mortality. Usage of low- and medium-intensity regimens often allows to avoiding significant toxicity and demonstrates high efficacy in patients with remitting MS. The issue of choosing of conditioning regimen still remains open in cases of progressive MS.

5. **The AHSCT** procedure requires thawing and transfusion of the transplant to the patient (day 0). The duration of the procedure is less than half an hour. The primary goal of an autograft transfusion is to trigger fast recovery of the naive immunocompromised cell pool and to make cytopenic period shorter.

6. **Immunotherapy** includes usage of antithymocyte globulin (ATG) for additional exhaustion of T-lymphocytes in the transplant as well as lymphocytes in blood flow that survived after chemotherapy. In addition, ATG has an immunomodulating effect, due to increased expansion of T-regulatory cells, which, in turn, positively influences the processes of immunological tolerance [13].

7. **The period of cytopenia** is characterized by low leukocyte level in circulation. It is a regular complication of HDIT, but it is not the target when treating autoimmune disorders. In the framework of standard protocols, the massive accompanying anti-infectious therapy is carried out at this stage and, if necessary, transfusions of blood products are provided.

8. **The period of hemopoietic recovery** is achieved upon reconstitution of blood leukocytes to subnormal levels ("exit" from cytopenia). At this stage, G-CSF may be used to reduce the period of cytopenia by an average of 5-7 days. The patient can be discharged from the hospital after sustained hemopoiesis recovery to >1×10^9/l leukocyte levels; neutrophils to >0.5×10^9/l; platelets to >20×10^9/l, does not require transfusions of blood components, in absence of toxic organ, infectious and hemorrhagic complications.

9. **Consolidation** is a feasible therapeutic option to maintain the HDIT effect (for example, in fast-progressing/aggressive MS). The consolidation treatment (remission support) may include complementary immunosuppressive therapy and is administered exclusively within the framework of internal protocols of specialized centers. To date, there is no consensus protocol for post-transplant management of patients with MS.

The HDIT-AHSCT stages are shown in Figure 1.

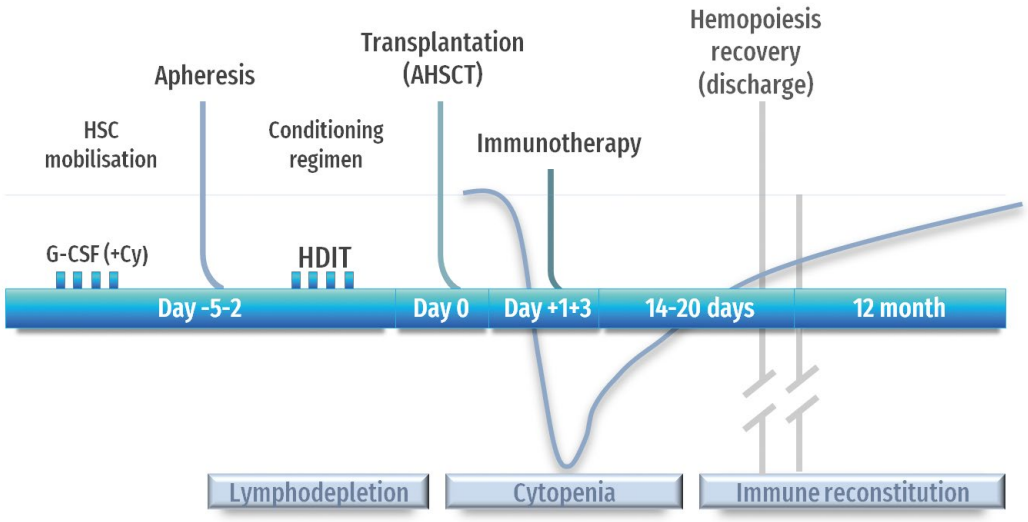

Figure 1. Steps of the high-dose intensive therapy (HDIT)-autologous stem cell transplantation (AHSCT)

Notes: G-CSF, Granulocyte Colony Stimulating Factor; HSC, Hematopoietic Stem Cells; HDIT, High-Dose Immunosuppressive Therapy; AHSCT, Autologous Hematopoietic Stem Cell Transplantation; Cy, Cyclophosphamide.

Immunopathogenic rationale of HDIT-AHSCT in MS

Multiple sclerosis is a promising disease for the potential HDIT-AHSCT application since it represents a classical autoimmune disease associated with impaired immunological tolerance followed by a sequence of immunopathogenic events directed against the nervous system, including altered antigen recognition and presentation, activation, proliferation and cell differentiation in the course of adaptive immune response. The notion that HSC in autoimmune diseases are intact, and the pathological process involves immunocompetent cells at the early stages of differentiation, was suggested and confirmed by the efficacy of autologous and syngeneic bone marrow transplantation in experimental models for rheumatoid arthritis and experimental autoimmune encephalomyelitis using immunoablation with high-dose cyclophosphamide and total body irradiation (TBI) [14-16].

Potential efficacy of HDIT preceding the AHSCT is based on a double effect upon immune system: a) elimination of pathogenetically significant autoreactive T- and B-lymphocytes using high-dose immunosuppressive therapy followed by *de novo* repopulation of "naive" lymphocytes from the transfused autologous cells, and b) due to generation of immunological tolerance to the disease-specific autoantigens [17-19]. The proof of concept for HDIT-AHSCT is based on 2 pre-requisites: (1) achievement of immune reconstitution after profound lymphodepletion and restoration of adequate balance between autoreactive cells, and (2) presumed effects of emerging immune cells responsible for immunosuppression and immunoregulation. The expected effect also includes achievement of long-term immunological autotolerance. The absence of radiological activity and clinical relapses after HDIT-AHSCT in patients with aggressive MS forms correlates with a decrease in circulating cell subpopulations of proinflammatory Th17 and dpTh1/Th17 [17].

Due to the intactness of stem cells, the autoimmune diseases (AID) do not require myeloablative conditioning. This concept allowed to eliminate highly intensive myeloablative conditioning, while maintaining the immunoablative action, thus providing total elimination of autoreactive clones of T- and B-cells [20, 21].

However, the use of a nonmyeloablative conditioning for experimental autoimmune encephalomyelitis without hematopoietic stem cell support (only HDIT without AHSCT) did not result in long-term remission, suggesting possible immunomodulating effects of AHSCT [22]. Some studies have shown that the supposed diversification of immune cell repertoire (immunological reconstitution) may occur after AHSCT. One may also expect selective expansion of minor autoreactive T-lymphocyte clones that survived the conditioning treatment immediately after reinfusion of autologous stem cells. Moreover, the transplant itself also contains an admixture of T lymphocytes, which may be a cell substrate for subsequent immune reconstitution. Immunotherapy with ATG on the first days after AHSCT (D+1, D+2, D+3) leads to additional lymphodepletion and exhaustion of T-lymphocyte subpopulations from MAIT (mucosal associated invariant), characterized by CD8+ phenotype, proinflammatory IL-17 and interferon-γ [23].

The second phase of T-cell reconstitution begins in the thymus, where immunological "learning", differentiation and maturation of T-lymphocytes occur. Thereafter, "naive" T cells circulate in the blood and peripheral lymphoid organs and, hence, participate in "reboot" of the immune system. Patients without signs of activity show early expansion of CD8+PD-1+ T-lymphocytes, and inversion of CD4/CD8 ratio. Over the first months after the procedure, the repertoire of CD8+ and (to a lesser extent) CD4+ T-cells undergoes sufficient expansion. It is also known that autologous CD34+ cells may be involved in differentiation of GFAP-producing reactive astrocytes. After 1-2 years, expansion of naive CD4+ and CD8+ thymic cells is observed, which exhibit wider clonal diversity. The regulatory pool of CD4+CD25+CD127 FoxP3+ T-lymphocytes (promoters of immunological tolerance) is also increasing with time [24].

The B-cell repertoire is also changing as seen by the profile of recovering B-lymphocytes after HDIT-AHSCT which differs from B lymphocytes prior to therapy. The peculiarity of post-transplant B-cell reconstitution is a predominance of "naive" phenotype (CD27-), whereas an imbalance towards proinflammatory profile was evident before AHSCT. For this reason, the reduced secretion of proinflammatory cytokines (FNO, IL-6, GM-CSF) was detected, and an increase of IL-10 was achieved [25]. These changes contribute to the recovery of immunological autotolerance, which may be long-lasting [26]. The changes of adaptive immune response persist for a long time after HSCT and the initial lymphocyte repopulation phase. This hypothesis confirms the concept of immune "reboot" [27].

Clinical Studies of HDIT-AHSCT in multiple sclerosis

According to the data of Autoimmune Diseases Working Party (ADWP), about 4000 SCT for autoimmune diseases (AID) have been performed and officially registered by the European Society for Blood and Marrow Transplantation (EBMT). [28, 29]. More than half of the HDIT-AHSCT were administered in cases of multiple sclerosis. The largest register of the Mexican group, where more than 1000 SCT for MS have been performed, is also known [30].

Despite the experience gained so far, the number of completed clinical trials is limited, and the data obtained are difficult to compare for the patient groups, procedure protocols (CR) and test endpoints (Table 1), and to perform proper statistical evaluation, due to their heterogeneity.

According to the HALT-MS study, the patients with active relapsing-remitting MS (RRMS) had sustained clinical remission in 77% of cases during the 5-year follow-up [32]. According to the ASTIMS study, the number of T2-lesions (MRI) was decreased in 79% of patients during 4-year follow up after HDIT-AHSCT [33]. High-intensity CR (Bu-Cy-ATG) showed full clinical and radiological remission in 84% of patients with long-term observation for an average of 6.7 years (3.9 to 12.7) [12].

Data on the efficiency of HDIT-AHSCT according to the NEDA (No Evidence of Disease Activity) criteria in different studies are compared to results of immunotherapy in

MS patients (Fig. 2). Absence of clinical exacerbation, progression of disability and physical activity according to MRI data (the summary NEDA estimate) during the three-year observation was observed in 70-94% of patients after HDIT-AHSCT compared to 22-48% following standard immunosuppressive therapy [12; 32; 34-36] with alemtuzumab (anti-CD52), ocrelizumab (anti-CD20) and daclizumab (anti-CD25) (different monoclonal antibody drugs from the group of "highly effective MS therapy") [37-39]. In this regard, interesting data were obtained at the most active transplant centers in Italy over the period of 1996 to 2016, where, after HDIT-AHSCT protocol (BEAM-ATG) applied in 122 patients (59% relapsing-remitting MS (RRRS)), 3-year relapse-free outcomes were registered in 91% of patients with RRMS and in 62% of cases with progressive-type MS ($p<0.001$). One should note that clinical exacerbations are rarely observed in secondary-progressive MS (SPMS), extremely rare in primary-progressive MS (PPMS). According to the single-center study performed by Mancardi et al., the NEDA criteria were achieved in 72% of RRMS patients and in 55% of SPMS patients within 5 years after HDIT-AHSCT ($p=0.07$) [26].

Table 1. Trials for clinical efficiency and safety of HDIT-AHSCT for multiple sclerosis [31]

Name of trial	NCT index	Conditioning regimen	Comparison group	Phase
MIST	00273364	Cy-ATG	DMT 2	II
BEAT-MS	04047628	BEAM-ATG	DMT 2	III
RAM-MS	03477500	Cy-ATG	Alemtuzumab	III
HALT-MS	00288626	BEAM-ATG	DMT 2	II
MOST	03342638	Cy-ATG+i/v Ig	-	III
COAST	-	Cy-ATG	Alemtuzumab/ Ocrelizumab	II
NET-MS	-	BEAM-ATG	PITERS 2 lines	II
ACTiMuS	01815632	Early HDIT-AHSCT	Late HDIT-AHSCT	II
Immunoablation and AHST for aggressive MS	01099930	Bu-Cy-ATG	DMT	II
ASTIMS	EudraCT 2007-000064-24	BEAM-ATG	Mitoxantrone	II

Notes: Bu – Busulfan; BEAM – Bis-chloroethylnitrosourea (BCNU), Etoposide, cytosine Arabinoside, (Ara-C; cytosine-arabinozide), Melphalan; Cy – Cyclophosphamide, ATG – Antithymocyte immunoglobulin; DMT – Disease-modifying therapy; NCT – National Clinical Trials; AHSCT – autologous hematopoietic stem cell transplantation; CR – conditioning regimen.

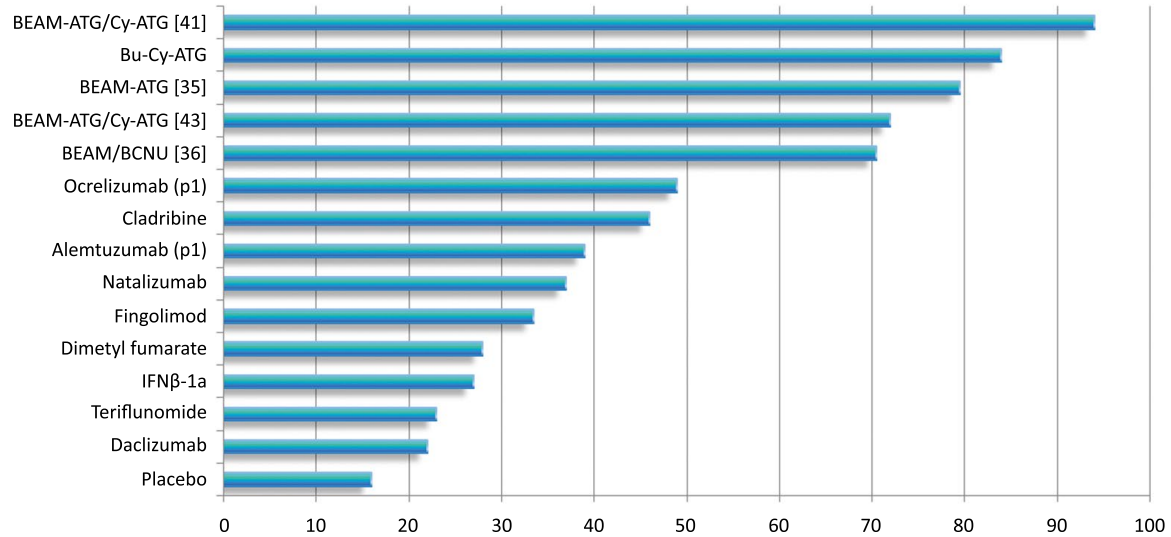

Figure 2. Effectiveness of different therapies in MS, according to the NEDA criteria. Presented a comparative analysis of the results of clinical trials (12-24 months from the beginning of therapy) and HDIT-AHSCT (30-80.4 months from therapy) [12; 34-36; 40-46]

Notes: p1 – Phase 1 trial, NEDA - No Evidence of Disease Activity; IFNβ-1a –interferon beta-1a.

The above data point to the effectiveness of HDIT-AHSCT, in advanced-stage MS patients. However, direct comparison of these results is not possible due to the differences in patient selection criteria, follow-up terms, and performance evaluation.

According to meta-analysis by Reston J.T. et al., the success rates of relapse-free period in MS after medium-intensity conditioning (BEAM/carmustine) may be higher than with high-intensity therapy including total body irradiation: 79.4% (69.9-86.5%) and 44.6% (26.5-64.3%) at the observation terms of 6-72 and 6-60 months, respectively [47].

In the MIST study, 110 patients were treated with HDIT-AHSCT (n=55) and with DMT (n=55). After a year of treatment, the disease progression with increasing neurological deficit (EDSS scale) was recorded in only 3 patients after HDIT-AHSCT *versus* 34 patients who received DMT. The total HDIT-AHSCT group showed an improvement by 1.02 points on the EDSS scale (decreased symptoms), and clinical worsening by 0.67 points in the DMT group (cross-group comparison, 1.7; 95% CI, 2.03 to 1.29; p<0.001). Despite the impressive results, it should be noted that the study had certain limitations, e.g., absence of patients in the group of DMT receiving high-efficiency treatment with ocrelizumab and alemtuzumab [48].

A long-term study of HDIT-AHSCT efficiency in MS from 1990 to 2000 was based on the inclusion of patients with a predominantly high disability levels (EDSS >6.5 points), and 20% of them were with PPMS. Relapse-free course was achieved in 60-80% of patients within 3 years of follow-up [43]. With a 10-year observation after treatment, 65% of SPMS patients had no MS symptoms, and 40% of PPMS patients showed a positive effect in terms of improved quality of life and cognitive functions [49, 50]. The limitations of this study relate to the issues of the outcome assessment, since, as noted above, the frequency of exacerbation for progressive forms of MS are difficult to evaluate in optimal manner.

Table 2. Characteristics of the patients who have undergone HDIT-AHSCT for multiple sclerosis in 2000-2012

Number		25
Age		33±6 y.o.
Type of MS	RRRS	4
	SPMS	10
	PPMS	10
EDSS	Total	6.0±1.0
	0-4.0	3
	4.5-6.0	13
	6.5-8.0	8
Conditioning regimen	BEAM-ALG/ATG	15
	Flu-Mel	9

Notes: BEAM – Bis-chloroethylnitrosourea (BCNU), Etoposide, cytosine Arabinoside, (Ara-C; cytosine-arabinozide), Melphalan; ATG – Antithymocyte immunoglobulin; ALG – Antilymphocyte immunoglobulin; Flu – Fludarabine; Mel – Melphalan.

According to the data of R.M. Gorbacheva Research Institute (Pavlov University, St. Petersburg), over the follow-up period of 19 to 7 years after HDIT-AHSCT only minimal progression of neurological deficit, i.e., 0.5±1.1 EDSS points was documented after treatment (the characteristics of the study group are presented in the Table 2).

The MSSS progression score at the time of HDIT-AHSCT was 76.5±21.36, compared to 62.43±25.05 after 13±2.5 years (p=0.015), which may indicate a delay of progression after treatment [51]. The obtained results (Fig. 3) show that HDIT-AHSCT allowed to influence the aggressive clinical course and to shift the average rank value of MSSS from the group "Fast Progressing Current 3B" to the group "Progressing Current 3A". In general, our results are in accordance with previously reported EBMT data [43, 52, 53].

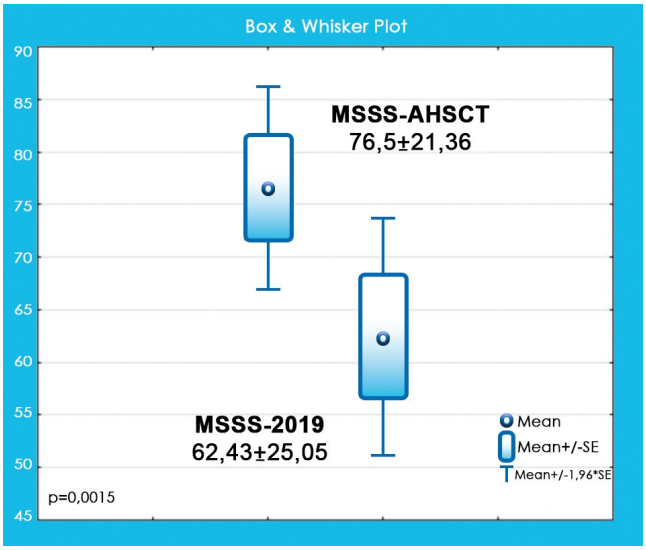

Figure 3. Delayed MS progression after HDIT-AHSCT

Notes: MSSS – Multiple Sclerosis Severity Score [54].

Unresolved issues in conditioning regimens

As mentioned above, the conditioning regimes (CR/HDIT) differ in immunosuppressive effects: high-, medium- and low-intensity regimens. The most commonly used CRs are presented in Table 3.

Established variants of high-dose conditioning regimens depending on the level of immunosuppression [5, 8-10, 12, 20, 28, 32-36, 41, 43, 58].

As shown in Table 3, the high-intensity conditioning regimens were used predominantly in North America. The European transplant centers applied mostly reduced intensity protocols. Before 2010, high- and medium-intensity regimens were mainly used, followed by later shift towards the use of cyclophosphamide-containing regimens, thus enabling implementation of this approach even in younger MS patients with under 18 years [55].

Duration of the relapse-free course in MS as well as the severity of early and late HSCT complications is shown to depend on the intensity of conditioning regimen. In the report of the EBMT Registry (2005), a stable clinical response

Table 3. Predoninant conditioning regimens, according to the CIMBTR and EBMT data

Regimen	CIMBTR	EBMT
High-intensity CR		
Cy-Alemtuzumab	+	-
TBI-Cy-ATG	+	-
Bu-Cy-ATG	+	-
Moderate-intensity CR		
BEAM-ATG	+	+
BEAM	-	+
Thiotepa-Cy	-	+
Flu-Mel	-	+
Cy-ATG	+	+
Low-intensity CR		
Flu-Cy (120 mg)	-	+
Cy-R	+	-
Cy	-	+

Notes: CIMBTR – Center for International Blood and Marrow Transplant Research; EBMT – European Society for Blood and Marrow Transplantation; TBI – Total Body Irradiation; BCNU – bis-chloroethylnitrosourea; Bu, Busulfan; BEAM – Bis-chloroethylnitrosourea (BCNU) and Melphalan; Cy – Cyclophosphamide; ATG – Antithymocyte immune globulin; Flu – Fludarabine; Mel – Melphalan; R – Rituximab.

was observed in 78% of patients who received high-intensity treatment, compared to 68% for medium- and 30% for low-intensity conditioning (p=0.0001) [56]. However, according to Reston et al. (2011), the patients with SPMS had a longer relapse-free course after medium-intensity conditioning than after high-intensity therapy (Bu-Cy, TBI-Cy, etc.) [47]. According to Arruda et al. the efficiency of conditioning regimen in MS depends more on lymphodepletion than on myeloablation, i.e., prolonged lymphopenia correlates with a longer period of relapse-free course [57].

Current principles of HDIT-AHSCT in MS

The basic principles of HDIT-AHSCT for MS are based on the recommendations of the European and American Societies for Blood and Bone Marrow Transplantation (resp., EBMT and ASBMT) [28, 58-61] being summarized as follows:

Level S/I (treatment standard/efficacy proven in at least one randomized CT):

1. HDIT-AHSCT should be offered to the patients with MS:
- with high clinical and MR-activity (at least two clinical exacerbations or one clinical exacerbation with signs of MR-activity in the form of accumulating contrast substance (Gd+) in post-concussive T1 or 1 new T2 lesions in the last 12 months);
- if one or more DMT are ineffective.

2. The factors of potential effectiveness are:
- the independence in moving (EDSS no more than 5.5);
- age under 45 years;
- the duration of the MS no more than 10 years.

Level CO/II (clinical option, no "corroborating" results of randomized CT/efficiency based on non-randomized CT data, cohort analytical studies):

1. Patients with aggressive MS (criteria: at least 2 clinical exacerbations or one clinical relapse with a centre accumulating contrast agent or a new T2 foci in the last 12 months) with disability in the last 12 months – are the candidates. In view of the potentially irreversible disability, such patients could be considered for HDIT-AHSCT before completing the full course of DMT;

2. Patients with SPMS should be considered for HDIT-AHSCT mainly with inflammatory activity (clinical relapses and Gd+/new lesions on T2 MRI) with documented progression in the previous 12 months;

3. Patients with PPMS should be considered for HDIT-AHSCT only with inflammatory activity (Gd+ and new lesions on T2 MRI) with documented apparent progression of disability in the previous 12 months;

4. Patients with MS under 18 years of age can be considered for HDIT-AHSCT only in case of aggressive MS with selection of less toxic protocols of CR;

5. The criteria for selecting patients are based on the aggressiveness of the disease, analysis of the patient's anamnesis and comorbidity, analysis of the risk-benefit ratio of the method, and from the personal and social aspects of the patient.

Conclusion

Critical evaluation of the world experience with HDIT-AHSCT in MS allows to consider this therapeutic option as highly effective treatment of multiple sclerosis if applied at early stages of the disease progression, at predominance of active autoimmune inflammation, but not at the stage of neurodegeneration prevalence. In the cases of progressive course of the disease, at a stage where neurodegenerative processes prevail, the method may have a certain delayed stabilizing effect. The selection criteria for HDIT-AHSCT in MS patients should include demographic factors, physical/social activity, type of disease and prognostic factors of adverse MS course as well as safety criteria based on present comorbidities and realistic expectations of the patient. Over last 10-15 years, taking into account the experience of multiple transplant centers, due to lower toxicity of conditioning regimes, we were able to reduce the severity of complications, however, keeping high clinical efficiency of AHSCT. Pathophysiology of multiple sclerosis, as well as in other neurological diseases, does not allow to compensate the irreversible pathomorphological changes that occurred in central nervous system before the therapy, but HDIT-AHSCT allows suppression of the current autoimmune process and, therefore, to avoid further damage and death of nervous tissues, accompanied by progression of irreversible neurological deficiency. When the desired long-term

relapse-free course is achieved, an obvious advantage of this approach may be a withdrawal of disease-modifying therapy, which complies with optimal principle of disease control using the "one-off disease control" therapy.

Conflict of interest

The authors state that there is no conflict of interest. The authors bear full responsibility for providing the final version of the manuscript to the press. All authors took part in the development of the concept of the article and the writing of the manuscript. The final version of the manuscript was approved by all authors.

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Высокодозная иммуносупрессивная терапия с аутологичной трансплантацией гемопоэтических стволовых клеток при рассеянном склерозе: современный взгляд на проблему

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Резюме

Высокодозная иммуносупрессивная терапия с аутологичной трансплантацией гемопоэтических стволовых клеток (ВИСТ-АТГСК) является перспективным и эффективным методом лечения аутоиммунных заболеваний, включая рассеянный склероз. За последние 15-20 лет уменьшились частота и тяжесть нежелательных явлений при ВИСТ-ТГСК, что было достигнуто при помощи снижения интенсивности режимов кондиционирования. Также привели к улучшению результатов более глубокое понимание иммунологических механизмов восстановления иммунитета и смена тактики отбора пациентов на процедуру. Учитывая возросшую заболеваемость рассеянным склерозом во всем мире, а также недостаточную эффективность стандартной терапии, введение аутологичной трансплантации в клинические рекомендации по лечению рассеянного склероза могло бы сохранить качество жизни молодым пациентам.

Ключевые слова

Рассеянный склероз, мобилизация, аферез, высокодозная иммуносупрессивная терапия, гемопоэтические стволовые клетки, трансплантация, иммунотерапия.