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High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation in multiple sclerosis: side effects and the tools of their reduction

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Summary

High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (HDIT-AHSCT) is a promising and effective method of treatment of autoimmune diseases, including multiple sclerosis. Over the past 20 years, the frequency and severity of side effects of therapy have been significantly reduced due to the accumulation of experience of transplant centers, changing principles of patient selection and decreased intensity of conditioning regimens. However, the medium-intensity therapeutic protocols may also be accompanied by complications. We have analyzed the literature data and our own experience on early and late side effects of HDIT-AHSCT. The profile of an appropriate schedule of HDIT-AHSCT is also presented, as determined by characteristics of the patients and the clinical course of multiple sclerosis. The types of HDIT-AHSCT are formulated, as based on the goals and expectations of the treatment approach.

Keywords

Multiple sclerosis, high-dose immunosuppressive therapy, hematopoietic stem cells, autologous transplantation, side effects, early complications, late complications, indications for transplantation.

Introduction

Long-term experience in usage of high-dose immunosuppressive therapy (HDIT) followed by autologous hematopoietic stem cell transplantation (AHSCT) has shown its efficiency in achieving clinical stabilization of multiple sclerosis (MS), thus potentially exceeding the results of highly effective drug immunotherapy [1-5]. However, due to usage of high doses of cytostatics, the safety issues of HDIT-AHSCT still remain relevant. At the same time, frequency and severity of complications in HDIT-AHSCT depends not only on the intensity of conditioning regimens (CR, chemotherapy protocol using cytotoxic drugs) [1; 6-8]. Analysis of data from the Registry of the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) presumes a dependence of favorable outcomes in HDIT-AHSCT on the quality of patients' selection and clinical expertise of the transplant center [9-12].

Analysis of research publications concerning the choice of optimal conditions and criteria for administering HDIT-AHSCT in multiple sclerosis, as well as a description of the main stages of the method, was presented earlier [13].

The purpose of this review is to analyze the clinical research data about complications of HDIT-AHSCT in MS, as well as potential factors that may reduce the risk of their occurrence.

Materials and methods

Literature search

We have searched scientific publications in the "Pubmed" and "Scopus" databases. The search algorithm included *articles and review articles* with the following queries: "stem cells" and "multiple sclerosis". The literature data were analyzed and summarized for the following items: 1) variants of conditioning regimens in HDIT-AHSCT; 2) early complications of HDIT-AHSCT; 3) late complications of HDIT-AHSCT in MS; 4) risk factors for complications of HDIT-AHSCT associated with clinical profile of the HSCT recipient.

Conditioning regimens (CR)

Currently, the most common HDIT regimens in MS treatment today are the protocols of medium-intensity (Table 1). High-intensity protocols may potentially cause a broader range of side effects, whereas low-intensity CR, in turn, may be less effective. At the same time, it should be emphasized that HDIT-AHSCT can only be performed in hematological transplant clinics with aseptic wards and a skilled multidisciplinary team.

Absence of a generally accepted conditioning regimen, and the use of several CR variants, even within the same transplant centers, reflect a number of issues that need to be addressed in the course of treatment. The choice of CR is determined by: a) the predominant mechanisms of action on cells of the applied scheme; b) expected positive and negative effects; c) safety issues for the given patient, taking into account his clinical and demographic features and comorbidity, as well as characteristics of the underlying disease. It is the CR schedule that largely determines the safety issues of HDIT-AHSCT.

HDIT-AHSCT is associated with undesirable effects which may occur early (expected effects, due to profound immunosuppression), or may be observed at later terms.

Early complications of HDIT-AHSCT develop, mainly, due to conditioning treatment, with period of cytopenia, and during the post-transplantation period (up to D+100). Infectious complications of immunosuppressive therapy are expected, being observed in almost all cases, and are often caused by reactivation of pathogens persisting in the body. Among early infectious complications, neutropenic fever, septicemia, urinary tract infections, mucositis, gastrointestinal infections, chronic latent infections (e.g., reactivation/reinfection of cytomegalovirus and Epstein-Barr virus) may be observed. In most cases, they are prevented with antibacterial, antimycotic and antiviral therapy according to the algorithm adopted at each HSCT center. Nevertheless, according to the recent publications, infectious mortality during HDIT-AHSCT in MS can reach 0.2-1% [3; 5; 14-16]. Of particular importance may be organ toxicity associated with CR, in particular, impairment of heart, liver, kidney and lung functions.

Among the early side effects of HDIT-AHSCT, transient neurological disorders may be present, which are nonspecific in most cases, reflecting constitutional or cerebral symptoms, associated with fever or allergic reactions to injected colony stimulating factor (CSF) or ATG, e.g., headache, dizziness, asthenia. The list of expected complications occurring at the early stage of HDIT-AHSCT when using the recently recommended conditioning in MS therapy [5] is presented in Table 2 [1-4; 17-21; own data].

Intensity of the conditioning regimen directly correlates with both hematological toxicity (anemia, leukopenia, neutropenia, thrombocytopenia) and systemic/organ damage (hepatitis, cystitis, diarrhea, encephalopathy, alopecia).

Table 1. Average-intensity conditioning regimens in MS therapy

(BEAM-ATG and Cy-ATG)

Protocol of HDIT	Drug	Dose	Day of drug administration (D)
BEAM-ATG: **B**is-chloroethylnitrosourea (BCNU) **E**toposide **A**ra-C (cytosine Arabinoside) **M**elphalan	 Carmustine Etoposide Cytarabine Melphalan	 300 mg/m^2 150 mg/m^2 twice a day 200 mg/m^2 twice a day 140 mg/m^2	 D-7; D-6,-5,-4,-3 D-6,-5,-4,-3 D-2
Anti-**T**hymocyte **G**lobulin	Anti-thymocyte globulin ATGAM or Thymoglobulin	 20 mg/kg/day 2.5 mg/kg/day	 D-3,-2,-1 or D+3,+2,+1
Cy-ATG:	Cyclophosphamide	50 mg/kg/day	D-5,-4,-3,-2
Cyclophosphamide **Anti-Thymocyte Globulin**	Anti-thymocyte globulin ATGAM or Thymoglobulin	 20 mg/kg/day 2.5 mg/kg/day	 D-3,-2,-1 or D+3,+2,+1

Notes: 1. In addition to HDIT, the protocol includes supportive therapy at all stages of the procedure; 2. D, day pre- and posttransplant with transfusion of thawed autograft on D0; ATG, Antithymocyte globulin.

During the period of neutropenia, episodes of febrile fever are frequent, both in presence of the current infectious process, and without signs of infection. High-intensity conditioning regimens are characterized by longer pancytopenia, which seems to be are associated with adverse outcomes. Low-intensity conditioning regimens produce milder side effects and absence of transplant-associated mortality.

Late complications, as well as therapeutic effects of HDIT, may develop due to the dynamic process of immunosuppression which accompany the posttransplant reconstitution, mainly, following myeloablative treatment. On the background of complications (especially "Blood and immune system disorders"), an imbalance in the functioning of the immune system leads to a violation of immunological surveillance, which may result into bacterial infections, including opportunistic pathogens, as well as development of oncological disorders, secondary autoimmune, and allergic conditions.

The risks of long-term opportunistic infections after medium- and low-intensity conditioning are, generally, low. A possible increase in the reactivation of herpesviruses mainly concerns herpes simplex (HSV 1, 2) and Varicella Zoster (VZV). It refers to events that are significant but could be canceled by standard antiviral drug therapy regimens, and occurs more often in the early post-transplant period. The probability and severity of late complications may depend on the intensity of CR and is inversely proportional to the duration of antiviral therapy after HDIT-AHSCT [4].

Progressive multifocal leukoencephalopathy (PML) caused by the transformation of latent infection with JC virus occurs rarely when using modern CRs. According to the EBMT registry, no PML cases were reported, including the patients previously treated with natalizumab, and those with high JCV titers [22].

Table 2. Early complications of HDIT-AHSCT observed in patients with multiple sclerosis (classified by CTCAE 5.0)

Group of complications (CTCAE Term)	Type of complication	%	References
Complications at the stage of stem cell mobilization*			
General disorders and administration site conditions	Headache, ossalgia	40	own data
Infections and infestations**	Neutropenic fever, cystitis, viral infections of the upper respiratory tract	20-23	[1; 21]
Early complications of HDIT*			
Blood and lymphatic system disorders	Lymphopenia, leukopenia, neutropenia, thrombocytopenia	100	[2; 17]
	The need for platelet transfusions	77	[21]
	Need for a blood transfusion (low Hb)	47	[21]
	Anemia	80	[17]
General disorders and administration site conditions	General weakness (asthenia)	83-100	[2; 17]
	Neutropenic fever	31-51	[2; 17; 21]
	Toxic hepatitis (Grade I-II)	42-48	[2; 17]
Skin and subcutaneous tissue disorders	Alopecia	80-100	[2; 17]
	Skin allergy	8,4	[17]
Gastrointestinal disorders	Nausea, vomiting	94	own data
	Toxic mucositis	8-17	[19; 21]
	Enteropathy	7,4-50	[2; 17; 21]
Infections and infestations	Bacteremia	46	[19]
	- other streptococcus	27	
	- alpha-hemolytic streptococcus	23	
	- staphylococcus	18	
	- clostridial infection	4	
	- candidosis (Candida albicans)	2	
	Sepsis	2-13	[1; 2;17]
	Pneumonia	2	[17]
	VZV-reactivation	2	[20]
Nervous system disorders	Transient neurological manifestations (paresthesia, tremor, syncope, etc.)	17-30	[1-3; 18; 33]
Immune system disorders	Serum sickness (ATG)	4-44	[18; 19]

Note: *, all complications are potentially expected and treatable at the inpatient stage; **, complications observed only with cyclophosphamide-induced mobilization of hematopoietic stem cells (not used in most transplant centers); VZV, varicella zoster virus/herpes zoster; EBV, Epstein-Barr virus; AID, autoimmune diseases; UT, urinary tract.

HDIT may cause damage to the ovaries and reproductive function, thus leading to impaired fertility in females, early menopause caused by chemotherapy, and longitudinal consequences of estrogen deficiency [23-25]. Restoration of the menstrual cycle after HDIT in women under 32 years old was recorded in all cases and occurred within 5 to 12 months. From our experience (Pavlov University, St. Petersburg), the median recovery time of the menstrual cycle occurs after 3±2.56 months (1 to 12 months after HDIT-AHSCT) in the group of respondents (57 women at 36±5.6 y.o. were questioned since 2018). Restoration of the menstrual cycle is much less common in the women >41 y.o., i.e., only in 38% of cases [21, 26]. Meanwhile, despite the risk of secondary infertility, the known cases of childbirth in patients with MS after HDIT-AHSCT proceeded, without complications for the mother or child. According to the EBMT registry, the postpartum women with MS, in contrast to the group with systemic sclerosis or rheumatoid arthritis, did not experience exacerbations [27, 28]. There have been no studies evaluating the effect of disease modifying therapies (DMT) on reproductive function [29], thus precluding comparisons with the risks of HDIT option.

Secondary autoimmune diseases (AID) comprise another group of late complications of HDIT-AHSCT, described at a frequency of 4-10% in MS patients [3, 5, 30]. The most expected complications are hypothyroidism, hyperthyroidism, autoimmune thrombocytopenic purpura.

According to the scarce literature data, the probability of developing endocrinopathies after chemotherapy is reported for 4-17% of cases when using medium-intensity regimens, thus being significantly lower than their frequency with high-intensity conditioning regimens (up to 26%) [3, 21].

In general, when using medium-intensity CR, the severity of HDIT complications according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0) is mostly considered mild and moderate (Grade 0-3). Table 3 presents a list of potential late complications of HDIT-AHSCT when using the recommended protocols for MS [1, 4, 5, 13, 19-21, 30-32].

Potential neurotoxicity of HDIT

High doses of cytostatic therapy are associated with a wider range, frequency, and severity of complications, with neurodegenerative component of MS being the potential feature of HDIT neurotoxicity [34-38]. Chemotherapeutic drugs used for immunoablation in MS are administered selectively, taking into account their ability to penetrate the blood-brain barrier [39], which seems to be especially relevant in progressive forms of MS, when autoimmune inflammation is "compartmentalized" with its predominance within central nervous system.

There are no data on the relevance of clinically significant neurotoxicity of chemotherapy drugs used in the protocols in the available literature. It has been proven that neurotoxicity associated with busulfan usage is transient and does not extend to the post-transplant recovery period [40]. Petzold A. et al. have shown that the blood concentration of heavy neurofilament chains of (NfH) correlating with axonal damage increased by 79% of patients with MS, and in 49% of patients with hematological malignancies after total body irradiation (TBI) and ATG treatment. However, this protocol (with TBI) is not used for treatment of MS due to high risks of adverse events [36, 41].

The potential neurotoxicity of HDIT-AHSCT is associated with MRI markers commonly used in clinical studies, e.g., dynamics of changing volumes for the distinct brain structures. The ratio of atrophy, "pseudoatrophy" and slowing down of the atrophy of the medulla is still a controversial issue in HDIT-AHSCT. After 6-24 months of HDIT-AHSCT, according to MRI data, an increased loss of brain matter can be detected [44], and without additional biomarkers that may be interpreted in two ways. On the one hand, the acceleration of atrophy associated with the neurotoxic effects of chemotherapy cannot be ruled out. On the other hand, a well-studied MRI phenomenon in the pharmacotherapy of MS is "pseudoatrophy" – a faster decrease in brain volume compared to the initial rate in the first year of treatment with DMTs, which quickly suppress autoimmune

Table 3. Possible late complications of HDIT-AHSCT in patients with multiple sclerosis (according to CTCAE 5.0)

Group of complications (CTCAE Term)	Type of complication	%	References
Infections and infestations	Reactivation of Herpes zoster viral infections	2.6-26	[4]
	Herpes simplex	4	[19]
	- VZV-reactivation	2-4	[1, 19]
	- EBV-reactivation	3	[1]
Reproductive system and breast disorders	Amenorrhea	10	[21]
Endocrine disorders	Hyperthyroidism	1-10	[20, 21, 30]
	Hypothyroidism	3-6	[1, 21]
Blood and lymphatic system disorders	Autoimmune thrombocytopenic purpura	3-6	[20]
Renal and urinary disorders	Pyelonephritis	2	[19]
Vascular disorders	Deep vein thrombosis	2	
Neoplasms benign, malignant and unspecified	Oncological diseases	1.5	[20]

inflammation and eliminate the accompanying tissue edema. According to some researchers, it is precisely in line with the effect of inflammation on the volume of brain tissue before HDIT-AHSCT (brain enlargement due to inflammatory infiltration and edema). Therefore, that the optimal assessment of brain volume is possible as late as 2 years after HDIT-AHSCT [42]. According to Roccatagliata L. et al. and Atkins H. et al., the usage of HDIT-AHSCT in aggressive forms of MS (RRMS and SPMS) having been observed during 5-year period, is followed by a slowdown in the rate of brain volume atrophy from 50% to the pathophysiological level recorded in the general population free of MS [40, 43, 44]. These data prompted the workers to suggest a long-lasting anti-inflammatory effect of immune reconstitution after HDIT-AHSCT, which is confirmed by the almost complete absence of MR activity for 5 years, or more in 70-94% of patients [19, 44-46].

Mortality

Since 1997, there has been a consensus elaborated by the European League Against Rheumatism (EULAR) with the European Group for Blood and Bone Marrow Transplantation (EBMT), that allogeneic (related/unrelated) HSCT is unacceptable in autoimmune diseases due to transplant-related mortality (TRM). The TRM rates reached 15-35% and in most cases was due to graft-versus-host disease [47]. In contrast to allogeneic transplants, the EBMT reports for 2002 and 2006 reported much lower mortality associated with autologous HSCT (6% and 5.3%, respectively), as seen in Fig. 1 [1, 6]. According to the EBMT report of 2005, it was noted that therapy-associated mortality following high-intensity CR in all autoimmune diseases, was higher than in the moderate-intensity CR group. Protocols with the maximal available doses of busulfan were associated with higher risk of therapy-associated mortality (p=0.001) in the patients with progressive forms of MS [1]. Lower risk of mortality with busulfan-containing protocols was shown in the patients with shorter duration of MS [48]. However, when comparing CRs with busulfan (high intensity) and cyclophosphamide CRs (medium/low intensity) in the group of patients with MS (unlike SLE and scleroderma), the difference was not significant [49].

Fig. 1 shows growing rates of transplantation activity with CR using cyclophosphamide (Cy-ATG), and decreased usage of BEAM-ATG regimen. In accordance with reduced CR intensity, there is a decrease in TRM.

According to EBMT reports, a significant decrease in TRM (from 7.3% to 1.3%) occurred since 2002-2005 [51]. The improvement in this important index was achieved primarily due to rejection of high-intensity CR (protocols with busulfan and total body irradiation), as well as selection of younger patients with less pronounced neurological deficit [52]. The dynamics of the paradigm shift in the patients' selection for HDIT-AHSCT is presented in Fig. 2.

Fig. 2 shows a paradigm shift in priority of HDIT-AHSCT usage in relapsing-remitting MS, which is generally characterized by a shorter duration of the disease, lesser severity of neurological deficit, and predominance of inflammatory processes over neurodegeneration.

It should be emphasized that the most dramatic effect exhibiting clinical improvement and long-term stabilization of the condition after timely HDIT-AHSCT may be observed in patients with malignant forms of MS in presence of a rapid progression of neurological deficit [16, 53-55]. Moreover, preserved quality of life is expected with the use of HDIT-AHSCT in all the MS phenotypes [56].

On the basis of data from research publications reflecting modern approaches to the treatment of MS, and results of studies using the HDIT-AHSCT, one may proposed a

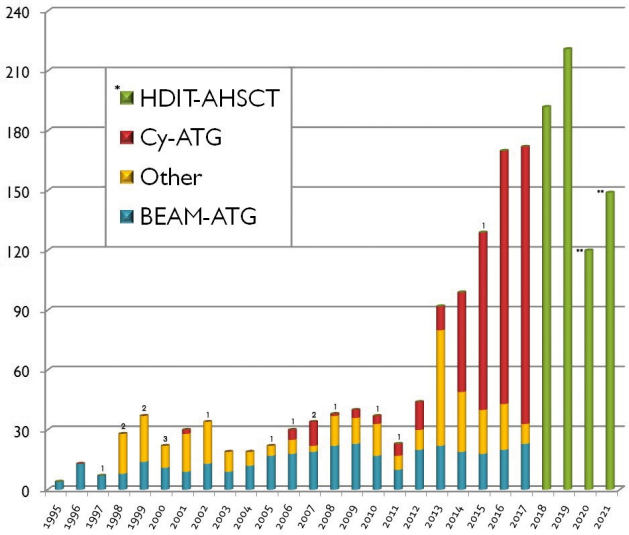

Figure 1. EBMT Registry data on usage of different CRs for HSCT in MS (1995-2021) (adopted from [3; 11; 50 and data of EBMT register])

Notes: *, the analysis on differentiation of CRs was not carried out; **, HSCT restrictions during COVID-19; 1-3, number of transplant-related mortality (TRM) cases.

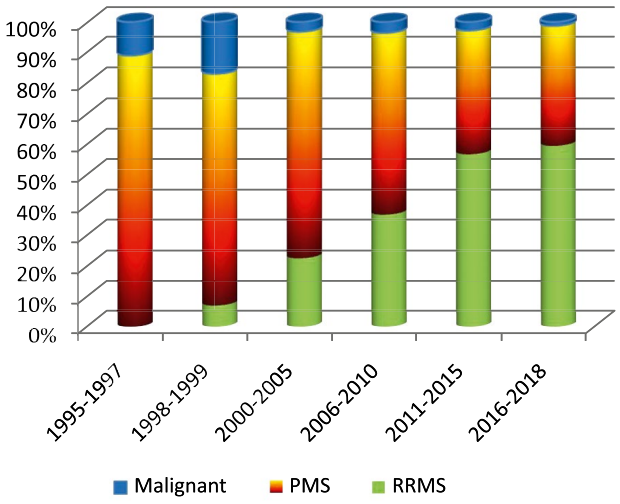

Figure 2. The ratio of patients with different types of multiple sclerosis selected for HDIT-AHSCT, %

Notes: RRMS, relapsing-remitting multiple sclerosis; PMS, progressive multiple sclerosis. Comment: malignant multiple sclerosis (aggressive) MS is characterized by an abrupt onset with several consecutive exacerbations within a short period of time, resulting into severe disability and extensive MRI lesions [5].

patient profile which is the optimal candidate for HDIT-AHSCT with a potential positive therapeutic effect from treatment (Table 4).

Transplantation centers with a long history of AID treatment take into account the optimal characteristics of a patient with MS for HDIT-AHSCT, i.e., younger age, short duration of the disease, type of clinical course, e.g., RRMS or early stages of transition to SPMS, mild or moderate neurological deficit, the presence of MRI activity (appearance of gadolinium-positive lesions in central nervous system).

As mentioned above, expectations for efficiency of HDIT-AHSCT should be based on the timely implication of the method, taking into account the disease evolution pattern in a particular patient. The types of HDIT-AHSCT by goals and time frames are presented in Tab. 5.

To date, the HDIT-AHSCT is not performed at later terms (in cases of long duration of the disease, with PPMS, EDSS >6.5 points), despite proven efficiency of canceling MS progression, with respect to potential risks and benefits of the method. This approach should be recommended to patients with similar characteristics who are motivated to carry out this treatment method, as well as to physicians involved into the decision.

Table 4. Expected effect from HDIT-AHSCT on the basis of clinical and demographic characteristics of the patient

Measure	Positive effect	+/-	No positive effect
Age, years	< 30	30-45	>45
Duration from the first symptoms of MS, years	5-10	>10	>15-20
EDSS	<3,5	3,5-5,5	>6,0
Type of MS	RRMS	PPMS	SPMS
Enhancing lesions (Gd+) according to MRI	Gd+	Gd-, new lesions	Gd- with new lesions / no new lesions
Accompanying illnesses	-	+	++

Note: a decrease in the EDSS score by 0.5 or more is considered a positive effect, however, patients with PMS also include stopping of further progression (stabilization).

Table 5. Types of HDIT-AHSCT in multiple sclerosis [12, 33, 57-61, adapted]

Types of HDIT-AHSCT	Pathogenic target	Clinical purpose	Eligible patients/ Time of application
Emergency (EDSS may exceed 6.5)	Canceling active diffuse inflammation of the CNS in order to prevent the development of irreversible changes in the CNS (the concept "time is brain")	To improve the patient's quality of life, prevent disability	Progressive deterioration of EDSS condition with Gd+ lesions visible on MRI
Early (EDSS 1.5-3.0)	Prevention of of irreversible changes in the CNS (the concept of «time is brain»)	To maintain the patient's quality of life, prevent disability	Patients with duration of the disease of <5 years
Consecutive (EDSS 3.5-6.5)	Canceling progression of MS in presence of self-sustaining immunopathological process, existing lesions of irreversible changes and partially lost functions, prevention of new lesions	To improve the quality of life of the patient and keep it at the highest possible level, to prevent the deepening of the patient's disability	At various stages of MS progression, in cases which are not controlled by standard treatment; in cases of refractory to standard therapy course of MS
Late (EDSS 7.0-8.0)	Stopping progression of MS in presence of irreversible changes and significantly impaired functions, prevention of new lesions	To maintain the patient's quality of life at the highest possible level, to prevent the onset of critical disability	At advanced stage of the disease with high activity of immunopathological process; steady progression of the patient's disability

Pre-requisites for the potential success of HDIT-AHSCT in multiple sclerosis are as follows:

- optimal selection of patients, taking into account their demographic and clinical characteristics;

- choice of the conditioning regimen intensity depending on activity and severity of MS, as well as patient risk factors, including comorbidities;

- clinical activity of the transplant center must comply with the criteria of the Joint Ac-creditation Committee ISCT-Europe & EBMT (JACIE);

- the main activity of the transplant center should be centered on treatment of hematological patients, thus providing organizational basis for quick coping with problems of therapy and prevention of adverse events;

- involvement of a multidisciplinary team (hematologist, transfusiologist, neurologist), radiologist). The specialists should have experience in treating the appropriate cohorts of patients and participate in decision-making not only at HSCT, but also at the pre-transplant stage and during long-term observation;

- dynamic follow-up of the patient's condition with clinical examination, monitoring of immune functions, neuroimaging should be carried out in order to prevent exacerbations in patients with refractory/malignant forms of MS;

- implementation of effective specialized measures for physical rehabilitation at all stages of HDIT-AHSCT, including physical therapy before admission to the transplant center (preparation regimens for long-term hospitalization and physical rehabilitation);

- obligatory keeping of the therapeutic window between the last course of DMT and the scheduled HDIT (Table 6).

Conclusion

According to current literature data, HDIT-AHSCT may produce a wide range of significant complications. However, a trend for usage of reduced (medium) intensity conditioning regimens and better (more careful) selection of patients led to minimization of adverse events. The moderate-intensity HDIT (conditioning regimens for HSCT) may be less effective than high-intensity protocols, but their use at early stages of the disease may be of maximum benefit to individuals with MS refractory to standard therapy.

HDIT-AHSCT cannot be the method of choice for all categories of patients with multiple sclerosis, since the expected clinical effect may be not justified, due to risks of complications, in particular in cases with a long duration of the disease, severe neurological deficit and lack of activity (no new lesions or gadolinium enhancement) of the process. The maximal effect can be expected in the case of early HDIT-AHSCT, and in aggressive forms of MS, where the efficiency can be considered life-determining. If such a category of patients does not meet the criteria that preclude HDIT-AHSCT, their chances for clinical improvement and/or long-term stabilization of clinical state are very high, with minimal probability of adverse events.

The costs of this treatment option are relatively high. However, taking into account the expected effectiveness, i.e., long-term relapse-free course of the disease and improved quality of life, especially in young people of working age, its inclusion into the list of standard methods of therapy for MS patients is extremely important and potentially cost-effective after the prospective comparative studies.

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Conflict of interest

The study had no sponsorship. Authors declare no conflict of interest. The authors are fully responsible for submitting the final version of the manuscript. All the 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.

Compliance with ethical principles

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

Table 6. "Therapeutic window" between the last administration of DMT and the start of HDIT

DMT	"Window", months	Note
INF	1	-
Fingolimod	3	-
Natalizumab	6	According to EBMT, there is no effect on HDIT-AHSCT [21]
Rituximab	3-6	Depending on the achievement of the reference values of CD19+ and CD20+
Ocrelizumab	6	
Alemtuzumab	10 (6-12)	Early switching to HDIT-AHSCT increases the risk of secondary AID, hemorrhagic cystitis, CMV, EBV, paraproteinemia [19]

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Высокодозная иммуносупрессивная терапия с аутологичной трансплантацией гемопоэтических стволовых клеток при рассеянном склерозе: побочные эффекты и способы их ослабления

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Резюме

Высокодозная иммуносупрессивная терапия с аутологичной трансплантацией гемопоэтических стволовых клеток (ВИСТ-АТГСК) является перспективным и эффективным методом лечения аутоиммунных заболеваний, в том числе, рассеянного склероза. За последние 20 лет значимо уменьшена частота и выраженность нежелательных явлений терапии за счет накопления опыта трансплантационных центров, изменения принципов отбора пациентов и снижения интенсивности режимов кондиционирования. Однако терапевтические протоколы средней интенсивности также могут приводить к нежелательным последствиям. В работе проанализированы данные литературы и собственный опыт по ранним и отсроченным осложнениям ВИСТ-АТГСК. Также представлен профиль вероятного кандидата на ВИСТ-АТГСК исходя из характеристик пациента и течения заболевания. Сформулированы виды ВИСТ-АТГСК исходя из целей и ожиданий от проводимого метода лечения.

Ключевые слова

Рассеянный склероз, высокодозная иммуносупрессивная терапия, гемопоэтические стволовые клетки, аутологичная трансплантация, побочные эффекты, ранние осложнения, отсроченные осложнения, показания к трансплантации.