REVIEW ARTICLE

High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation in Crohn's disease

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SUMMARY

The aim of our review was to assess current status of high-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (HDIT-AHSCT) in the treatment of Crohn's disease (CD), a chronic intestinal disorder with sufficient autoimmune component. Over recent decades, an increased incidence of CD was observed. The response rate of CD patients to conventional biological drugs ranges from 20 to 50%, and up to 80% of patients need surgical treatment. Due to suboptimal efficiency of therapy, an extensive search for new therapeutic options is underway, including HDIT-AHSCT. In the Russian Federation, some workers used mesenchymal stem cells for the treatment of CD, however, no data were reported on HDIT-AHSCT in inflammatory bowel diseases (IBD). According to the EBMT Registry, more than 4000 HDIT-AHSCT were performed in patients with autoimmune diseases over the period of 1994 to 2023, with proportion of CD patients of about 6% of total case number. Most of publications on the use of HDIT-AHSCT in CD were not uniform for the selection and management of patients. Currently, a single completed randomized clinical trial on the use of HDIT-AHSCT in CD has been published, which did not yield definite clinical results. However, this treatment option may be considered for a cohort of patients with refractory CD. The review presents clinical indications and original selection criteria for the HDIT-AHSCT protocol.

Keywords: Crohn's disease, refractory, high-dose immunosuppressive therapy, hematopoietic stem cell transplantation, autologous.

INTRODUCTION

Epidemiological data indicate an increase in the incidence of inflammatory bowel diseases (IBD) [1-3]. In particular, clinical course of Crohn's disease (CD) is also becoming more aggressive. The inflammatory form remains predominant at the time of diagnosis, and in a quarter of cases, it is complicated by intestinal strictures or penetration within the first year of disease [4]. Despite recent advances in biological therapy and small molecules in treating severe CD, their efficiency is limited: the response to biological therapy persists for one year in 25% of patients treated with infliximab or adalimumab; 32%, with vedolizumab, and 53%, with ustekinumab [5-7]. The results of clinical trials with upadacitinib do not exceed 60% [8].

When using second-line therapy, the response rate tends to decrease, and 80% of patients eventually require surgical intervention [5-7]. Surgical treatment is not a curative option, and repeated surgery is required in 30% of cases [9]. Therefore, the search for new therapeutic options is continuing.

The strategy of high-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (HDIT-AHSCT) is actively being studied for autoimmune disorders (AIDs) resistant to standard therapy, i.e., multiple sclerosis (MS), systemic sclerosis (SSc), type 1 diabetes (T1D), systemic lupus erythematosus (SLE) and CD [10]. There is clinical experience with HDIT-AHSCT for severe AIDs in Russian Federation, but it is mainly limited to MS. To lesser extent, this option was used in patients with SLE and rheumatoid arthritis [11-15]. In Russian Federation, some researchers used mesenchymal stem cells for the treatment of CD [16-18], but the studies on usage of HDIT-AHSCT (CD34+ hematopoietic cells) in IBD are lacking.

This review considers the data from scientific publications concerning efficacy and safety of HDIT-AHSCT in CD, as well as indications and patient selection criteria for this treatment mode.

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MAIN STAGES OF HDIT-AHSCT

The HDIT-AHSCT procedure consists of several stages: mobilization of autologous hematopoietic stem cells (HSCs), collection of HSCs, cryopreservation of HSCs, immunoablative conditioning, and reinfusion of autologous HSCs. The scheme is presented in Figure 1.

1. Mobilization of Autologous HSCs: This step involves stimulating the release of HSCs from the bone marrow into the peripheral blood for subsequent collection. Previously, autologous HSCs were harvested, mainly, by bone marrow aspiration, but in recent years, peripheral blood has become a more available HSC source. Granulocyte colony-stimulating factor (G-CSF) with or without cyclophosphamide (Cy) is used for mobilization. The use of cyclophosphamide at a dose of 2-4 g/m^2 for mobilization is based on the concept of lower content of immunocompetent cells in the graft. However, there is no convincing evidence of increased relapse-free/progression-free survival in patients with autoimmune diseases when using CD34+ selection in the graft [19-21]. HSC mobilization from peripheral blood is carried out in a hospital setting under close supervision, and in cases of Cy usage, antibacterial prophylaxis and treatment of infectious complications during the neutropenic period are required [19-22].

2. Stem cell apheresis and enrichment: This procedure includes collection of the required number of HSCs as a fraction of mononuclear cells from peripheral blood using automatic blood separators. According to EBMT recommendations, the minimum required dose of CD34+ cells is 2×10^6/kg, regardless of graft manipulation, and the optimal dose for subsequent engraftment is considered to be $3\text{-}5\times10^6$/kg of body weight [19-21, 23]. The collected graft may be subject to additional *ex vivo* selection of CD34+ cells. Theoretically, CD34+ cell selection minimizes the number of autoaggressive lymphocytes in the graft. However, none of the analyses performed by the European Society for Blood and Marrow Transplantation (EBMT) have shown advantages of CD34+ cell selection in terms of clinical outcomes, despite significantly higher costs for the procedure.

3. Cryopreservation of the graft: After adding 10% dimethyl sulfoxide (DMSO) as a cryoprotectant, the obtained graft can be stored for a long time in liquid nitrogen at -180°C [19-21].

4. Conditioning Regimen: The HDIT means immunoablative cytostatic treatment, in order to deplete autoreactive T- and B-lymphocyte clones and promote restoration of near-normal immune regulation, thus creating a new auto-tolerant immune repertoire with reduced inflammatory background leading to long-term remission. The effect of HDIT-AHSCT is based on the immunoablative conditioning regimen, which avoids myeloablative doses of chemotherapy and associated complications [19-21].

In general, the conditioning regimens can be classified as cytostatic treatment of different intensity. High-intensity protocols may include total body irradiation or high doses of busulfan; medium-intensity therapy use cyclophosphamide at a dose of 200 mg/kg, melphalan, fludarabine, whereas rituximab and low-dose cyclophosphamide are applied in low-intensity regimens [24]. For the treatment of AIDs, medium- and low-intensity protocols are used [25]. Although high-intensity regimens may provide a more effective response in AIDs, the risks of potential toxicity may outweigh the expected positive effect of the intervention. Currently, two main protocols are used for the treatment of AIDs: BEAM-anti-thymocyte globulin (ATG) and cyclophosphamide-ATG (Table 1).

5. AHSCT procedure: It includes thawing and infusion of the cell graft (Day 0). Since the high-dose conditioning with immunosuppressants is required to eliminate the autoimmune cell repertoire, the re-infusion of autologous HSCs allows avoid a prolonged post-cytostatic cytopenia (a complication of the conditioning regimen) by faster recovery of both immune and hematopoietic system *via* re-diversification of the pool of naive immunocompetent cells. After AHSCT, repopulation of bone marrow and restoration of hematopoiesis is shortly observed, and autotolerant immunity is formed [26].

During the phase of aplastic hematopoiesis until engraftment, supportive therapy is required, including the use of broad-spectrum antibiotics, antifungal and antiherpetic

Table 1: Standard HDIT-AHSCT protocols for the treatment of autoimmune diseases

HDIT protocol	Drugs used for conditioning	Day (D)	Dosage
Cy-ATG:	Cyclophosphamide	D-5,-4,-3,-2	50 mg/kg/day
Cyclophosphamide **A**nti-**T**hymocyte **G**lobulin	Antithymocytic globulin (ATGAM or Thymoglobulin)	D-3,-2,-1 or D+3,+2,+1	20 mg/kg/day 2.5 mg/kg/day
BEAM-ATG:			
Bis-chloroethylnitrosourea (BCNU)	Carmustine	D-7;	300 mg/m^2
Etoposide	Etoposide	D-6,-5,-4,-3	150 mg/m^2 × 2 t/d,
Ara-C (cytosine Arabinoside)	Cytarabine	D-6,-5,-4,-3	200 mg/m^2 × 2 t/d,
Melphalan	Melphalan	D-2	140 mg/m^2
Anti-**T**hymocyte **G**lobulin	Antithymocyte globulin: ATGAM or Thymoglobulin	D-3,-2,-1 or D+3,+2,+1	20 mg/kg/day 2.5 mg/kg/day

Note: 1. The protocol, in addition to HDIT, includes accompanying therapy at all stages of the procedure; 2. D is the day relative to the day of transplantation (transfusion of the thawed graft), designated as D0.

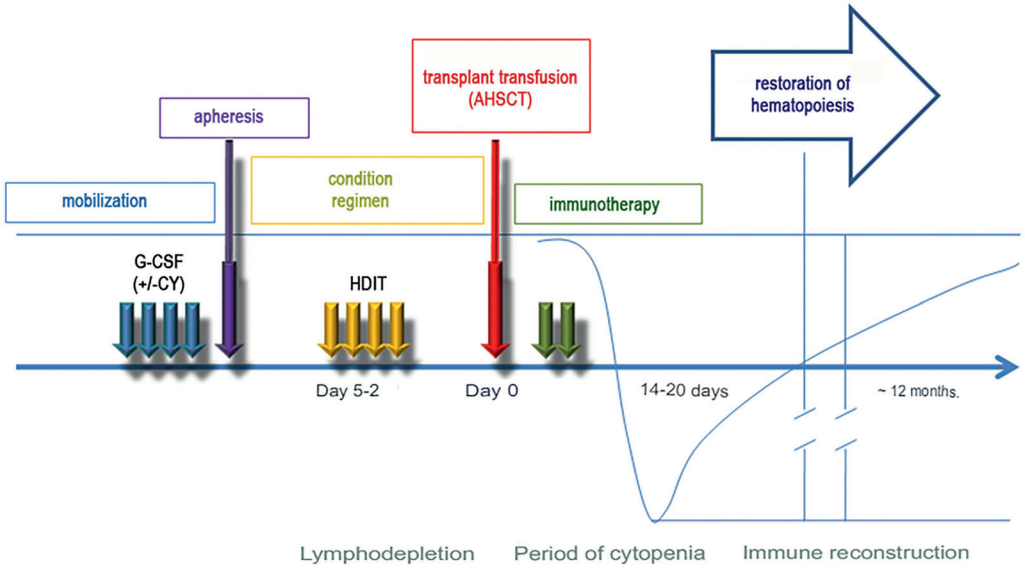

Figure 1: Flow chart of HSC mobilization/collection, high-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation

Note: G-CSF, granulocyte colony stimulating factor; CF, cyclophosphamide; HDIT, high-dose immunosuppressive therapy; HSC, hematopoietic stem cells.

agents, G-CSF, and transfusion support for at least 14 days after transplantation. The engraftment terms are confirmed at the day when the neutrophil counts exceed 0.5×10^6/L and platelets are $>20\times10^6$/L for 3 days without supportive therapy [20-22].

IMMUNE EFFECTS OF HDIT-AHSCT TREATMENT IN CROHN'S DISEASE

Immunosuppressive drugs and biological therapy can suppress autoimmune reactions at different levels of pathogenesis. The concept of HDIT-AHSCT presumes a deep impact on the course of the disease. Along with depletion of autoaggressive cell clones, it includes a possible "reset" of immunity due to destruction of autoreactive immunological memory followed by de novo restoration of auto-tolerant immune background as the basis for achieving sustained remission [27, 28]. CD is a disease with a genetic predisposition, and the immune reset after autologous transplantation seems more appropriate in terms of risk-benefit than allogeneic transplantation with complete genotype renewal of the blood system. Allogeneic HSCT is currently not recommended for the treatment of CD due to the high risk of severe complications and treatment-related mortality [20, 29]. Thus, the impact of HDIT-AHSCT on the immune system presumes correction of both innate and acquired immunity with subsequent recovery of auto-tolerant immune control [21].

After HDIT-AHSCT, all components of innate immunity are depleted. The granulocyte populations are the first to recover, followed by NK cells, and some lymphoid cell clones lacking antigen-specific receptors. The constitutively activated dendritic cells and macrophages secreting pro-inflammatory cytokines in secondary lymphoid organs and mucosal structures are also inactivated after AHSCT, with subsequent renewal from the transplanted CD34+ hematopoietic cells [20].

The effect of HDIT-AHSCT on the acquired immune system of CD patients results in elimination of CD4+ Th17/Th1 cells, along with recovery of the T-cell compartment, including Foxp3+ Treg, from the transplanted HSCs with renewal of the T-cell receptor (TCR) repertoire by the reactivated thymus [27]. Thus, in patients with refractory CD, a dominant expansion of individual T-cell clones was observed in the intestinal mucosa before HDIT-AHSCT, then followed by development of polyclonal TCR repertoire post-transplant [30]. The renewal of B-cell populations may be associated with return to auto-tolerance state due to the optimization of the B-cell receptor repertoire and increased production of IL-10 by B-regulatory cells [28]. In a study by Corraliza A.M. et al. (2019), which examined differences in immune cell populations in peripheral blood and tissues after HDIT-AHSCT in CD, a significant decrease in the total content of memory T cells, neutrophils, and macrophages was shown in the intestinal mucosa of CD patients who responded to HDIT-AHSCT with endoscopic intestinal remission. This effect, unlike the depletion of T cells in peripheral blood, was not observed in patients who did not respond to HDIT-AHSCT, thus convincingly indicating that the depletion of T cells in gut mucosa is associated with the effectiveness of treatment [31].

AHSCT also plays an additional role in the regeneration of intestinal mucosa. Active healing of affected gastrointestinal mucosa begins in CD after the restoration of hematopoiesis, [21, 22, 32]. Blood precursor cells derived from the bone marrow graft are suggested to integrate into the damaged segments of intestinal crypts without the intermediate formation of intestinal stem cells. These cells may subsequently divide and differentiate into mature epithelial cells [33-35]. Hence, the potential mechanisms of the positive impact of HDIT-AHSCT on CD are multifaceted and multiple, thus determining the relevance of these studies.

CLINICAL STUDIES OF HDIT-AHSCT IN CROHN'S DISEASE

According to the EBMT Registry, from 1994 to 2023, more than 4000 HDIT-AHSCT procedures were performed in patients with AIDs. The main indications for HDIT-AHSCT were multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, and CD. The proportion of CD was 6.13% of all transplant procedures performed [10].

Since early 1990's, the available clinical reports concerned, mostly, small series of IBD patients who received HDIT-AHSCT and subsequently experienced improvement or remission of primary disorder [36-41], as shown in Table 2. These data prompted the studies on efficacy of HDIT-AHSCT as a specific therapy for refractory CD.

The first study of this kind was the randomized multicenter Autologous Stem Cell Transplantation International Crohn's Disease (ASTIC) trial. As Burt et al. (2017) notes, there were

Table 2: Studies of the HDIT-AHSCT method in refractory CD

Source/ year	Type of research	Number of patients, CD phenotype	Mobilization	Conditioning regimen	CD34+ selection	Results
Burt et al., 2003 [42]	Clinical case	n=2 A1B2L3p A1B2+3L3+4	Cy 2 g/m^2	Cy 200 mg/kg+ hATG	yes	Withdrawal of immunosuppressive therapy. CDAI <100 after 6 months, persists for 12 months. Endoscopic improvement at 6 months
Kreisel et al., 2003 [43]	Clinical case	n=1 A2B3L3p	Cy 2 g/m^2	Cy 200 mg/ kg noATG; the stage has been postponed for 1 year.	yes	Clinical remission on Prednisone 7.5 mg, ASA 2.5 mg/kg after the mobilization stage. Deterioration after 9 months, HSCT was performed with the achievement of drug-free clinical and endoscopic remission for 9 months. There was an endoscopic deterioration, therapy with prednisone 5 mg/day, MTX 15 mg/week was resumed
Scime et al., 2004 [44]	Clinical case	n=1 A3B1L2	Cy 2 g/m^2	Cy 200 mg/kg+ hATG	yes	Drug-free clinical remission, endoscopic improvement after the mobilization stage; clinical remission, endoscopic improvement for 5 months after HSCT
Oyama et al., 2005 [45]	Observational prospective study I	n=12 A1B1L3p A1B2L2p A2B2B3L3p A1B2L2p A2B1L3p A2B2L3+4p A1B2+3L3p A1B1L1+4p A2B1L3p A2B1L2p A1B2+3L1 A1B2L2p	Cy 2 g/m^2	Cy 200 mg/kg+ hATG	yes	Drug-free clinical remission (CDAI <150), endoscopic improvement in 11 out of 12 patients for 18.5 months (range 7-37 months) after HDIT-AHSCT. In 1 out of 12 patients, clinical and endoscopic deterioration with the need for GCs + MTX occurred 15 months after HSCT
Cassinotti et al., 2008 [46]	Observational prospective study	n=4 A1B2L3 A2B1L3p A2B1L2p A2B1L3p	Cy 1.5 g/m^2	Cy 200 mg/kg+ rATG	no	Clinical remission in 4 patients, endoscopic remission in 2, and endoscopic improvement in 1 3 months after HSCT. Three patients had drug-free clinical and endoscopic remission for 16.5 months (range 11-20 months) after HDIT-AHSCT
Burt et al., 2010 [47]	Observational prospective study I/II	n=24 (including 12 from the Oyama 2005 study) A1 13 (55%) A2 11 (45%) B1 19 (79%) B2 1 (4%) B3 4 (17%) L2 5 (21%) L3 1 (4%) L2+4 18 (75%) p 16 (66%)	Cy 2 g/m^2	Cy 200 mg/kg+ h/r ATG	yes	No need for immunosuppressive therapy after HSCT: 91% of patients after 1 year, 63% after 2 yes, 57% after 3 yes, 39% after 4 yes, 19% after 5 years. At the end of the follow-up: 9 patients without relapses (4 patients in the study from 6 to 36 months), 15 resumed therapy, 8 of them achieved drug-free remission
Hommes et al., 2011 [48]	Observational prospective study	n=3 A3B2+3L1+4 A2B3L2 A2B3L2p	Cy 4 g/m^2	Cy 200 mg/kg+ hATG	yes	Clinical and endoscopic remission in 2 patients for 5-6 years after HDIT-AHSCT on BT (started 12-24 months after HDIT-AHSCT). Non-drug clinical and endoscopic remission in 1 patient for 2 years after the mobilization stage, refused conditioning

Source/ year	Type of research	Number of patients, CD phenotype	Mobilization	Conditioning regimen	CD34+ selection	Results
Clerici et al., 2011 [49]	Observational study	n=6 A2B3L3p A2B3L2p A2B3L3p A2B2L3 A2B3L2p A2B1L2	Cy 1.5 g/m^2	Cy 200 mg/kg+ rATG	no	Clinical remission in 6 patients, endoscopic remission in 4 patients, and endoscopic improvement in 2 patients after 3 months. Drug-free clinical and endoscopic remission in 5 patients after 12 months. 1 case of deterioration that required surgery, followed by a complete response to conventional therapy
Kountaras et al., 2011 [50]	Clinicalcase	n=1 A2B3L3+4	Cy 4 g/m^2	Cy 200 mg/kg+ rATG	no	Clinical and endoscopic remission for 31 months
Hasselblatt et al., 2012 [51]	Observational prospective study I/II	n=11 completed mobilization, (9/11 completed conditioning) A2B3L3 A2B1L2 A2B1L3 A3B1L3L4 A2B3L3p A2B1L2 A2B2L1L4 A1B3L3p A2B1L2	Cy 4 g/m^2	Cy 200 mg/kg noATG	yes	Clinical remission in 4 out of 8 patients, 4 showed clinical improvement 6 months after HSCT. Endoscopic remission in 5 out of 9 patients, and endoscopic improvement in 3 patients after 9 months. Relapse in 7 out of 9 patients after 10.9 months (6-14 months), 6 of them responded to post-treatment with immunosuppressants, 1 responded to BT
Lopez-Garcia et al., 2017 [52]	Observational prospective study	n=35 mobilization was completed, 29 HDIT-AHSCT. 13 patients were included in the ASTIC A28,8 (16.5-49.3) B1 21 (72%) B2 3 (10%) B3 5 (17%) L1 1 (3%) L2 7 (24%) L3 14 (48%) L1+L4 1 (3%) L3+L4 6 (21%) p 16 (55%)	Cy 4 g/m^2	Cy 200 mg/kg+ rATG	no	Drug-free clinical remission in 70% of patients after 6 months. Drug-free remission (CDAI < 150, SES-CD < 7) in dynamics: 61% after 1 year, 52% after 2, 47% after 3, 39% after 4 and 15% after 5 years. Clinical and/or endoscopic recurrence in 52% of patients occurred on average 53.1 weeks after HDIT-AHSCT, 80% of them responded to TNFi therapy in combination or without immunosuppressants, the rest needed colectomy. The absence of a positive effect of HDIT-AHSCT on undrained perianal lesions
Hernanz et al., 2018 [53]	A retrospective study	n=7 mobilization was completed, 7 HDIT-AHSCT A 26 (16-43) B1 5 (71%) B2 2 (29%) B3 0 (0%) L1 2 (29%) L2 4 (57%) L3 1 (14%) p 3 (43%)	Cy 4g/m^2	Cy 200 mg/kg+ rATG	no	Three patients (43%) showed clinical and endoscopic remission; one patient (14%) showed clinical improvement without remission, and three patients (43%) remained active with the need to resume treatment when assessing the initial response to HSCT (after six months). Symptoms recurred in five out of seven patients (71%), and all of them had to resume treatment after an average of 13.8 months (range: 3-30 months). Only one patient required surgery after HSCT. At the end of the follow-up, after an average of 48 months (range: 17-78 months), 5/7 (71%) patients had clinical remission with or without treatment

Note: the phenotype of Crohn's disease was established according to the generally accepted Montreal Classification (2005), the data were omitted in the absence of information about the phenotype; Cy – cyclophosphamide; ATG - antithymocyte globulin (r – rabbit, h – horse); MTX – methotrexate; AZA – azathioprine; BT – biological therapy; TNFi – inhibitors of tumor necrosis factor alpha; SGCs – systemic glucocorticosteroids; RCT – randomized controlled trial; CDAI – Crohn's disease activity index, Crohn's disease activity index; HDIT-AHSCT, high-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation; SES-CD is a simple endoscopic score for Crohn's disease, a simple endoscopic index of Crohn's disease activity.

fundamental methodological limitations in this study: the use of an excessively strict combined endpoint that is not used in other studies in CD, which led to a false negative result, and the comparison of the HSCT group with a control group receiving 50% of the dose of the same drug (cyclophosphamide), which made the comparison incorrect [54]. In the research which included 45 patients with refractory CD (treatment failure with, at least, three immunosuppressive agents – thiopurines, methotrexate, and infliximab). [55] All patients underwent stem cell mobilization with CF 4 g/m², after which patients were randomized to the HDIT-AHSCT group (n = 23) and the control group (n = 22). Conditioning was performed with Cy (200 mg/kg) with ATG; CD34+ cell selection was not performed. The primary endpoint was determined as a sustained disease remission at 12 months post-transplant, defined as a combination of three components: clinical remission (CDAI <150), no active CD therapy for the preceding 3 months, and no mucosal ulceration on endoscopy. At the 12-month assessment of the primary endpoint, it was found that sustained disease remission was achieved in only 2 patients in the HDIT-AHSCT group (8.7%), compared with 1 patient in the control group (4.5%). Secondary endpoint results were as follows: 8 (34.8%) compared with 2 (9.1%) patients were in endoscopic remission (ulcer healing); 10 *versus* 2 patients had CDAI <150; 14 (61%) patients after HDIT-AHSCT, compared with 5 (23%) patients in the control group, did not receive maintenance therapy for the subsequent 3 months. As a result, HDIT-AHSCT was not recommended for widespread use as a therapy for refractory CD [55].

Some authors also noted that it is inappropriate to regard the results of ASTIC as unambiguously negative due to the lack of supportive therapy after HSCT [56]. At the mobilization stage and before randomization, all patients received a high dose (4 g/m²) of Cy, and the comparison group should be considered as another experimental group [22]. This fact explains the high level of adverse events. After the completion of the ASTIC study, 17 patients from the comparison group underwent HDIT-AHSCT. Analysis of the combined patient cohort (as suggested by Burt et al. 2017) showed that 3-month steroid-free clinical remission was observed in 13 (38%) of 34 patients; 16 (43%) of 37 patients were in steroid-free remission for 1 year. Complete endoscopic healing occurred in 50% of patients, and 47% were considered healthy based on endoscopic and radiological assessment at 1 year. Combined data show a significant reduction in clinical and endoscopic disease activity at 1 year, this confirms the potential of the method in eliminating the methodological shortcomings of the original design of ASTIC [57]. HDIT-AHSCT does not provide indefinite remission, and there is a high frequency of drug therapy resumption, but in many cases, sensitivity to therapy was restored after previous refractory state.

The question of the optimal time to start and the need for continuing previous basic immunosuppressive therapy after HDIT-AHSCT remains open. Similar to other AIDs, the use of biological therapy is justified if necessary at early inpatient stage, or within 12 months after HDIT-AHSCT, in order to maintain remission [58], but requires special discussion and additional studies.

In a retrospective study evaluating the safety and efficacy of HSCT in patients with CD in Europe, beyond the ASTIC study, 82 patients from 19 centers in seven countries, have been observed after HSCT, according to the EBMT registry [59]. Of them, 53/78 patients (68%) had complete remission or significant improvement in symptoms with a median follow-up of 41 months [range 6-174 months]. Notably, in 27% of cases after HSCT, resumption of immunosuppressive drug therapy was not required. Among patients previously completely or partially resistant to treatment, its resumption in 57% of cases led to the development of disease remission or significant regression of symptoms. In 54% of patients, disease remission was maintained for 1 year after HSCT without administration of basic therapy. In a multivariate analysis, perianal involvement was associated with the need to resume CD therapy after HSCT (HR, 2.34; 95% CI 1.14-4.83, p=0.02). One patient died due to infectious complications (cytomegalovirus infection) on day 56 post-transplant [59].

Adverse events are the leading issue of the HDIT-AHSCT application in CD, the most important of which are infectious complications in presence of cytopenia. In the ASTIC study, one fatal outcome was recorded due to sinusoidal obstructive syndrome, caused by a high dose of Cy [54], or liver damage during sepsis [54]. It was believed that the side effects could be alleviated by changing the chemotherapy regimen, which is why the multicenter randomized clinical trial CT ASTIClite was proposed [19]. However, this trial has been early terminated, with only 23 patients enrolled. 13 patients were randomized to the HDIT-AHSCT group and 10 received usual care. Only 7 participants in the HDIT-AHSCT group and 6 in the group with conventional care have completed the study at 48 weeks. All patients in the HDIT-AHSCT group experienced, at least, one adverse event (a total of 38 serious adverse events), including two patients who died. In the standard care group, 4 out of 10 patients experienced side effects (a total of 16 serious adverse events). Although HDIT-AHSCT with ASTIClite protocol reduced Crohn's disease activity (with endoscopic remission in 3 out of 7 patients), the sufficient number of serious and unexpected adverse effects means that this treatment plan is not suitable for further clinical use [60].

In contrast to traditional conditioning regimens for auto-HSCT, Burt et al. (2020) proposed a non-myeloablative allogeneic approach (Cy 200 mg/kg + fludarabine 75-125 mg/m² + alemtuzumab 30-90 mg), which, even without implantation of donor cells, led to 100% remission in all patients for 5 years or more, which has not yet been described for patients after auto-HSCT. This pilot study included 9 patients, 3 of whom were transplanted from compatible siblings and 6 patients with cord blood cells. After transplantation, patients received a calcineurin inhibitor for 6 to 9 months in order to minimize the graft-versus-host reaction (GvHD) and graft rejection. In the post-transplant period (after 3 months), one fatal case was reported due to systemic adenovirus infection after contact with a patient with adenovirus conjunctivitis and one case of chronic GvHD manifested by dry mouth and eyes. The results of this study indicate a potential role for immune reconstruction after conditioning and subsequent administration of a calcineurin inhibitor. This study opens up new possibilities for optimizing auto-HSCT [67].

According to a recent systematic review with meta-analysis, which included 12 different studies on the use of auto-HSCT in refractory CD, the effectiveness of the method was confirmed in terms of induction and maintenance of clinical remission, as well as for the treatment of perianal fistulas. Collaborative work of the medical team is essential to minimize the risk of adverse events and ensure the effectiveness of the procedure [61].

CLINICAL CRITERIA FOR HDIT-AHSCT USAGE IN CD

The basic principles of selecting potential candidates for HDIT-AHSCT in CD are based on the recommendations of the EBMT and European Crohn's and Colitis Organisation (ECCO) [19-21, updated].

Indications for HDIT-AHSCT in CD include:

1. Severe Crohn's disease with no response to immunosuppressive drugs (methylprednisolone at a dose of 1 mg/kg for 4-6 weeks, inability to discontinue the drug without relapse, or the presence of relapse within 1 year after completing a course of glucocorticosteroids; inability to maintain steroid-free remission with azathioprine at a dose of 1.5-2.5 mg/kg/day, mercaptopurine – 0.75-1.5 mg/kg/day, and methotrexate – 25 mg/week for 16 weeks) and inefficacy of biological drugs (primary inefficacy at 12-14 weeks for anti-TNF agents, at 8 weeks for ustekinumab, and at 14 weeks for vedolizumab, or secondary loss of response).

2. Persistent disease activity: Crohn's Disease Activity Index (CDAI) >250 for 3 months prior to inclusion in the study and two of the following parameters: increased C-reactive protein levels; endoscopic activity confirmed by histological examination; CD activity in the small intestine confirmed by imaging studies (MR enterography or barium passage radiography).

3. Lack of indications and/or ineligibility for surgical treatment of Crohn's disease: extensive resection with the risk of developing short bowel syndrome; patient refusal to undergo surgical treatment with stoma placement.

Inclusion and exclusion criteria for the use of HDIT-AHSCT are presented in Table 3 [19, 27, 62, updated].

CONCLUSION

HDIT-AHSCT is a promising therapeutic method for patients with severe refractory Crohn's disease who suffer from a high disease burden and associated poor quality of life. HDIT-AHSCT has the potential to induce profound changes in the immunopathogenesis of CD patients due to ablation of autoreactive immune cells, followed by immune system renewal. Immune reconstitution in a significant proportion of patients may lead to at least partial restoration of autotolerance, translating into clinical and endoscopic remission and restoration of response to immunosuppressive therapy.

According to some, SCT functions as a myeloid-directed cellular therapy in CD involving HSC-associated reconstitution

Table 3: Inclusion and Exclusion Criteria for Patients for the Use of HDIT-AHSCT in Crohn's Disease

Inclusion Criteria	Exclusion Criteria
- Age from 18 to 60 years - The patient must have adequate nutrition and a healthy weight (usually BMI > 18.5); - Diagnosis of CD confirmed by endoscopic, histological, and/or imaging studies; - Disease duration of at least 6 months; - Disease extent accessible for endoscopic evaluation (jejunum and ileum, ileocecal region, or colon); - Severe clinical activity of CD with impaired quality of life at any time within 3 months prior to enrollment in clinical studies as assessed by a gastroenterologist; - Inefficacy or intolerance to azathioprine, 6-mercaptopurine, or methotrexate; - Inefficacy or intolerance to two classes of biological therapy (BT), despite dose optimization; - Ineligibility for surgical treatment of Crohn's disease or high risk of developing short bowel syndrome; - Endoscopic confirmation of disease activity at the screening visit (endoscopic assessment by SES-CD ≥ 2 in at least one segment). SES-CD will be used as an endoscopic evaluation standard for patients with diseases of the ileum and/or colon. If the disease spreads only proximally to the ileum, the SES-CD will still be used to assess the relevant segment of the intestine.	- Ulcerative colitis or indeterminate colitis - No data on clinical and endoscopic activity of CD at the screening visit; - Inability to diagnose active endoscopic disease due to strictures; - Undrained perianal fistulas (patients with prior perianal manifestations of CD or current perianal manifestations with adequate drainage using setons may be candidates for clinical studies); - Presence of an undrained perianal abscess according to screening pelvic MRI; - Short bowel syndrome; - Signs of intra-abdominal abscess/infiltrate according to abdominal MRI; - Active or latent mycobacterial infection; - History of hepatitis B, hepatitis C, or human immunodeficiency virus infection; - Signs of intestinal or systemic infection; - Pregnancy, breastfeeding, or planning pregnancy during the study. Current pregnancy will be confirmed by a pregnancy test during screening; - Unwillingness to use adequate contraception (if necessary) for at least 12 months after the last dose of the study drug; - Contraindications to the use of cytotoxic or immunotherapy used in conditioning regimens; - Comorbid chronic or psychiatric diseases; - Significant language barriers that may affect the participant's understanding of the study or ability to complete outcome questionnaires; - Concurrent participation in another interventional clinical study

Note: AZA – azathioprine, 6-MP – 6-mercaptopurine, MTX – methotrexate, BT – biological therapy, SES-CD – Simple Endoscopic Score for Crohn's Disease, ATG – anti-thymocyte globulin.

of intestinal macrophages capable of supporting mucosal healing. Some findings suggest that future conditioning regimens may improve clinical efficacy through plerixafor-based mobilisation strategies (cyclophosphomide free) that enrich healthy long-term progenitors to facilitate complete immune reconstitution [63-66].

Taking into account data on allogeneic transplantation [67] requires a revision of traditional ideas about the mechanisms of action of HSCT in Crohn's disease, especially in the context of the choice of conditioning regimen.

However, the most effective protocol for the treatment of Crohn's disease to date has been shown in the R. Burt's pilot study of nonmyeloablative allogeneic HSCT with unselected matched sibling PBSC in three and umbilical cord blood in six patients (when a matched sibling donor was not available) where remission was observed for more than 5-10 years [67]. Despite the fact that in 1997, based on consensus [68], was decided that it was inappropriate to use allogeneic HSCT due to the high risks of an adverse outcome, modern advances in donor typing allow us to discuss the use of this method again in order to more effectively apply immune reconstruction methods in autoimmune diseases.

Given the significant procedure-related risks, HDIT-AHSCT should only be performed in specialized centers with multidisciplinary expertise and robust safety protocols. Future research directions should focus on:

1) Refining patient selection criteria through predictive biomarkers,

2) Optimizing conditioning regimens to balance efficacy and safety,

3) Developing standardized protocols for post-transplant maintenance therapy.

Further studies on HDIT-AHSCT in CD, aimed at improving safety, as well as predicting outcomes and patient selection [25], may lead to the expansion of treatment approaches and improved outcomes for patients who have exhausted standard therapy options.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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