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REVIEW ARTICLE

Autologous hematopoietic stem cell transplantation for refractory Crohn's disease

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Abstract

Despite recent advances in Crohn's disease (CD) therapy, with ever-new treatments available, there is still a relevant percentage of patients with refractory disease who do not achieve adequate clinical response and are not amenable to intestinal surgery. A joint consensus of the European societies for blood and marrow transplantation and inflammatory bowel disease has recognized the therapeutic role of autologous hematopoietic stem cell (HSCs) transplantation in this cluster of patients. The therapy produces a reset of patients' immune system and the subsequent recovery of more self-tolerant inflammatory cells. In several case series and prospective clinical trials, this treatment was demonstrated to be able to induce clinical remission and heal mucosal damage, although providing only a temporary improvement. The use of deep immunosuppression as part of transplanting protocols represents the major limitation of this technique as causes a high adverse event rate, including mortality of up to 2%. Many new protocols have been assessed and are under investigation with the intent to reduce complications. The present review summarizes evidence of the efficacy and safety of autologous HSCs transplantation in refractory CD.

Keywords: *Transplant. Crohn. Refractory. Hematopoietic.*

Introduction

Since the first description of Crohn's disease (CD) in 1932 many advances have been achieved toward the control of clinical symptoms and the improvement of patients' quality of life; however, there is still no cure for the disease[1]. CD has now become a global disease with an increased incidence in newly industrialized countries and with a stable incidence in Western countries[2]. Being a multifactorial disease involving genetic susceptibility, environmental factors and intestinal microbiota, current therapeutic strategies, targeting one or few potential causes of the disease, only ensure a temporary control and improvement but not a definite solution.

Not all patients with CD show the same disease course, with the majority of cases with mild or well-controlled disease and a relevant percentage of patients with a severe course that requires several changes in therapeutic strategies, including surgery[3].

Medical therapies have changed significantly over the years, currently including steroids, immunosuppressive drugs and multiple biologic agents; moreover, new drug classes have been developed and are under investigation[4]. However, up to 30% of CD patients do not achieve clinical remission despite currently available treatments[3]. This cluster of patients represents a challenge for gastroenterologists and obliges them to explore the use of limited evidence immunomodulators, dietary strategies, and participation in clinical trials or invasive surgeries.

Refractory Crohn's disease

In 2021, an international consensus from the European Crohn's and Colitis Organization defined the

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characteristics of refractory inflammatory bowel disease (IBD)[5]. Refractory CD refers to patients who do not achieve adequate response despite the use of all available medical therapies (primary and/or secondary failure) and may not be amenable to intestinal surgery due to extensive intestinal disease, at risk for short bowel syndrome, previous multiple surgeries and, in some cases, the unwillingness of the patient to accept a permanent ostomy. There are no direct predictors of refractoriness; however, a more severe course of the disease is usually associated with age at onset < 40 years, perianal disease, upper gastrointestinal, and ileocolonic location[6,7].

The availability of medical therapies changes over time with new molecules possibly available in the next future, such as Janus kinase 1 inhibitors, sphingosine 1-phosphate receptor modulators (ozanimod), or the possibility to combine treatments (dual therapy)[8]. Thus, the definition of refractory CD is variable and evolving and must be carefully applied according to patients' medical history figure 1.

Hematopoietic stem cell (HSCs) transplantation

HSCs are characterized by the ability to self-renew and differentiate into all mature blood lineages[9,10]. This process is regulated by a complex network of stromal interactions with soluble and cell-bound cytokines[11]. The therapy of HSC transplantation allows to reset patient's immune system (lymphoablation) and restarts it with the generation of new self-tolerant immune cells, thus permitting a temporary remission of the disease. The most common technique of HSC transplantation adopted in CD is based on peripheral blood cell collection. After the recipient's bone marrow ablation (conditioning), the migration and "homing" of intravenously transplanted stem cells to the hematopoietic microenvironment in the bone marrow niches of the recipient allows the reconstitution of the cell pool[12].

The transplant may be allogeneic, syngeneic, and autologous, depending on the donor's availability and indications for transplantation. The most common indications for allogeneic HSCT are hematological malignancies and premalignant conditions[13]. Syngeneic or allogeneic HSCTs are also used for acquired disorders of marrow function (i.e., aplastic anemia) and correction of congenital hematopoietic or immunological defects (i.e., thalassemia and immunodeficiency syndromes)[14,15]. In refractory CD, autologous HSCT is considered the safest option[16].

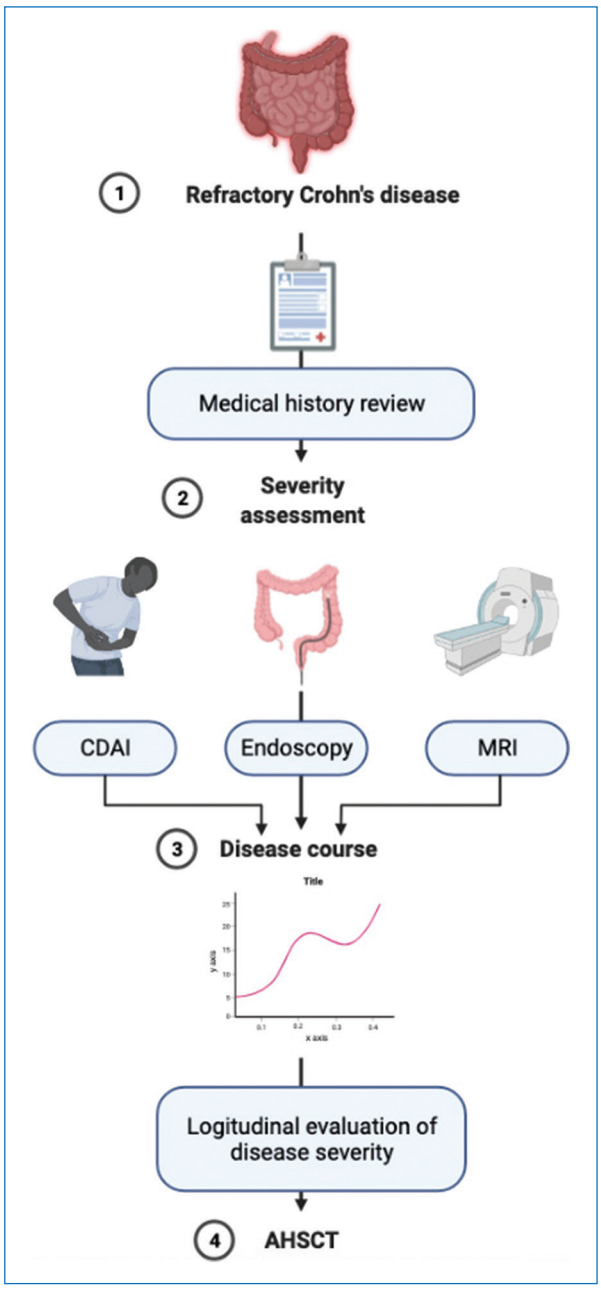

Figure 1. Eligibility assessment for autologous HSCT. CDAI: Crohn's disease activity index, MRI: magnetic resonance imaging, AHSCT: autologous hematopoietic stem cell transplantation.

Autologous HSCs transplantation in CD

Eligible candidates and screening

Potential candidates are strictly selected by a review of their medical history to confirm refractoriness to correctly and adequately administered therapies. Patients must show a severe disease activity, evaluated according to

Table 1. Standard protocol for autologous HSCT in Crohn's disease

Screening	– Confirm eligibility (refractory Crohn's disease) – Exclude severe comorbidities, pregnancy – Cardio-respiratory function assessment, bone marrow aspiration, DEXA scan, exclude latent infections, fertility preservation
Mobilization and harvesting	– Hospital admission – Safety protocols – Cy 2g/m^2/day (2 days) + G-CSF 10 mcg/Kg/day (after 5 days) – Minimum recollection 3 × 10^6 CD34+ /Kg
Conditioning and transplant	– Hospital admission – Safety protocols – Cy 200 mg/kg + rATG 7.5 mg/kg (+ CCS) – CD34+ cells reinfusion – Engraftment if neutrophils > 0.5 × 10^9/L and platelets > 20 × 10^9/L (at least for 3 consecutive days)
Follow-up	– Hematological and gastroenterological follow–up during at least 1 year

DEXA: dual-energy X-ray absorptiometry, CY: cyclophosphamide, rATG: rabbit anti-thymocyte globulins, CCS: corticosteroids.

clinical scores such as crohn disease activity index (CDAI), endoscopic exploration, and radiology (entero- Magnetic resonance imaging). Moreover, a longitudinal evaluation of severe disease course is necessary to identify eligible patients. No concomitant medications are allowed, except for steroids. Thiopurines must be suspended 2 weeks before, biologics 4 weeks before transplant.

Patients considered eligible for autologous HSCT must pass a full medical assessment, including bone marrow aspirate, left ventricle ejection fraction, pulmonary function test, dental evaluation, and bone densitometry (DEXA scan). Potential latent infections must be ruled out: cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus, Epstein-Barr virus (EBV), human T-lymphotropic virus Type 1 and 2, hepatitis viruses, human immunodeficiency virus, Toxoplasma gondii, and tuberculosis. Fertility preservation is highly recommended. Patients with severe comorbidities, poor compliance, or pregnant women are excluded from transplantation. The protocol is summarized in table 1.

Mobilization and harvesting

Mobilization has the objective to release HSCs (CD34+ cells) into the blood torrent. The most common protocol is based on the combination of a priming agent, intravenous cyclophosphamide (Cy) 2 g/m^2/day on 2 consecutive days, and subcutaneous granulocyte colony-stimulating factor (G-CSF) 10 mcg/kg/day after 5 days from last Cy infusion until leukapheresis is completed[17,18]. This regimen requires patient hospitalization in a safe setting with the use of antibiotic prophylaxis and, in some cases, parenteral nutrition, due to the high risk of infectious complications. For leukapheresis (harvesting), the minimum requirement of CD34+ cells mobilized and extracted is 3 × 10^6 CD34+/kg and, whether possible, at least 2 × 10^6 CD34+/kg cells for emergency use. In most protocols unselected CD34 + cells are used, since no clear benefits have been described with CD34+ cell-enriched or selected transplants[19]. HSCs are cryopreserved in dimethyl sulfoxide 10% until transplantation.

Recently, a new mobilization protocol, which avoids using Cy as a priming agent to minimize adverse events, has been presented. It is based on the use of G-CSF 12–16 g/kg/day up to 5 days and the optional injection of plerixafor (AMD 3100) 240 g/day in case of inadequate mobilization; this protocol does not require patient hospitalization during mobilization[20].

Conditioning and transplantation

A nonmyeloablative conditioning regimen is generally administered with a total dose of 200 mg/kg of Cy and 7.5 mg/kg of rabbit anti-thymocyte globulin (ATG); 500 mg of corticosteroids are added for 3 days to reduce adverse effects of rabbit ATG. Harvested HSCs are finally infused and engraftment is confirmed by hematologic recovery when the absolute neutrophil count is > 0.5 × 10^{9}L and platelet count > 20 × 10^9/L for at least 3 consecutive days.

Recently, an alternative protocol has been presented as part of a multicenter observational study (ASTIC lite): patients were mobilized with low-dose Cy (1 g/m^2) and G-CSF, whereas conditioning was based on fludarabine (125 mg/m^2), Cy (120 mg/kg) and rabbit ATG

(7.5 mg/Kg); however, the study was suspended due to safety concerns.

During conditioning and transplantation, it is extremely important to offer supportive care, including hospitalization in isolated rooms equipped with high-efficiency particle arresting (HEPA) filters and antimicrobial prophylaxis, targeting the most common bacteria, *Pneumocystis jiroveci* and HSV; prophylaxis is maintained until immune system recovery. A low microbial diet is adopted until CD4 recovery (> 400/mm^3) and antifungal prophylaxis until neutrophil recovery (> 500/mm^3). Patients may need irradiated transfusions of red cells or platelets and only in case of prolonged neutropenia, the use of G-CSF. During the aplasia period, parenteral nutrition is required. Patients are followed-up by both hematologists and gastroenterologists during the 1st year[21].

Efficacy

The concept and application of HSCT as primary treatment in immune-mediated inflammatory diseases (IMIDs) started at the end of the '90s and for decades it was supported by experiments on animals or by unexpected healing of IMIDs observed in patients treated due to hematological or oncological diseases. In 1997, the European group for Blood and Marrow Transplantation (EBMT) defined guidelines on indications, contraindications, and protocols of HSCT in autoimmune diseases, moreover, they created a database to collect clinical data and monitor the efficacy, toxicity, and viability of different protocols of transplantation[22].

In the IBD field, autologous HSCT was applied almost exclusively in CD and many single case reports or case series were described until the publication of the "Autologous Stem Cell Transplantation International Crohn's Disease" (ASTIC) prospective study in 2015. See Table 2.

In 2005, the University of Chicago published the first evidence of the efficacy of autologous HSCT in treating 12 patients with refractory CD and described a remission rate of 91.6%[23]. The authors observed symptomatic improvement in the majority of patients after mobilization of hematopoietic progenitors; however, it was attributed to the immunomodulatory effects of drugs used in this phase (Cy). Later, in 2010 the same group published a phase I study with a 5-year follow-up in 24 patients, including 12 patients from the previous study, to evaluate the safety and efficacy of autologous HSCT in patients with severe CD refractory to anti-TNF therapy[24]. HSCs were mobilized with Cy 2 g/m^2 and G-CSF 10 μg/kg/day, *enriched ex vivo* by selecting CD34+ cells and re-infused after conditioning with Cy 200 mg/kg and horse ATG 90mg/kg or rabbit ATG 6 mg/kg. Eighteen patients out of 24 were followed up for 5 years after transplanting. In the short-term, all patients entered remission (CDAI < 150). The percentage of patients free from CD therapy after transplant was 91% at 1 year, 63% at 2 years, 57% at 3 years, 39% at 4 years, and 19% at 5 years. The percentage of patients in remission (CDAI < 150), free from steroids and free from medications at any time interval after transplanting was 70%, 80%, and 60%, respectively.

In 2008, an Italian series of four patients was published: no CD34+ cells selection was performed but the results were comparable to previous studies. After 3 months, all patients achieved clinical remission, whereas endoscopic remission was achieved by two out of four patients[19]. Interestingly, the authors observed a worsening in the clinical conditions of patients during and after mobilization. A German case series including 12 patients described a conditioning regimen with high-dose Cy, without the use of ATG: 7 out of 9 patients showed an early relapse during follow-up, and this was partially explained by eliminating ATG from the conditioning regimen[25]. ATG is composed of purified gamma globulins containing primarily IgG against T cells and reduces the chance of relapse by contributing to the elimination of autoimmune cells[26].

In 2015, the first clinical trial of autologous HSCT for refractory CD (ASTIC) was conducted to confirm the efficacy of transplantation and assess the role of immunosuppression with Cy[17].

The ASTIC study compared the clinical benefits of mobilization of HSCs followed by conditioning and transplant (group of early transplanting) versus mobilization only followed by ordinary clinical practice; this last group could be rescued with autologous HSCT in case of persistent symptoms after 1 year from mobilization (group of late transplanting). The primary endpoint was the combined medication-free clinical and endoscopic remission at 1 year from transplant and was achieved only by 2 patients in the early transplanting group. However, in comparison with the mobilization-only arm, a secondary analysis showed that more patients in the transplanted group could stop the immunosuppressive therapy (35.3% at 3 months) and more patients in the transplanted group were in clinical and endoscopic/radiologic remission at 1 year of follow-up[27]. These results supported the concept of the beneficial effects of transplanting and not of mobilization, moreover, in line with subsequent observations, the study

Table 2. Clinical studies on autologous HSCT in Crohn's disease

Authors	Year (study design)	Transplanted patients	Harvesting	Remission rate (patients)	Relapse rate/ follow-up	Mortality rate (patients)
Oyama et al.	2005 (Phase I clinical study)	12 pts	Enriched CD34+	91.6% (11/12)	16.7%/18 months	0
Cassinotti et al.	2008 (Prospective study)	4 pts	Unselected CD34+	100% (4/4)	25%/16.5 months	0
Burt et al.	2010 (Phase I-II clinical study)	24 pts	Selected CD34+	100% (24/24)	9%/1 year 43%/3 years 81%/5 years	5% (1)
Clerici et al.	2011 (Phase I-II clinical study)	6 pts	Unselected CD34+	100% (6/6)	16.7%/1 year	0
Hasselblatt et al.	2012 (Phase I-II clinical trial)	9 pts	Selected CD34+	55.5% (5/9)	77.8%/3.1 years	0
Snowden et al.	2014 (Retrospective study)	6 pts	Unselected CD34+	83.3% (5/6)	NA	0
Hawkey et al.[17]	2015 (Multicenter prospective clinical trial)	23 pts	Unselected CD34+	8.7% (2/23) Sustained remission	NA 56.8%/1 year	4.3% (1)
Lindsay et al.[27]	2017 (Retrospective analysis)	40 pts		38.5% (15/39)		2.2% (1)
Ruiz et al.[36]	2017 (Prospective study)	14 pts	Unselected CD34+	92.9% (13/14)	NA	0
Jauregui -Amezaga et al.[21]	2016 (Safety study)	26 pts	Unselected CD34+	NA 70% (20/29)	NA 39%/1 year 48%/2 years	5% (1)
Lopez-Garcia et al.[18]	2017 (Single-center prospective study)	29 pts			53%/3 years 85%/5 years	3.4% (1)

CD: cluster of differentiation, NA: not applicable.

suggested that sustained clinical remission after autologous HSCT was not probably determined by the administration of Cy and G-CSF[28,29].

The largest case series, with 29 refractory CD patients treated with autologous HSCT at a single center, was described by the group of Barcelona[18]. Patient population showed refractoriness to corticosteroids, thiopurines, methotrexate, and anti-TNF agents. Patients passed a rigorous eligibility assessment and were hospitalized during mobilization (mean hospitalization time of 22 days) with the intent to maximize procedure safety. A standard mobilization regimen was used (Cy + G-CSF). HSCs were collected from peripheral blood by apheresis. The conditioning regimen consisted of Cy + rabbit ATG and, during the past 3 days, high-dose steroids (500 mg daily). In addition to the security measures applied during mobilization, both conditioning and transplanting included patient isolation in special rooms with high rendering filters (HEPA), prophylactic antibacterial and antifungal treatment, and prophylaxis for HSV (in patients with positive serology) and *P. jirovecii*. The transfusion of irradiated red blood cells or platelets was administered according to standard practice. Parenteral nutrition was administered during the period of aplasia. At 6 months from transplant, 70% of patients showed medication-free clinical remission (CDAI < 150). The proportion of patients in medication-free clinical and endoscopic remission (CDAI < 150, SES-CD < 7) was 61% at 1 year, 52% at 2 years, 47% at 3 years, and 15% at 5 years. Patients who relapsed during follow-up were retreated with biologics (anti-TNF with or without immunosuppressive drugs), recovering clinical remission in 80% of cases.

In 2018, a survey from the EBMT registry defined an overall 68% rate of remission or significant symptomatic improvement in patients with refractory CD with a median follow-up of 41 months, moreover, in those patients who had reinitiated a medical therapy, 57%

could achieve again clinical remission or significant improvement[16].

These data suggest that autologous HSCT does not represent a "cure" for CD; however, it can change the disease's natural history and permit to recover response to medications that patients were refractory to.

Finally, still little is known about predictors of response to autologous HSCT. According to the previous studies, colonic location and inflammatory phenotype with endoscopic lesions were associated with a better response to treatment, whereas structuring and penetrating phenotypes showed no benefit from transplanting[17,18].

Safety

The major complications of HSCT are septic and related to the use of high chemotherapy doses; moreover, drug toxicity and prolonged immunodeficiency cause an extended recovery process[30]. Adverse events can be controlled by the design of risk-specific supportive care regimens that reduce the incidence of transplantation morbidity and mortality[21].

Normally HSCT-related complications are broadly classified into infections, early non-infectious complications (within 3 months from HSCT), late non-infectious complications (after 3 months from HSCT) and graft-versus-host disease, which may require prolonged immunosuppressive therapy. In autologous HSCT the engraftment is rapid (7-14 days), thus the incidence of infections is lower than in allogeneic transplants and graft-versus-host disease is rare.

The EBMT registry described a high complication rate, mainly infections, for autologous HSCT in IMIDs and a mortality rate of up to 11%, depending on the protocol used and the disease treated, being higher in systemic diseases and lower in localized ones[31]. Mortality from autologous HSCT in IMIDs is associated with the grade of experience of the medical center as a higher number of transplants means a more rigorous selection of candidates and better management of possible complications[32]. In the case of CD mortality accounts for up to 2%[33].

In the last decades, the safety of HSCT has increased notably, due to the reduction of the intensity of conditioning regimens, the use of peripheral blood stem cells and the improvement of measures to support and select patients. In the Barcelona cohort, one patient died due to a systemic infection for CMV despite early antiviral therapy 2 months after transplantation and one patient required colectomy for a CMV and EBV co-infection. In the first transplanted patients, severe infections were observed during mobilization and conditioning phases, including bacteremia and septic shock, consequently, several measures to increase safety were adopted. The change in prophylactic antibiotic therapy, the use of a food safety-based diet and parenteral nutrition during the periods of aplasia achieved a reduction in the incidence of severe infectious events[21]. Moreover, smoking and perianal disease were identified as risk factors for adverse events[18].

Among new strategies to reduce complications, less aggressive chemotherapy regimens during mobilization and conditioning phases have been evaluated. For two decades Cy has been the standard treatment in mobilization regimens. Its use at high doses causes the liberation of proteases and the cleavage of adhesion molecules (VCAM-1 and CXCR4) culminating in the release of HSCs into the peripheral blood, although with significant cytotoxicity causing numerous side effects[34]. Moreover, whilst in many cases of HSCT for malign hematologic diseases the use of Cy is endorsed for its therapeutic role on the disease, in the case of CD, there is no need for a cytotoxic effect during mobilization[27]. Recently, with the intent to reduce the impact of chemotherapies on autologous HSCT, a Cy-free mobilization regimen has been proposed. It is based on the use of G-CSF alone, which was demonstrated to mobilize HSCs in up to 70-80% of treated patients[35]. In case of mobilization failure (< 20.000 CD34+/kg) after 7 doses of G-CSF, a rescue strategy is applied using subcutaneous plerixafor. Preliminary data suggest a better safety profile of this protocol, which allows to perform mobilization in the outpatient setting[20].

Conclusion

Refractory CD still represents a challenge for IBD specialists as there are no clear predictors to identify the disease course and therapies are insufficient in this group of patients. Autologous HSCT is a rescue therapy as it eliminates the self-reactive lymphocytes with different regimes of immunosuppression and restores a normal immunological tolerance. However, acting only on one of the mechanisms of disease pathogenesis, HSCT may not be considered a cure but rather an alternative therapeutic strategy. It may stop or slow disease progression and achieve prolonged periods of remission, thus modifying the disease's natural history without the need for chronic maintenance with steroids or immunosuppressive drugs and their related side effects. Safety is the major concern of this therapy due to the high rate of septic adverse events. Future efforts

are directed toward reducing complications and improving efficacy together with identifying predictors of response.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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