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**Hematopoietic stem cell transplantation for Crohn’s disease: Gaps, doubts and perspectives**

Ruiz MA *et al*. Crohn’s disease HSCT treatment

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**Abstract**

Crohn’s disease (CD) is an inflammatory bowel disease that can affect any site of the digestive system. It occurs due to an immunological imbalance and is responsible for intestinal mucosal lesions and complications such as fistulas and stenoses. Treatment aims to stabilize the disease, reducing the symptoms and healing intestinal lesions. Surgical procedures are common in patients. Cell therapy started to be used in this disease in patients for whom autologous and allogeneic transplantation was indicated to treat lymphomas and leukemias. After the transplantation, an improvement was also observed in the CD. In 2003, the procedure started to be indicated for the disease itself and several case series and randomized studies have been published since then; currently this approach comprises a new option in the treatment of CD. However, several gaps in our knowledge and doubts exist in relation to cell therapy for CD, which is restricted to the autologous modality of hematopoietic stem cell transplantation and experimentally, to mesenchymal stromal cells to treat lesions of the anal mucosa directly. This article presents the indications for transplantation and aspects related to the mobilization regime, conditioning and perspectives of cell therapy.

**Key words:** Crohn’s disease; Stem cell therapy; Hematopoietic stem cell transplantation; Treatment

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**Core tip**: Crohn’s disease (CD) is an inflammatory bowel disease that can affect any part of the digestive tract. Hematopoietic stem cell transplantation is considered an option in cases of severe disease refractory to conventional treatment. To date the results are promising but many gaps and doubts remain regarding the procedure and the indication of cell therapy still need answers. The aim of this editorial is to discuss these aspects and the future of cell therapy in CD.

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**INTRODUCTION**

Crohn’s disease (CD) is an inflammatory bowel disease that can affect any section of the digestive tract[1]. More common in the United States, Western Europe, Australia and New Zealand, there have recently been increases in the frequencies of cases in Asia, Eastern Europe and South America[2]. These increases are attributed to the globalization of diet and customs[3]. CD is a chronic, heterogeneous disease of unknown etiology that may occur with extra-intestinal manifestations or be associated with other autoimmune diseases[1,2]. The Genome-wide Association Study (GWAS) Project identified hereditary and genetic factors as possible indicators of susceptibility for the disease and triggers of the immunological imbalance found in patients[4].

Treatment aims to stabilize the disease, reduce symptoms and heal the intestinal lesions of the patients. Anti-inflammatory drugs, immunosuppressive agents, corticosteroids and biological agents are prescribed alone or as combinations. The drugs are usually administered in a step-wise sequence, called Step Down, but there are controversies and doubts at this point as to the early indication of biological agents in association with immunosuppressants in cases considered more serious (a treatment plan called Top Down)[1].

Surgical treatment is common in CD cases and depends on the extension and location of the disease. There is a need for surgical procedures of varying complexity in more than 50% of patients within five years of diagnosis[1,5].

**STEM CELL THERAPY**

Cell therapy emerged as a form of treatment in CD due to the chronicity of the disease, lack of therapeutic options in refractory patients and the description of improvements of the disease in cases that were submitted to hematopoietic stem cell transplantation (HSCT) for concomitant leukemia or lymphomas[6-8]. This was the first modality of cell therapy exclusively used for the treatment of CD. Initially it was described in sporadic cases and afterwards with a number of long-term and randomized studies of autologous HSCT placed the procedure on the map of the treatment of the disease similar to other autoimmune diseases[9-11].

HSCT by definition refers to any procedure that uses hematopoietic stem cells from any donor or from the recipient to repopulate or replace hematopoietic tissue completely or in part. The goal of this procedure in CD is to reprogram the immune system.

Despite the existence of established standard treatment, according to the European Bone Marrow Transplant Society (EBMT), the indication of autologous HSCT for CD is the same as for other serious, progressive and refractory autoimmune diseases as a Level II clinical option. This states that the procedure should be indicated only after careful considerations of the risks and benefits to patients. Allogeneic HSCT is generally not recommended for CD because of the inherent toxicity risks of the procedure and because of graft-*vs*-host disease (GVHD)[12].

Thus, the criteria for the indication of HSCT for CD always includes patients refractory to immunosuppressive and biological agents, the persistence of disease activity proven by endoscopy, colonoscopy or magnetic resonance enterography, as well as extensive disease for which an imminent surgical procedure exposes the patient to the risk of short bowel syndrome or refractory colonic disease. Another criterion is the presence of a persistent perianal lesion where coloproctectomy with a definitive stoma implant is not accepted by the patient[13].

Even so, doubts persist in the medical and academic community regarding HSCT for the treatment of autoimmune diseases including CD. The main fears regarding HSCT is the toxicity related to chemotherapeutic and immunosuppressive agents, the risk of infections due to the period of aplasia that commonly occurs after the conditioning regimen and to the transplant itself, the day of infusion of hematopoietic progenitor cells. In relation to toxicity, in the past, the morbidity rate was much higher. Today, death, although practically nonexistent, still occurs due to complications or infections by resistant germs, which often exist in immunosuppressed patients in a hospital environment[14].

Thus, the selection of cases for elective HSCT should be rigorous, and the patients evaluated must be monitored and followed up meticulously throughout the procedure. Patient selection should rule out comorbidities such as cardiac and pulmonary diseases, and other preexisting anomalies, clinical situations that add risk to the procedure. In short, the procedure should be carried out under the care of a multidisciplinary team and in an institution that meets the national and international legal criteria and those of good medical practices[12].

The standard mobilization regimen in CD patients is cyclophosphamide (Cy) associated with granulocyte colony stimulating factor (G-CSF). Until recently there was doubt as to the dose of Cy, whether 4 g/m2 or 2 g/m2 should be administered. It has been demonstrated that, with high doses of Cy, there is an increased risk of cardiac toxicity in addition to the risks of bladder toxicity. It has also been proven that no benefit is gained from the use of high doses in terms of obtaining a higher number of cells for HSCT both in CD and in other autoimmune diseases[15]. CD patients are often super-mobilizers and present a rapid recovery with low toxicity after HSCT. These conditions have an impact with an improvement in the quality of life soon after the procedure. In relation to Cy there are already proposals to reduce the dose in the mobilization regime to 1 g/m2.

Another question concerns the manipulation or selection of cells for HSCT. Several reports used selection or enrichment of CD34+ to reduce the volume and increase the efficacy of the product to be infused. From a study with four patients in which manipulation was not used and considering the technical difficulties to select and enrich cells, manipulation is no longer performed and several authors have reported successful treatment without affecting the results of HSCT[16]. Generally, the dose of G-CSF for mobilization is 10 µg/kg per day from the 5th day after the administration of Cy. There is no certainty of the best day to start the administration of the cytokine, nor are there reports of its use alone in the mobilization of patients with CD. This has probably not been tried to date due to reports of flares or disease exacerbation in other autoimmune diseases[17]. However, it should be noted that there are references that G-CSF provides benefits to CD patients[18].

The standard conditioning regimen for CD is the association of Cy with rabbit or horse antithymocyte globulin (GAT). The doses of Cy, rabbit GAT and horse GAT are 200 mg/kg, 6.5 mg/kg and 90 mg/kg, respectively split over four consecutive days. The regimen usually leads to peripheral pancytopenia, which often occurs one to seven days after the infusion of cells. In this period, the patient is subject to the possibility of infectious complications and care should be doubled depending on the patient's previous alterations, such as perianal disease, fistulas or the presence of an implanted colostomy. Cy and GAT should be administered carefully to avoid the inherent and habitual adverse effects of these medications.

There is now doubt as to whether it is a good idea to reduce the dose of CY or to introduce another chemotherapeutic or immunosuppressant agent instead of GAT in the conditioning regimen for HSCT.

The results of HSCT have an impact on the patients' immediate and long-term quality of life[19]. However, the clinical evaluation of patients submitted to HSCT is mandatory, and the understanding of the signs indicating the patients will benefited from HSCT in the long term is very important.

There are also no specific reports of patients who relapsed after HSCT or their evolution after the reintroduction of biological agents or other treatments. There are vague citations reporting that patients previously refractory to certain biological agents prior to HSCT cease to be refractory after HSCT. Furthermore, doubts exist regarding the selection of cases, which, as already mentioned, are restricted to severe cases without other therapeutic options. It is not clear whether an early indication of HSCT would be beneficial to newly diagnosed patients before they become dependent on corticosteroids and develop severe perianal disease. Thus, the prognostic factors related to HSCT have not yet been determined.

Another relevant aspect is the need for studies to determine the minimum immunological screening necessary prior to HSCT. It is essential to evaluate the immunological reconstitution of patients submitted to HSCT and then to determine possible markers and predictive factors of relapse after the procedure.

Another type of experimental cell therapy that has been advocated is using mesenchymal stromal stem cells (MSCs) systemically or directly administered to perianal lesions[13]. A systematic review and meta-analysis concluded that, in spite of the heterogeneity of the selected studies, the administration of MSCs provides benefits to patients with evident improvement of the lesions and even more importantly, the absence of adverse effects[20].

**CONCLUSION**

Thus, the current results 25 years after of the first reported use of HSCT in CD allow us to conclude that cellular therapy has a place in the treatment of CD, a heterogeneous disease with multiple facets. However, systematization with stratification of cases is necessary in order to determine the proper place and time for its indication.

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