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

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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 was initially used to treat this disease in patients who also suffered from lymphoma and leukemia and were considered to be good candidates for autologous and allogeneic transplantation. After transplantation, an improvement was also observed in their CD. In 2003, the procedure began to be used to treat the disease itself, and several case series and randomized studies have been published since then; this approach currently comprises a new option in the treatment of CD. However, considerable doubt along with significant gaps in our knowledge continue to exist in relation to cell therapy for CD. Cell therapy is currently restricted to the autologous modality of hematopoietic stem cell transplantation and, experimentally, to mesenchymal stromal cells to directly treat lesions of the anal mucosa. This article presents the supporting claims for transplantation as well as aspects related to the mobilization regime, conditioning and perspectives of cell therapy.

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

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INTRODUCTION

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

Treatment aims to stabilize the disease, reduce symptoms and heal the patient’s intestinal lesions. Anti-inflammatory drugs, immunosuppressive agents, corticosteroids and biological agents are prescribed alone or in combination. Drugs are usually administered in a step-wise sequence, called “Step Down”. Nevertheless, controversies and doubts remain regarding early indications of biological agents associated with immunosuppressants in cases considered to be more serious (“Top Down” treatment plan).

Surgical treatment is common in CD cases and depends on the extent 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.

STEM CELL THERAPY

Cell therapy emerged as a form of CD treatment due to the chronicity of the disease, lack of therapeutic options in refractory patients, and the description of disease improvements in cases with concomitant leukemia or lymphoma that were submitted for hematopoietic stem cell transplantation (HSCT). This was the first modality of cell therapy exclusively used for the treatment of CD. It was initially described in sporadic cases, yet a number of long-term and randomized studies of autologous HSCT have since placed the procedure on the map as an appropriate disease treatment for similar autoimmune diseases.

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

Despite the existence of established standard treatments, according to the European Bone Marrow Transplant Society, 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 recommended only after careful consideration of the risks and benefits to patients. Allogeneic HSCT is generally not recommended for CD because of the inherent toxicity risks of the procedure as well as the risk of graft-vs-host disease.

Thus, the criteria for the indication of HSCT for CD always includes: (1) patients refractory to immunosuppressive and biological agents; (2) the persistence of disease activity proven by endoscopy, colonoscopy or magnetic resonance enterography; and (3) extensive disease for which an imminent surgical procedure exposes the patient to the risk of short bowel syndrome or refractory colonic disease. A fourth criterion is the presence of a persistent perianal lesion where coloproctectomy with a definitive stoma implant is not accepted by the patient.

Even so, doubts persist in the medical and academic communities regarding HSCT for the treatment of autoimmune diseases like 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 the transplant itself (when hematopoietic progenitor cells are infused). In the past, the morbidity rate was much higher in relation to toxicity. Today, although death as a result is practically nonexistent, it still occurs due to complications or infections caused by resistant germs, which often exist in immunosuppressed patients within a hospital environment.

Thus, the selection of cases for elective HSCT should be rigorous, and the patients who are evaluated must be monitored and followed-up meticulously throughout the procedure. Patient selection should rule out comorbidities such as cardiac and pulmonary diseases, as well as other preexisting anomalies, such as clinical situations that add risk to the procedure. In short, the procedure should be carried out under the care of a multidisciplinary team and within an institution that meets national and international legal criteria with a
history of good medical practices\(^{12}\).

The standard mobilization regimen in CD patients is cyclophosphamide (Cy), which is associated with granulocyte colony stimulating factor (G-CSF). Until recently, there was contention over whether the administered dose of Cy should be 4 g/m\(^2\) or 2 g/m\(^2\). High doses of Cy were shown to correlate with an increased risk of cardiac toxicity, in addition to risks of bladder toxicity. In addition, no benefit is gained from the use of high doses, in terms of obtaining a higher number of cells for HSCT either in CD or other autoimmune diseases\(^{15}\). CD patients are often super-mobilizers and rapidly recover with low toxicity after HSCT. These conditions improve the quality of life soon after the procedure. In relation to Cy, there are already proposals to reduce the mobilization regime dose to 1 g/m\(^2\).

Another question concerns the manipulation or selection of cells for HSCT. Several reports used the selection or enrichment of CD34\(^{+}\) cells to reduce the volume and increase the efficacy of the product to be infused. From a study with four patients where manipulation was not used, due to the technical difficulty of selecting and enriching 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 5\(^{th}\) day after Cy administration. It is not clear which day is optimal for starting administration of the cytokine, nor are there any reports of its use alone in the mobilization of CD patients. This has likely 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 claiming 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. This regimen usually leads to peripheral pancytopenia, which often occurs one to seven days after cell infusion. In this period, the patient is subject to the possibility of infectious complications, so 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 carefully administered 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 chemotherapy or immunosuppressant agent instead of GAT in the conditioning regimen for HSCT.

The results of HSCT have an impact on the patient's immediate and long-term quality of life\(^{19}\). However, the clinical evaluation of patients submitted to HSCT is mandatory, and understanding the signs that indicate that the patient will benefit long-term from HSCT is very important.

There are also no specific reports of patients who relapse after HSCT, or their evolution after the reintroduction of biological agents or other treatments. There are vague citations reporting that patients who were 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 first 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 the administration of mesenchymal stromal stem cells systemically, directly, or to perianal lesions\(^{13}\). A systematic review and meta-analysis concluded that, in spite of the heterogeneity of the selected studies, the administration of mesenchymal stromal stem cells provides benefits to patients by improving lesions without causing adverse effects\(^{20}\).

CONCLUSION

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

REFERENCES

1. Baumgart DC, Sandborn WJ. Crohn’s disease. Lancet 2012; 380: 1590-1605 [PMID: 22914295 DOI: 10.1016/S0140-6736(12)6026-9]
2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JYJ, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018; 390: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]
3. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. Gastroenterology 2017; 152: 313-321.e2 [PMID: 27793607 DOI: 10.1053/j.gastro.2016.10.020]
4. Verstockt R, Smith KG, Lee JC. Genome-wide association studies in Crohn’s disease: Past, present and future. Clin Transl Immunology 2018; 7: e1001 [PMID: 29484179 DOI: 10.1002/cti2.1001]
5. Baumgart BC, Daniel C. The natural history of inflammatory bowel disease. In Crohn’s Disease and Ulcerative Colitis. New York, NY: Springer US, 2012 [DOI: 10.1007/978-1-4614-0998-4]
6. Drakos PE, Nagler A, Or R. Case of Crohn’s disease in bone marrow transplantation. Am J Hematol 1993; 43: 157-158 [PMID: 8342550 DOI: 10.1002/ajh.2830430223]
7. Quevedo FJL, López PL. Vacunas en Pediatría. 3\(^{rd}\) ed. Madrid: Editorial Medica Panamericana, 2008: 306
Autologous bone marrow transplantation for non-Hodgkin’s lymphoma resulting in long-term remission of coincidental Crohn’s disease. Br J Haematol 1998; 103: 651-652 [PMID: 9595867 DOi: 10.1046/j.1365-2141.1998.01059.x]

Oyama Y, Craig RM, Traynor AE, Quigley K, Statkute L, Halverson A, Brush M, Verda L, Kowalska B, Kronsjar N, Kletzel M, Whittington PF, Burt RK. Autologous hematopoietic stem cell transplantation in patients with refractory Crohn’s disease. Gastroenterology 2005; 128: 552-563 [PMID: 15765390 DOi: 10.1053/j.gastro.2004.11.051]

Burt RK, Craig RM, Milantei F, Quigley K, Goeziakz P, Bucha J, Testori A, Halverson A, Verda L, de Villiers WJ, Jovanovic B, Oyama Y. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. Blood 2010; 116: 6123-6132 [PMID: 20837778 DOI: 10.1182/blood-2010-06-292391]

Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, Rogler G, Rovira M, Satsangi J, Danese S, Russell N, Gribben J, Johnson P, Larghero J, Thibielemont C, Aridzzone S, Dierickx D, Itatie A, Littlewood T, Onida F, Schanz U, Veermeire S, Colombel JF, Jouet JP, Clark E, Saccardi R, Tyndall A, Travis S, Farge D. Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. JAMA 2015; 314: 2524-2534 [PMID: 26670970 DOI: 10.1001/jama.2015.16700]

Sureda A, Bader P, Cesaro S, Deger P, Duarte RF, Dufour C, Falkenburg JH, Farge-Bancel D, Gennery A, Kröger N, Lanza F, Marsh JC, Nagler A, Peters C, Velardi A, Melnyk M, Madrigal A. Indications for allo- and auto-SCT for haemato logical diseases, solid tumours and immune disorders: current practice in Europe, 2015. Bone Marrow Transplant 2015; 50: 1037-1056 [PMID: 25798672 DOI: 10.1038/bmt.2015.6]

Snowden JA, Panèis J, Alexander T, Allez M, Ardizzone S, Dierickx D, Finke J, Hassellatt P, Hawkey C, Kasmi M, Lindsay JO, Onida F, Salas A, Saccardi R, Veermeire S, Rovira M, Ricard E, European Crohn’s and Colitis Organisation (ECCO); European Society for Blood and Marrow Transplantation (EBMT); Autoimmune Diseases Working Party (ADWP); Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and EBMT (JACIE). Autologous Haematopoietic Stem Cell Transplantation (AHSC) in Severe Crohn’s Disease: A Review on Behalf of ECCO and EBMT. J Crohns Colitis 2018; 12: 476-488 [PMID: 29325112 DOI: 10.1093/ecco-jcc/jjx184]

Daikeler T, Tichelli A, Passweg J. Complications of autologous hematopoietic stem cell transplantation for patients with autoimmune diseases. Pediatr Res 2012; 71: 439-444 [PMID: 22430379 DOI: 10.1088/pr.2011.57]

Blank N, Lisenko K, Pavel P, Bruckner T, Ho AD, Wuchter P. Low-dose cyclophosphamide effectively mobilizes peripheral blood stem cells in patients with autoimmune disease. Eur J Haematol 2016; 97: 78-82 [PMID: 26381040 DOI: 10.1111/ejh.12686]

Cassinotti A, Annaloro C, Ardizzone S, Onida F, Della Volpe A, Clerici M, Usardi P, Greco S, Maconi G, Porro GB, Deliilliers GL. Autologous hematopoietic stem cell transplantation without CD34+ cell selection in refractory Crohn’s disease. Gut 2008; 57: 211-217 [PMID: 17895375 DOI: 10.1136/gut.2007.128694]

Openshaw H, Stuve O, Antel JP, Nash R, Lund BT, Weiner LP, Kashyap A, McSweeney P, Forman S. Multiple sclerosis flares associated with recombiant granulocyte colony-stimulating factor. Neurology 2000; 54: 2147-2150 [PMID: 10851379 DOI: 10.1212/wnl.54.11.2147]

Mannon PJ, Leon F, Fuss IJ, Walter BA, Begnami M, Quezado M, Yang Z, Yi C, Groden C, Friend J, Hornung RL, Brown M, Gurprasad S, Kelsall B, Strober W. Successful granulocyte-colony stimulating factor treatment of Crohn’s disease is associated with the appearance of circulating interleukin-10-producing T cells and increased lamina propria plasmacytoid dendritic cells. Clin Exp Immunol 2009; 155: 447-456 [PMID: 19094118 DOI: 10.1111/j.1365-2249.2008.03799.x]

Rui MA, Kaiser RL Jr, de Quadros LG, Piron-Ruiz L, Peña-Arciniegas T, Faria MAG, Siqueira RC, Pirozzi FF, Kaiser FSL, Burt RK. Low toxicity and favorable clinical and quality of life impact after non-myeloablative autologous hematopoietic stem cell transplantation in Crohn’s disease. BMC Res Notes 2017; 10: 495 [PMID: 28985769 DOI: 10.1186/s13104-017-2824-1]

Lightner AL, Wang Z, Zubair AC, Dozois EJ. A Systematic Review and Meta-analysis of Mesenchymal Stem Cell Injections for the Treatment of Perianal Crohn’s Disease: Progress Made and Future Directions. Dis Colon Rectum 2018; 61: 629-640 [PMID: 29578916 DOI: 10.1097/DCR.0000000000001093]

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