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REVIEW

Hematopoietic stem cell transplantation for non-malignant gastrointestinal diseases

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Abstract

Both, autologous and allogeneic hematopoietic stem cell transplantation (HSCT) can be used to cure or ameliorate a variety of malignant and non-malignant diseases. The rationale behind this strategy is based on the concept of immunoablation using high-dose chemotherapy, with subsequent regeneration of naive T-lymphocytes derived from reinfused hematopoietic progenitor cells. In addition, the use of HSCT allows for the administration of high-dose chemotherapy (whether or not combined with immunomodulating agents such as antithymocyte globulin) resulting in a prompt remission in therapy-refractory patients. This review gives an update of the major areas of successful uses of HSCT in non-malignant gastrointestinal disorders. A Medline search has been conducted and all relevant published data were analyzed. HSCT has been proved successful in treating refractory Crohn's disease (CD). Patients with refractory celiac disease type Ⅱ and a high risk of developing enteropathy associated T-cell lymphoma have shown promising improvement. Data concerning HSCT and mesenchymal SCT in end-stage chronic liver diseases are encouraging. In refractory autoimmune gastrointestinal diseases high-dose chemotherapy followed by HSCT seems feasible and safe and might result in long-term improvement of disease activity. Mesenchymal SCT for a selected group of CD is promising and may represent a significant therapeutic alternative in treating fistulas in CD.

Key words: Hematopoietic stem cell transplantation; Mesenchymal stem cells; Non-malignant gastrointestinal diseases; Celiac disease; Refractory celiac disease; Lymphoma; Crohn's; Ulcerative colitis; Cirrhosis

Core tip: Hematopoietic stem cell transplantation (HSCT) can be used to treat malignant and non-malignant diseases. This therapeutic modality is based on using immunoablation followed by reinfusion of hematopoietic progenitor cells to regenerate naive T-lymphocytes. HSCT and mesenchymal SCT have been proved successful in treating refractory inflammatory conditions such as Crohn's disease and refractory celiac disease type Ⅱ. The ultimate target of aggressively treating this type of celiac disease is to prevent development of lymphoma. Data in end-stage liver diseases are also encouraging.

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INTRODUCTION

In cancer patients, myeloablative doses of radiation or high dose chemotherapy (HDC) or both have been used followed by infusion of autologous hematopoietic cells to restore bone marrow function[1-3].

Recently, HDC followed by hematopoietic stem cell transplantation (HSCT) has been applied increasingly thanks to the availability of supportive measures, such as availability of antibiotics to prevent or treat infections during marrow aplasia, improvement in transfusion support and the use of hematopoietic growth factors to "mobilize" HSCs to shorten the recovery time of marrow function[1]. In addition, an important progress has been achieved in manipulating, mobilizing bone marrow stem cells and recruitment of hematopoietic stem cells (HSCs) from the peripheral blood[3,4].

The peripheral blood contains HSCs[4-6]; these cells can be easily harvested and then utilized to hasten hematological recovery after ablative therapy[7]. Specific chemotherapeutic regimens, granulocyte colony stimulating factor and/or new agents such as Plerixafor effectively increase the number of HSCs in the peripheral blood providing adequate autologous stem cell harvest[8,9].

In the last two decades, HSCT is gaining wider acceptance in the management of difficult to treat autoimmune diseases[10-16].

HSCT has been conducted in treating refractory Crohn' s disease (CD). More recently, mesenchymal SCT (MSCT) has been explored in the management of CD complicated by fistulas. Encouraging results have been reported. In a group of refractory celiac disease, we have reported impressive results using autologous SCT (*auto*-SCT).

The efficacy and safety of HSCT and MSCT are being evaluated in patients with end-stage chronic liver diseases, both viral and autoimmune-induced, and the preliminary results seem to be promising. So far, limited data have been published about *auto*-SCT in autoimmune liver diseases.

We tried here to provide an overview of the experience gained thus far in treating non-malignant gastrointestinal diseases.

BACKGROUND

HSCs are capable of regenerating immune cells; this characteristic provides the theoretical possibility of resetting the immune system without autoimmunity. Meanwhile, MSCs have immunosuppressive effect, which might be beneficial in different inflammatory disorders[17,18].

The possible mechanism for using stem cell therapy for inflammatory disorders is to induce a state of immunoablation using HDC followed by reinfusing hematopoietic progenitor cells to achieve regeneration of naive T-lymphocytes derived. This procedure could reset the immune system after first eliminating the patient's own system by preparative chemo[-immuno] therapy[1].

Animal studies and the use of HSCT in experimental forms of autoimmune diseases have contributed significantly to the knowledge and subsequently the application of auto-HSCT in autoimmune diseases[19-21].

Clinical observations in patients with autoimmune diseases such as severe systemic sclerosis, who received HSCT to treat concomitant hematological diseases, paralleled the experience obtained from animal studies[22,23].

The limited therapeutic options for severe, uncontrolled autoimmune diseases made it necessary to explore HSCT as a treatment modality. To be acceptable for non-oncological indications this modality should have an acceptable mortality and morbidity rate. *Auto*-HSCT has gained priority over *allo*-HSCT because it is associated with low morbidity and mortality rates both in oncology[24,25] and in immune disorders (7%)[10].

For non-malignant conditions *auto*-HSCT may be applied using either myeloablative or non-myeloablative regimens[13]. Myeloablation results in an irreversible aplasia of the bone marrow; therefore HSCs should be provided to restore the marrow function. On the other hand, non-myeloablation is designed for autoimmune diseases; following such a regimen, hematopoietic recovery will occur without infusion of HSCs[13].

MSCs are distinct lineage of stem cells, having no unique phenotypic marker, representing 1 in 10000 nucleated cells in the bone marrow[26]. Different tissues can provide the source of these cells, *e.g.*, bone marrow, skeletal muscle, adipose tissue, synovial membranes, umbilical cord blood and placenta[27].

MSCs give rise to many cell lineages, thus promoting regeneration of damaged tissue *in vivo*[28]. Also these cells exert important immunomodulatory functions[29], can regenerate clonally[30] and exhibit anti-proliferative and anti-inflammatory properties, making them candidates for treatment of immune-mediated inflammatory diseases[31].

APPLICATION IN INFLAMMATORY BOWEL DISEASE

CD is a relapsing-remitting disorder with enhanced T-helper cell reaction[32-34]. HSCT is considered as a valuable option in the treatment of CD because it has been shown to be effective in treating autoimmune disorders sharing a similar pathogenic background.

The mechanism of positive effect of HSCT in not entirely clear; however *allo*-HSCT may change the genetic constitution that predisposes to CD. On the other hand, *auto*-HSCT helps to eliminate committed lymphocytes and also facilitates relatively safe use of immunosuppression[35].

The first evidence for using stem cell therapy in refractory CD came from reports showing that CD improves after stem cell therapy for other concomitant disorders[36].

In 1993 Drakos *et al*[37] reported an improvement of a patient with CD who received *allo*-HSCT for a malignant lymphoma. Five years later, *allo*-HSCT was performed in six non-Hodgkin lymphoma (NHL) patients who also had concomitant CD. Three patients remained in remission after withdrawal of immunosuppressives[38].

Table 1 Indirect evidence for efficacy of hematopoietic stem cell transplantation in inflammatory bowel disease

Ref.	SCT	Original indication	No./type IBD	Conditioning	Results/remarks
Drakos *et al*[37]	Allo-SCT	NHL	1/fistulizing CD	BCNU/Etoposide, Cy, ara-C and Melphalan	Remission/6 mo follow up
Kashyap *et al*[40]	Auto-SCT	NHL	1/Perianal CD	Cy,VP16+TBI	Remission 7 yr/Crohn's at age 13 yr ASCT at 20 yr
Lopez-Cubero *et al*[38]	Allo-SCT	Leukemia	5/CD	Cy/TBI	3 pts has lasting remission
Söderholm *et al*[41]	Auto-SCT	AML	1/Fistulizing CD	Cy/TBI	Remission 5 yr
Ditschkowski *et al*[39]	Auto-SCT	AML/CML/MDS	11/7 CD +4 UC	Various	Remission in 10/Follow up 34 mo
Anumakonda *et al*[42]	Auto-SCT	NHL	1/CD	CHOP	Remission 8 yr/Relapse after 8 yr

CD: Crohn's disease; NHL: Non-Hodgkin's disease; UC: Ulcerative colitis; Cy: Cyclophosphamide; AML: Acute myeloid leukemia; MDS: Myelodysplastic syndrome; CML: Chronic myeloid leukemia; TBI: Total body irradiation; CHOP: Cyclophosphamide Adriamycin Vincristine Prednisone.

In a report by Ditschkowski *et al*[39] Eleven inflammatory bowel disease (IBD) patients (seven CD and four ulcerative colitis) underwent *allo*-HSCT in connection with various hematology disorders. Ten transplant recipients stayed in remission, follow up 34 mo.

Numerous case reports and case series have been published dealing with the clinical response of CD who received *auto*-SCT to treat concomitant conditions[40-43]. One such example is a young patient diagnosed with CD and needed intensive treatment with anti-inflammatory and immunosuppressive agents[40]. He remained in remission after *auto*-HSCT for NHL.

Table 1 summarizes the literature on indirect evidence for effectiveness of HSCT in IBD. These data indicate that HSCT might benefit CD but this benefit is not universal.

In 2003, Burt *et al*[44] and Craig *et al*[45] provided the first direct evidence for the efficacy of HSCT for CD. In 2 patients diarrhea resolved following transplantation. Crohn's disease activity index (CDAI) is normalized. Simultaneously, another group reported a complete remission in one patient using the same conditioning regimen[46].

Another report by Oyama *et al*[47] has provided the results of using HSCT refractory CD. A total of 12 patients have been treated, eleven of them remained in remission [follow-up of 18.5 mo (range, 7-37 mo)].

In 2010 Burt *et al*[48] have presented their experience in using *auto*-HSCT for IBD. Twenty-four patients with CD were treated. 91% stayed in remission for 1 year post transplantation. A similar outcome was reported by another group who treated 10 CD patients (remission rates of 80% after 1 year)[49].

Hasselblatt *et al*[50] have reported the outcome of 12 patients with refractory CD treated with *auto*-HSCT. Five patients achieved a clinical and endoscopic remission within 6 mo after *auto*-HSCT. However, relapses occurred in 7 patients, but disease activity was mild and could be controlled by low-dose corticosteroids and immunosuppressive therapy.

Allo-HSCT for CD has also been performed; in 2009 a report on a successful use of *allo*-HSCT in treating a 9-year-old child was published[51]. The investigators have hypothesized that a nonsense mutation in the *IL10RB* gene is probably the genetic cause of IBD in the affected patient and given the severity of the disease, they considered *allo*-HSCT as treatment. The patient underwent conditioning with the use of alemtuzumab (1 mg/kg), fludarabine (180 mg/m^2), treosulfan (42 mg/m^2), and thiotepa (10 mg/kg). Anal fistulas resolved and the patient has remained in remission more than a year after HSCT.

MSCs have been tested for fistulizing and also luminal CD[52]. In fistulizing disease, the differentiation potential of these cells is thought to be necessary to achieve closure of fistulas, while their immunosuppressive effect is the rationale for their use in luminal disease.

Rectovaginal fistulas are difficult to treat. García-Olmo *et al*[52] used lipoaspirate to provide stem cells in a patient with rectovaginal fistula. Subsequently, the patient had no complains related to the fistula. The same group has tested the usefulness and safety of MSCT in treating fistulas[53]. Nine fistulas were treated. Six fistulas were considered healed (75%), (follow-up 22 mo; range 12-30).

Forbes *et al*[54] published the result of a phase II study using *allo*-MSCs for refractory luminal CD. An open-label, multicenter study included 16 patients (21-55 years old; 6 men) with infliximab-or adalimumab-refractory, endoscopically confirmed, active luminal CD (CDAI > 250). Subjects were given intravenous infusions of allogeneic MSCs (2×10^6 cells/kg body weight) weekly for 4 wk. The primary end point was clinical response (decrease in CDAI > 100 points) 42 d after the first MSC administration; secondary end points were clinical remission (CDAI, < 150), endoscopic improvement [a CD endoscopic index of severity (CDEIS) value, < 3 or a decrease by > 5], quality of life, level of C-reactive protein, and safety. Among the 15 patients who completed the study, the mean CDAI score was reduced from 370 (median, 327; range, 256-603) to 203 (median, 129) at day 42 ($P < 0.0001$). Twelve patients had a clinical response (80%; 95%CI: 72%-88%; mean reduction in CDAI, 211; range 102-367), 8 had clinical remission (53%; range, 43%-64%; mean CDAI at day 42, 94; range, 44-130). Seven patients had endoscopic improvement (47%), for whom the mean CDEIS scores decreased from 21.5 (range, 3.3-33) to 11.0 (range, 0.3-18.5).

Table 2 summarizes the literatures on direct evidence for effectiveness of HSCT and MSCT in IBD. We may conclude that *auto*-HSCT is feasible, safe and also effective in achieving and maintaining remission in CD. Furthermore, MSCT may represent a significant therapeutic

Table 2 Direct evidence for efficacy of hematopoietic stem cell transplantation and mesenchymal stem cell transplantation in inflammatory bowel disease

Ref.	SCT/MSCT	No. treated/type IBD	Conditioning	Results
Burt *et al*[44]	Auto-HSCT	2/Crohn's, fistulas, CDAI > 250	Cy + ATG	CDAI,CRP, albumin normalized; remission > 1 yr
Kreisel *et al*[46]	Auto-HSCT	1/ileocolic Crohn's	Cy + ATG	9 mo complete remission
García-Olmo *et al*[52]	Auto-HSCT Adipose tissue	1/recurrent rectovaginal fistulas	None necessary	3 mo asymptomatic
García-Olmo *et al*[53]	MSCT	5/fistulas	None necessary	Follow up 22 mo; 75% healing
Oyama *et al*[47]	Auto-HSCT	12/fistula 6, stenosis 3, perianal 4; most have surgery	Cy + ATG	11 sustained remission (CDAI < 150) after median 18.5 mo; 1 relapse > 15 mo
Cassinotti *et al*[49]	Auto-HSCT	4/stenosis, fistulas, bleeding	Cy + ATG	All clinical remission at 3 m, 1 relapse after 4 mo; Sustained remission in 3 after 16.5 m o
Glocker *et al*[51]	Allo-HSCT	1/perianal fistula	Alemtuzumab, fludarabine, treosulfan, thiotepa	Remission 2 yr; 9-year-old child
Burt *et al*[48]	Auto-HSCT	24/Crohn's	Cy + ATG	91% remission 1 yr, 57% for 3 yr, 19% for 5 yr
Cassinotti *et al*[49]	Auto-HSCT	10/Crohn's	Cy + ATG	80% remission > 1 yr, 40% > 3 yr and 30% > 5 yr
Hasselblatt *et al*[50]	Auto-HSCT	12/Crohn's	Cy + G-CSF	5 complete remission within 6 m, relapses occurred in 7. Mean follow-up 3.1 yr (range 0.5-10.3)
Forbes *et al*[54]	MSCT, weekly for 4 wk	16/Crohn's disease (CDAI > 250)	None necessary	CDAI declined from median 327 to 129 (day 42). Clinical response 12 pts; Clinical remission 8 pts. Endoscopic improvement in 7 pts

Cy: Cyclophosphamide; G-CSF: Granulocyte colony stimulating factor; HSCT: Hematopoietic stem cell transplantation; MSCT: Mesenchymal stem cell transplantation.

alternative in treating CD. Still larger randomized or observational multicenter trials are required to confirm the efficacy of this therapy.

Concerning ulcerative colitis, improvement of disease activity after stem cell transplantation for other indications has been reported. Four patients remained in remission after receiving *auto*-HSCT for leukemia[39]. Two patients with ulcerative colitis remained in remission after they underwent an *auto*-HSCT in connection with leukemia[55].

HSCT IN REFRACTORY CELIAC DISEASE

In celiac disease, gluten-derived peptides bind to HLA-DQ2 and HLA-DQ8 molecules on antigen-presenting cells[56]. These molecules then in turn present these peptides and induce a CD4+ T cell response which results in an inflammatory response[57-59]. In a small minority (0.5%-1%) of adult celiac patients symptoms persist despite strict adherence to a gluten free diet[60]. After excluding other causes of villous atrophy, these patients are diagnosed with refractory celiac disease (RCD).

These refractory patients are further subdivided into 2 types depending on immunophenotyping by flow cytometry[61-65] of the intraepithelial lymphocytes (IEL): patients with normal intraepithelial lymphocytes are classified as (RCD- Ⅰ), while those those with more than 20% aberrant intraepithelial lymphocytes are classified as (RCD Ⅱ)[59]. Aberrant IEL are characterized by T-cell specific CD3 in their cytoplasm, yet lack surface expression of CD3 and CD8. RCD-Ⅱ is usually resistant to any known therapy[66-71]. This entity frequently transforms into an aggressive enteropathy-type-associated T cell lymphoma (EATL)[71-73].

The safety and efficacy of *auto*-SCT in RCD type Ⅱ has been tested[74,75]. Between 2004 and 2010, 18 RCD-Ⅱ patients were evaluated for auto-HSCT as a consequence of unresponsiveness or partial response to cladribine therapy[74]. Thirteen patients underwent conditioning and transplantation. One patient died due to transplantation-related complications. In the majority of patients, clinical improvement was observed after *auto*-HSCT. Complete histological remission was achieved in 5 patients. One patient developed EATL despite auto-HSCT after a follow-up of four years. Recent, yet unpublished, data show excellent overall long-term survival of 87 mo.

Auto-HSCT seems safe and might result in a long-term clinical remission with a better quality of life in RCD-Ⅱ patients. Moreover, this treatment strategy seems to prevent or delay the development of EATL. These observations argue for an aggressive therapeutic approach for those RCD-Ⅱ patients eligible for *auto*-HSCT.

HSCT IN CHRONIC LIVER DISEASES

Liver transplantation is the standard treatment in advanced liver cirrhosis, however it has significant shortcomings, *e.g.*, a long waiting list, expensive and numerous complications[76-78]. In addition, the vastly increasing prevalence of end-stage liver disease without a parallel increase in donor livers has precipitated a search for alternative therapies.

Circulating stem cells can differentiate into mature hepatocytes or cholangiocytes *in vivo*[79]. MSCs differentiate into functional hepatocyte-like cells in animal experiments[79]. MSCs can protect against experimental liver fibrosis in rats[80] and also result in regression of fibrosis

in mice[81]. Therefore, stem cell therapy might be useful in treating chronic liver disease such as liver cirrhosis.

Patients with liver cirrhosis who had been treated with MSCs had a good clinical outcome with improvement in de Model End Stage Liver Disease score and quality of life[82-84].

The largest series thus far reported comes from Egypt[85] where *auto*-HSCT was conducted in 48 patients, 36 with chronic end-stage hepatitis C-induced liver disease and 12 with end-stage autoimmune liver disease. Treatment was generally well tolerated; 10 patients (20.8%) died during 12 mo of follow-up and two had developed portal hypertension. There was clinical and biochemical improvement. Patients had a statistically significant decrease in ascites and marked improvement in albumin, bilirubin, clotting status, and aminotransferase levels. However, the authors raise concern about the development of portal hypertension after HSCT. They further postulated that the incidence of this serious complication can be minimized by employing hepatic artery infusion as the sole approach to transplantation.

SAFETY ISSUES

The age limit of stem cell recipients has changed over time due to the availability of good supportive care. For RCD-Ⅱ, we use an age limit of seventy years[74,75].

Regimen-related toxicity can be serious; this is particularly true for recipients of *allo*-HSCT. Opportunistic infections and pancytopenia occur much less frequently after *auto*-HSCT than *allo*-HSCT recipients.

Intensive therapies including HSCT aim to reintegrate patients expeditiously in their work and social activities. Usually a good quality of life can be gained within few months after HSCT[86].

For MSCs, clinical risk data largely stem from studies in steroid-refractory graft versus host disease. Other than the possibility of an increased short-term risk of pneumonia in these highly immunocompromised patients, MSCs have been considered safe[87]. There are no reports of increased risk from other infections or tumors, despite concerns based on theoretical mechanistic grounds[88]. No significant adverse effects have been reported from CD studies of locally administered *allo*-MSCs[89], intravenous *auto*-MSCs[90], or intravenous *allo*-MSCs[91].

FUTURE PERSPECTIVES

Rigorous safety evaluations of new therapies are essential. Future prospective observational multicenter studies with standardized inclusion criteria, conditioning regimens, and if possible supportive care, are still necessary to substantiate the already published data. Still long term follow up data concerning response are lacking. Criteria for the selection and the timing of providing stem cell transplantation in patients with chronic inflammatory diseases and premalignant conditions are strongly needed. Standardization of immunosuppression, optimizing conditioning regimens and also integration of immunotherapy in treatment protocols are areas for future research. There is still much to learn and understand about MSC function, immunopathogenic mechanisms in treating different disease conditions and standardization of preparation methods.

In gastroenterology, it seems that HSCT and MSCT gain steadily, and deservedly, more grounds in the arsenal of treatment of inflammatory disease and premalignant conditions, like IBD, refractory celiac disease and liver cirrhosis.

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