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EDITORIAL

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

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, however many gaps and doubts remain regarding procedures for and indications of cell therapy, which still require improvement. 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]. Althought 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[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 associated with other autoimmune diseases[1,2]. 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[4].

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)[1].

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[1,5].

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)[6-8]. 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 has since placed the procedure on the map as an appropriate disease treatment for similar autoimmune diseases[9-11].

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[12].

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[13].

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[14].

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 5th 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 chemotherapeutic 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.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy and safety of autologous stem cell transplantation for decompensated liver cirrhosis: A retrospective cohort study

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Abstract

AIM

To evaluate the long-term efficacy and safety of autologous stem cell transplantation (SCT) for decompensated liver cirrhosis.

METHODS

Consecutive patients with decompensated liver cirrhosis were included and assigned into the SCT group and non-transplantation (non-SCT) group according to whether they received SCT treatment. Patients were

followed up for ten years. The long-term survival rate and incidence of hepatocellular carcinoma (HCC) were compared between groups.

RESULTS

A total of 159 patients were enrolled, including 27 cases in the SCT group and 132 cases in the non-SCT group. The baseline characteristics were significantly different between the two groups. Propensity score matching (PSM) was used to match SCT and non-SCT patients. After PSM, 92 subjects were enrolled in the final analysis, including 23 cases in the SCT group and 69 cases in the non-SCT group. The overall mortality was 73.9% and 55.1%, and the median survival period was 48 and 64 mo, respectively. However, no significant difference was found in the long-term survival rate between the two groups ($P > 0.05$). In addition, the incidence of HCC was higher in the SCT group than in the non-SCT group (47.8% *vs* 21.7%, $P < 0.05$). After adjusting for other covariates, SCT (OR = 3.065, 95%CI: 1.378-6.814) and age (OR = 1.061, 95%CI: 1.021-1.102) were independently correlated with the development of HCC in this decompensated liver cirrhosis cohort.

CONCLUSION

Autologous SCT may fail to improve the long-term efficacy and increase the incidence of HCC for decompensated liver cirrhosis. Close monitoring of HCC is strongly recommended in patients undergoing autologous SCT.

Key words: Decompensated liver cirrhosis; Stem cell transplantation; Hepatocellular carcinoma; Propensity score matching

Core tip: Stem cell therapy has shown short-term efficacy and safety for treatment of liver cirrhosis. However, the tumorigenicity of stem cells requires increased attention.

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INTRODUCTION

Liver cirrhosis is a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules[1]. Patients with decompensated liver cirrhosis usually have symptoms of portal hypertension and hepatic dysfunction, which greatly affects patients' quality of life and has a high mortality[2]. Currently, there is still a lack of effective treatments for decompensated liver cirrhosis, and symptomatic and supportive therapy and protection of residual hepatocytes remain the predominant strategy for the management of decompensated liver cirrhosis[3].

Orthotopic liver transplantation has been recognized as the best option for the treatment of decompensated liver cirrhosis, which improves both the quality of life and survival[1]. However, this treatment suffers from problems of huge shortage of donor livers, post-surgical complications, immune rejection, high medical expenditure and moral and ethical issues[4,5], which greatly limits its wide application in clinical practices. Development of regenerative treatment strategies for decompensated liver cirrhosis is therefore urgently needed[6,7].

Recently, stem cell-based therapy has become a novel strategy for the treatment of decompensated liver cirrhosis[8], and results from phase Ⅰ/Ⅱ clinical trials have shown generalized functional improvements and may be slightly superior to current conventional treatments[9]. It has been demonstrated that stem cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), may be induced to differentiate into hepatocytes under certain conditions, which may promote liver renewal, alleviate hepatic fibrosis and be involved in the repair and reconstruction of the damaged liver. In particular, bone marrow (BM)-MSCs have been prevalently utilized[10]. Results from clinical studies showed that the liver disease patients had alleviation of clinical symptoms following autologous stem cell therapy, suggesting that stem cell therapy has short-term efficacy and safety[11-15]. However, stem cells have multi-lineage differentiation capability[10,16], and stem cell tumorigenicity has been paid increasing attention to the identification of liver cancer stem cells[17-19]. In addition, a limited follow-up period and no controls were assigned in most of the previous clinical studies[11,13], and there is little knowledge on the long-term clinical efficacy and safety of stem cell transplantation (SCT) to date.

In this retrospective cohort study, we aimed to compare the survival rate and incidence of hepatocellular carcinoma (HCC) in decompensated liver cirrhosis patients with and without SCT, so as to evaluate the long-term efficacy and safety of SCT.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Fujian Medical University, Permission No. 2015[084]. All methods were performed in accordance with the Declaration of Helsinki regarding ethical standards for research involving human subjects.

Subjects

In this retrospective cohort study, patients with decompensated liver cirrhosis admitted to the First Affiliated Hospital of Fujian Medical University (Fuzhou, China) during the period from January 2008 through December 2010 were included. Decompensated liver cirrhosis was diagnosed by previous medical history, blood and imaging examinations or liver biopsy. Those who met the following criteria were excluded from the study: (1) subjects with HCC or cancers in other organs; (2) pregnancy; (3) subjects with severe heart, lung, renal or hematologic diseases; (4) subjects died within a month; (5) subjects with HIV infection, sepsis or other life-threatening infectious diseases; and (6) subjects without any follow-up after discharge from the hospital. All subjects were assigned into the SCT group and non-SCT group according to whether they have received SCT.

Laboratory examinations

Upon admission, all subjects received blood examinations for a prothrombin time (PT) test, a routine blood test, liver and kidney function tests and a blood glucose test, and for determining serum hepatitis B virus (HBV) markers, HBV DNA viral load and serum alpha fetoprotein (AFP) concentration. The liver function was quantified using the Child-Pugh classification and the model for end-stage liver disease (MELD) score. HCC was diagnosed according to the Expert Consensus on Standardization of the Management of HCC in China[20]. Abdominal B ultrasonography, CT or MRI scans were performed to exclude other disorders, including HCC.

SCT

Autologous bone marrow mesenchymal stem cell (BMSC) transplantation or peripheral HSC transplantation was performed according to the patients' willingness. All subjects signed the informed consent of SCT. For autologous BMSC transplantation, after skin sterilization and local anesthesia, marrow aspiration was performed in bilateral posterior-superior iliac crests. Approximately 100 mL of bone marrow (BM) was mixed evenly with BM storage buffer in a total volume of 180 mL and stored at 4 ℃ for subsequent experiments. For peripheral HSC transplantation, patients were given 300 μg (1.2 mL) recombinant human granulocyte colony stimulating factor injection for seven successive days to mobilize HSCs before transplantation, which has been demonstrated to be feasible and effective in previous studies[21,22]. HSCs were separated by a stem cell separator, and then 100 mL of HSCs were collected. The number of $CD34^+$ stem cells was counted using flow cytometry, and $CD34^+$ stem cells were obtained at a density of $(2.81 \pm 1.03) \times 10^6$ cells/mL.

Digital subtraction angiography-guided femoral artery puncture and catheterization was performed using the Seldinger technique, and hepatic angiography was conducted to identify the distribution of intrahepatic blood vessels. The catheter was inserted into the hepatic artery, and 100 mL of peripheral HSC (at a speed of 1.5 mL/min) or 180 mL of autologous BMSC (at 3 mL/min) were slowly injected with a microinfusion pump.

Follow-up

The survival and development of HCC was observed through outpatient follow-up visits. The follow up was performed during the period from the time of SCT to December 31, 2017 or death.

Statistical analysis

The patients' gender, age, cause and Child-Pugh classification were adjusted using propensity score matching (PSM)[23], and the number of cases and controls were matched at a ratio of 1:3 by means of the nearest neighborhood matching and caliper matching, with a caliper width set as 0.2. Non-normally distributed data were described as quartiles and compared using the rank-sum test. Normally distributed data were expressed as mean ± SD and compared using a Student's *t*-test. Differences of proportions were tested for statistical significance with a χ^2 test. Survival analysis was performed using the Kaplan-Meier method, and the survival rate and incidence of HCC were compared between groups with the log-rank test. The risk factors of HCC were identified using a Cox proportional hazards regression model. All data were analyzed by SPSS 18.0 software (SPSS Inc., Chicago, IL, United States), and a value of $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of baseline characteristics of overall cases between groups

A total of 218 patients with decompensated liver cirrhosis were admitted to the hospital during the period from January 2008 through December 2010, and 59 patients were excluded; finally, a total of 159 subjects were enrolled, including 27 patients undergoing SCT and 132 patients without transplantation (Figure 1). Of the 27 subjects undergoing SCT, there were 15 cases undergoing autologous bone-marrow SCT and 12 cases of peripheral hematopoietic SCT. There were significant differences in the prevalence of severe liver cirrhosis (Child-Pugh class C), PT, total bilirubin (TBIL) concentration, the prevalence of HBV infection and seropositive rate of HBsAg between the SCT group and the non-SCT group ($P < 0.05$) before PSM (Table 1). The overall mortality was 47.8% (76/159) in all study subjects, with 77.8% (21/27) mortality in the SCT group and 41.7% (55/132) in the non-SCT group ($P < 0.05$), and the overall incidence of HCC was 27.0% (43/159), with 40.7% (11/27) incidence in the SCT group and 24.2% (32/132) in the non-SCT group ($P < 0.05$).

Baseline characteristics of patients after PSM

Since the Child-Pugh classification, HBV infection, gender and age were reported to correlate with the pro-

Table 1 Comparison of the baseline demographic and clinical characteristics between the stem cell transplantation group and the non-transplantation group

Characteristic	Before propensity score matching			After propensity score matching		
	Stem cell transplantation group (n = 27)	Non-transplantation group (n = 132)	P-value	Stem cell transplantation group (n = 23)	Non-transplantation group (n = 69)	P-value
No. of male (%)	18 (66.7%)	100 (75.8%)	0.325	15 (65.2%)	45 (65.2%)	1
Age (yr)	53.7 ± 9.7	53.3 ± 10.8	0.84	53.0 ± 9.7	55.3 ± 9.8	0.351
History of smoking (%)	6 (22.2)	33 (25.0)	0.76	4 (17.4)	15 (21.7)	0.656
History of alcohol drinking, n (%)	8 (29.6)	33 (25.0)	0.616	6 (26.1)	20 (29)	0.789
Diabetes, n (%)	6 (22.2)	23 (17.4)	0.556	6 (26.1)	16 (23.2)	0.778
Family history of liver cancer, n (%)	3 (11.1)	10 (7.6)	0.541	3 (13)	3 (4.3)	0.144
Child-Pugh B to C ratio	4:23	67:65	0.001	4:19	17:52	0.473
MELD score	14.36 (9.33-18.69)	10.43 (7.22-15.91)	0.051	15.55 ± 7.66	14.21 ± 8.32	0.498
HBsAg positive, n (%)	20 (74.1)	127 (96.2)	0	20 (87)	66 (95.7)	0.144
PT (s)	21.5 (18.2-26.7)	18.2 (16.0-20.7)	0.003	22.0 (18.1-27.8)	19.3 (16.8-22.6)	0.143
TBIL (μmol/L)	88.7 (46.6-141.1)	38.4 (23.1-111.6)	0.012	73.2 (46.6-137.9)	46.4 (26.6-155.6)	0.21
ALB (g/L)	26.89 ± 4.36	28.16 ± 5.63	0.268	27.08 ± 4.59	26.27 ± 6.02	0.56
ALT (U/L)	45 (30-60)	54 (35-113)	0.055	47 (36-63)	48 (30-93)	0.701
PLT (× 10^9/L)	79.11 ± 40.39	92.66 ± 58.39	0.252	81.78 ± 41.33	90.49 ± 65.35	0.551
AFP (ng/mL)	7.62 (3.68-20.80)	6.90(2.73-33.87)	0.889	7.93 (3.9-29.37)	6.3 (2.47-23.88)	0.564
HBeAg titer (s/copies)	0.45 (0.34-11.26)	0.5 (0.34-24.68)	0.808	0.45 (0.34-11.26)	0.48 (0.34-22.13)	0.906
LogHBV DNA (IU/mL)	4.45 ± 1.21	4.47 ± 1.44	0.966	4.45 ± 1.21	4.65 ± 1.48	0.097
Cause, n (%)						
HBV infection	20 (74.1)	127 (96.2)	0	20 (87)	66 (95.7)	0.154
Alcohol drinking	4 (14.8)	1 (0.8)		1 (4.3)	0	
Others	3 (11.1)	4 (3)		2 (8.7)	3 (4.3)	

MELD: Model for end-stage liver disease; HBsAg: Hepatitis B surface antigen; PT: Prothrombin time; TBIL: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; PLT: Platelet; AFP: Alpha fetoprotein; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus.

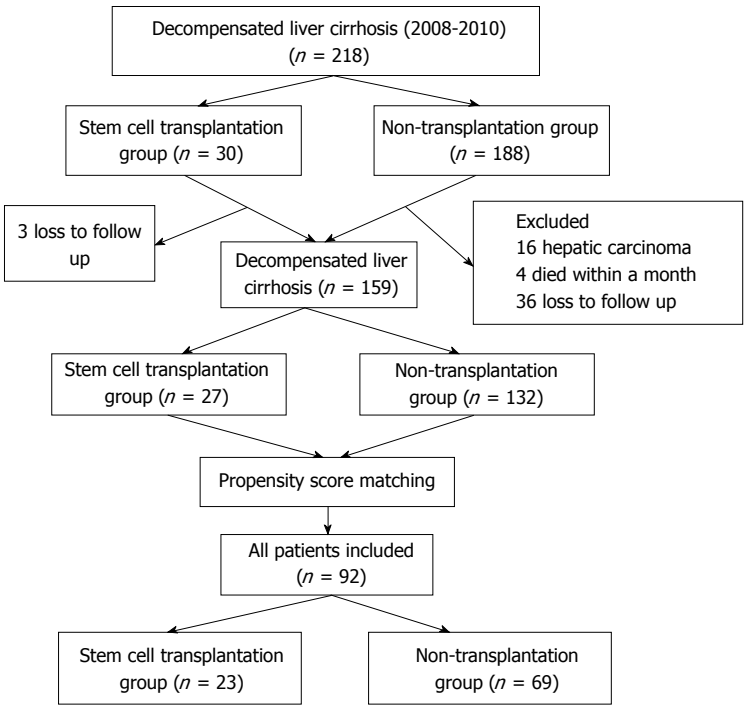

Figure 1 Flowchart of the study subject enrollment.

gnosis of liver cirrhosis[24,25], the subjects' gender, age, cause and Child-Pugh classification were adjusted using PSM at a caliper width of 0.2 and a ratio of 1:3, and finally 92 subjects were enrolled in the final analysis (Figure 1). The subjects in the SCT group after PSM (n = 23) had a mean age of 53.0 ± 9.7 years and included 12 cases undergoing autologous bone-marrow stem-cell transplantation and 11 cases of peripheral hemato-

Table 2 Comparison of the survival rate and incidence of liver cancer between the stem cell transplantation group and the non-transplantation group

	Time	Stem cell transplantation group (n = 23)	Non-transplantation group (n = 69)	χ^2 value	P-value
Survival rate	3-mo	95.70%	84.10%	0.951	0.33
	6-mo	91.30%	82.60%		
	1-yr	87.00%	73.80%		
	2-yr	73.90%	62.90%		
	3-yr	50.80%	58.10%		
	4-yr	46.20%	54.50%		
	5-yr	41.60%	50.70%		
	6-yr	32.30%	44.20%		
	7-yr	24.30%	39.50%		
Incidence of liver cancer	3-mo	0	0	6.3	0.011
	6-mo	4.80%	1.70%		
	1-yr	9.50%	5.50%		
	2-yr	20.80%	14.10%		
	3-yr	41.40%	19.30%		
	4-yr	49.80%	22.40%		
	5-yr	66.50%	29.00%		
	6-yr	66.50%	36.30%		
	7-yr	83.30%	42.70%		

poietic stem-cell transplantation, and the subjects in the non-SCT group (n = 69) had a mean age of 55.3 ± 9.8 years. The subjects in both groups had a median follow-up period of 42 mo (range: 1-118 mo). Following PSM, no significant differences were detected in the demographic and clinical features between the two groups (P > 0.05) (Table 1).

Impact of SCT on survival

Of the 92 patients with decompensated liver cirrhosis, there were 55 deaths during the study period, with an overall mortality rate of 59.8%. There were 17 deaths in the SCT group (73.9% mortality), including five cases dying of gastrointestinal bleeding, seven cases dying of end-stage HCC, three cases dying of hepatic failure and two cases dying of cerebrovascular accidents. There were 38 deaths in the non-SCT group (55.1% mortality), including 13 cases dying of gastrointestinal bleeding, 13 cases dying of hepatic failure, five cases dying of HCC, and seven cases dying of other causes (lung cancer, laryngeal cancer, arrhythmia, electrolyte disorders and infection). The median survival period was 48 mo in the SCT group and 64 mo in the non-SCT group (Figure 2). No significant difference was found in the survival rate between the two groups (P > 0.05) (Table 2 and Figure 2A).

Impact of SCT on the incidence of HCC

Of the 92 patients with decompensated liver cirrhosis, 26 patients developed HCC during the study period, with an incidence rate of 28.3%. There were 11 and 15 cases that developed HCC in the SCT group and non-SCT group, with 47.8% and 21.7% incidence, respectively, and a significant difference was observed between the two groups (P < 0.05). In addition, the 1-, 3-, 5- and 7-year incidence of HCC were all significantly higher in the SCT group than in the non-SCT group (P < 0.05) (Table 2 and Figure 2B).

Risk factors of HCC

In the univariate Cox regression analysis, SCT and age were found to correlate with the development of HCC (P < 0.05), while the medical history of diabetes, history of smoking, history of alcohol drinking, HBV infection, sex, Child-Pugh classification and family history of HCC in the first-degree relatives were not associated with the development of HCC (P > 0.05) (Table 3).

In the multivariate Cox regression, SCT (OR = 3.065, 95%CI: 1.378-6.814) and age (OR = 1.061, 95%CI: 1.021-1.102) were independently correlated with the development of HCC in this decompensated cirrhotic cohort (Table 3).

DISCUSSION

Recently, SCT has achieved great successes in the treatment of liver diseases[8]. However, there are still a large number of unsolved problems to date, such as the long-term efficacy and safety of SCT, which remain to be investigated[26].

Results from the clinical studies have shown that SCT achieves a satisfactory short-term efficacy for the treatment of decompensated liver cirrhosis[11,12]; however, the transplantation does not seem to increase the long-term efficacy[12,27,28]. In 53 liver failure patients caused by hepatitis B, a single transplantation with autologous BMSCs did not result in significant differences in liver function or MELD score between the transplantation group and controls three years after transplantation, and the 192-wk follow-up revealed no significant difference in the survival rate between the two groups, suggesting no marked improvements in long-term efficacy[12]. A recent meta-analysis to examine the clinical outcomes of the transplantation of stem cells

Table 3 Cox regression analysis of risk factors of hepatocellular carcinoma

Variable	Univariate Cox regression analysis			Multivariate Cox regression analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Stem cell transplantation	2.664	1.211-5.859	0.015	3.065	1.378-6.814	0.006
Age	1.055	1.016-1.096	0.006	1.055	1.016-1.096	0.006
Sex	1.588	0.728-3.467	0.246			
History of diabetes	1.098	0.439-2.741	0.842			
History of smoking	1.475	0.675-3.223	0.330			
History of alcohol consumption	1.546	0.698-3.423	0.283			
HBsAg positivity	0.664	0.086-5.117	0.694			
Child-Pugh classification	1.301	0.522-3.246	0.573			
Family history of liver cancer	1.283	0.303-5.444	0.735			

HBsAg: Hepatitis B surface antigen.

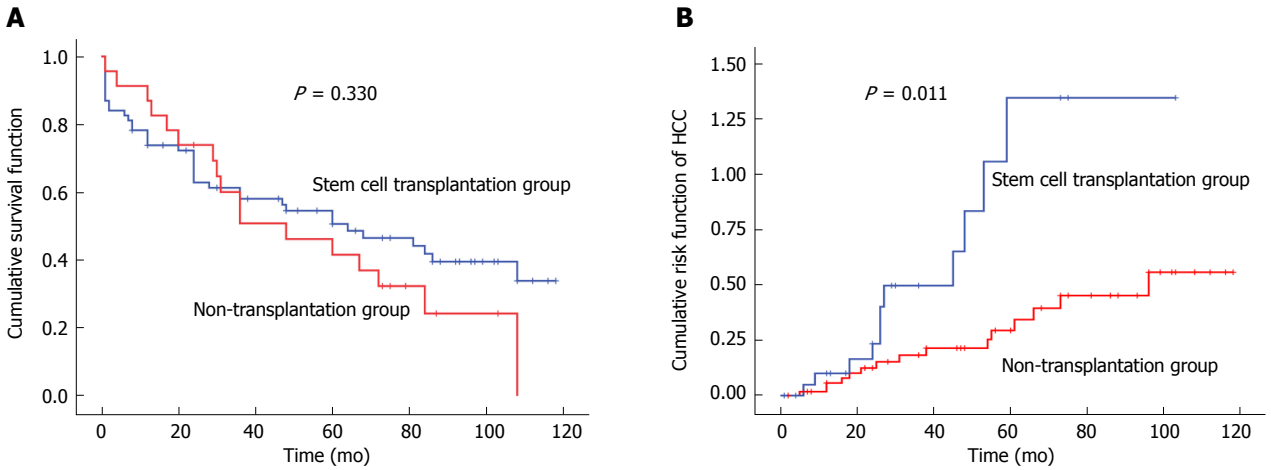

Figure 2 Long-term outcomes of the study subjects. A: Survival curve of the study subjects; B: Risk curve for hepatocellular carcinoma in the study subjects. HCC: Hepatocellular carcinoma.

from various human tissue sources in cirrhotic patients showed no significant difference in the mortality between the treatment and control groups, and concluded that SCT could improve liver function but appeared to not be significant in increasing the survival in cirrhotic patients[29]. In the current study, a 10-year follow-up revealed 73.9% (17/23) deaths in the decompensated liver cirrhosis cases undergoing SCT. We did not find a significant difference in the survival rate between the two groups, which was similar to previous reports[12,29]. The plausible explanation is that SCT can minimally reverse portal hypertension and the development of cancer in decompensated cirrhosis, as most causes of death were due to gastrointestinal bleeding and HCC in patients undergoing SCT in this cohort.

Previous studies have demonstrated the short-term safety of SCT[11,13,29,30]; however, its long-term safety has not been fully demonstrated. Results from previous clinical studies have demonstrated that SCT does not increase the risk of developing HCC[11-13,29,31]; however, the follow-up periods (no more than two years) in those studies were not long enough to observe the development of cancer. In this study, the 10-year follow-up showed a gradual increase in the incidence of HCC in the SCT group with the extension of the follow-up period. This significant difference between two groups suggested a possible tumorigenicity of SCT in patients with decompensated liver cirrhosis. Stem cells have a strong self-renewal capability and multi-lineage differentiation potential[16], and tumorigenicity of BM stem cell has been observed in animal experiments[32,33], which provides theoretical evidence for the findings from the present study. As reported by a recent review, the 5-year cumulative incidence of all second malignancies after autologous SCT for hematological disorders is 4.3%, and the 15-year cumulative incidence is 8%-15.3%[17], indicating a gradually increased risk for malignancy in patients with SCT therapy. The risk of HCC in cirrhosis patients might be associated with the activation of hepatic stellate cells and secretion of multiple growth factors and cytokines[34,35]. This may produce a microenvironment for developing HCC, thereby promoting the development and progression of HCC[35]. Follow-up of the fate of administered stem cells using combined imaging methods has been proposed as a method to discriminate tumorigenic transformation. In the future, this technology can be used to monitor liver cancer after SCT[36,37].

Approximately 80% of HCC develops from liver cirrhosis[1]. Multiple factors have been identified as the risk factors of HCC in liver fibrotic patients[31,38,39]. In

the current study, only two factors, SCT and age, were included in the multivariate Cox regression model. Multiple risk factors of HCC were excluded during PSM, such as HBV infection, resulting in no statistical significance of conventional risk factors during the univariate Cox regression analysis. However, this did not deny the significance of these variables. In addition, Cox hazard regression analysis identified age as the risk factor of HCC in patients with liver fibrosis, which may be attributed to the longer duration of liver fibrosis in older patients.

The current study has some limitations: (1) Considering the likelihood of tumorigenicity of stem cells, cancers may occur in both the liver and other organs[17,18]; however, we only found four cancers in organs other than the liver, which cannot be analyzed; and (2) This is a single-center retrospective cohort study, although we tried to match patients with and without SCT by PSM. However the selection bias and confounding bias cannot be completely excluded. Further randomized, prospective clinical trials with larger sample sizes and extension of follow-up period are required to evaluate the long-term efficacy and safety of stem cell therapy for decompensated liver cirrhosis.

In summary, the results of the present study demonstrate that SCT fails to increase the long-term survival rate and increase the incidence of HCC in patients with decompensated liver cirrhosis, indicating an unsatisfactory long-term efficacy and safety. It is suggested that close monitoring of HCC is required in patients with decompensated liver cirrhosis undergoing SCT.

ARTICLE HIGHLIGHTS

Research background

Decompensated liver cirrhosis greatly affects patients' life quality and expectancy. However, the tumorigenicity of stem cells impedes them as a basis for regenerative medicine treatment.

Research motivation

This study evaluates the long-term efficacy and safety of autologous stem cell transplantation (SCT) for decompensated liver cirrhosis based on ten years of follow-up.

Research objectives

We aimed to compare the survival rate and incidence of hepatocellular carcinoma (HCC) in decompensated liver cirrhosis patients with and without SCT, so as to evaluate the long-term efficacy and safety of SCT.

Research methods

Consecutive patients with decompensated liver cirrhosis were included and assigned into the SCT group and non-transplantation (non-SCT) group according to whether they received SCT treatment. Patients were followed up for ten years.

Research results

The incidence of HCC was higher in the SCT group than in the non-SCT group. After adjusting for other covariates, SCT and age were independently correlated with the development of HCC in this decompensated liver cirrhosis cohort.

Research conclusions

Autologous SCT may fail to improve the long-term efficacy and increase the incidence of HCC for decompensated liver cirrhosis.

Research perspectives

Close monitoring of HCC is strongly recommended in patients undergoing autologous SCT.

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