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REVIEW

Bone marrow derived stem cells for the treatment of end-stage liver disease

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Abstract

End-stage disease due to liver cirrhosis is an important cause of death worldwide. Cirrhosis results from progressive, extensive fibrosis and impaired hepatocyte regeneration. The only curative treatment is liver transplantation, but due to the several limitations of this procedure, the interest in alternative therapeutic strategies is increasing. In particular, the potential of bone marrow stem cell (BMSC) therapy in cirrhosis has been explored in different trials. In this article, we evaluate the results of 18 prospective clinical trials, and we provide a descriptive overview of recent advances in the research on hepatic regenerative medicine. The main message from the currently available data in the literature is that BMSC therapy is extremely promising in the context of liver cirrhosis. However, its application should be further explored in randomized, controlled trials with large cohorts and long follow-ups.

Key words: Liver cirrhosis; Liver regeneration; Hematopoietic stem cells; Mesenchymal stem cells; End stage liver disease

Core tip: In recent years, the role of bone marrow stem cells (BMSCs) in liver regeneration has been explored in various clinical trials. Because these trials were very diverse, we conducted a descriptive overview to understand the effects of BMSC transplantation on liver histology and morphology, on laboratory parameters and prognostic scores, and finally, on clinical manifestations and quality of life. This overview suggests that the efficacy of BMSC therapy might be temporary, and therefore, repeated cycles of BMSCs could be useful to achieve a sustained benefit.

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INTRODUCTION

End-stage disease due to liver cirrhosis is an important cause of death worldwide[1-3]. Currently, the only effective treatment is liver transplantation, but because of the lack of organ donors, surgical complications, risk of rejection and high costs[4,5], the pressure on finding new treatment strategies is increasing[6]. When a successful etiologic approach is unavailable or has failed, progressive, extensive fibrosis[7,8] with concurrently impaired

hepatocyte regeneration[9,10] leads to irreversible cirrhosis[11,12]. Therefore, the development of new techniques to stimulate liver regeneration and reduce the scarring process is urgently needed. In this respect, there is great interest in the potential of BMSC therapy to promote liver regeneration through the use of unsorted mononuclear stem cells (MNCs), hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). This review article summarizes the results of the main prospective clinical trials on BMSC transplantation in patients with cirrhosis, providing a descriptive overview of recent advances in the research on hepatic regenerative medicine.

Liver fibrosis

Cirrhosis is the common final outcome of chronic liver disease, leading to portal hypertension and end-stage liver disease (ESLD), and it is mainly caused by alcohol abuse and viral infections. The prevalence is estimated at 0.15% in the United States[6], and liver cirrhosis-related deaths constitute 1.8% of all deaths in Europe[13].

The main pathogenetic mechanism that leads to the subversion of liver architecture is an aberrant healing process referred to as fibrogenesis, which can be triggered by various factors such as viruses, alcohol abuse, steatohepatitis, autoantibodies, oxidative stress, and others. The common pathway leading to the deposition of extracellular matrix (ECM) is the activation of myofibroblasts. Myofibroblasts originate from different sources such as hepatic stem cells, portal fibroblasts and bone marrow (BM) derived fibrocytes (haematopoietic lineage) and mesenchymal cells. These cells can also arise from epithelial cells via epithelial to mesenchymal transition[8,14]. In the first phase of hepatic injury, the production of ECM is counterbalanced by the action of proteolytic enzymes such as matrix metalloproteinases (MMPs). With persistent damage, this equilibrium is compromised, and the presence of tissue inhibitors of MMPs abnormally enhances the deposition of ECM and ultimately leads to the alteration of normal liver structure[15].

Liver regeneration

The processes and the pathways responsible for liver regeneration are not yet completely understood. Under physiological circumstances, the ability of hepatocytes to re-enter the cell cycle enables liver regeneration and repair through compensatory hyperplasia and hypertrophy[16-18]. In the case of chronic liver injury, this ability is compromised, and liver regeneration is carried out by liver progenitor cells (LPCs). Progenitor-dependent regeneration takes place if hepatocytes are severely damaged and unable to regenerate efficiently, as occurs in cirrhosis. This hypothesis was first suggested by the finding that the LPC concentration in patients with chronic liver disease is greatly increased[19].

These cells were initially identified in animal models and called "oval cells". It has been demonstrated that they are a bi-potential progenitor for hepatocytes and biliary cells[20]. Highly conserved intracellular pathways are responsible for oval cell differentiation. In particular, Wnt signalling is involved in LPC proliferation, while *Notch* signalling is involved in biliary differentiation[21]. The human equivalent of oval cells have been detected in the canal of Hering, and according to the so called "streaming liver hypothesis", these cells migrate to the central vein and progressively differentiate into hepatocytes[22,23]. Conversely, Kuwahara *et al*[24] have suggested that LPCs can be located in four different cell niches: canal of Hering, intralobular bile ducts, periductular mononuclear cells and peribiliary hepatocytes. The space of Disse has also been reported to be a potential niche for LPCs[25].

The origin of LPCs is controversial; they might be *in situ* cells, descendants of the foetal ductal plate[26], or derive from BMSCs, as first described by Petersen *et al*[27]. Furthermore, it has also been hypothesized that they might arise from MSCs *via* the mesenchymal to epithelial transition[28].

Using Y chromosome tracking in rodents[29] and humans[30], it has also been reported that BMSCs may contribute to hepatocyte differentiation independently of mature hepatocytes and LPCs. This limited evidence highlights the fact that liver regeneration processes are not yet fully understood, and only with a better understanding of these molecular and cellular mechanisms will it be possible to develop a targeted therapy for liver fibrosis.

STEM CELL THERAPY

In recent years, unsorted MNCs, HSCs and MSCs have been employed in research focused on liver regeneration[31,32].

HSCs are traceable using CD34 and CD133 markers. The latter is believed to represent a subpopulation of the $CD34^+$ cells that have a higher differentiation potential[33]. HSCs can be obtained by BM aspiration or from peripheral collection through leukapheresis after granulocyte-colony stimulating factor (G-CSF) administration, whereas MNCs and MSCs can be harvested mainly by BM aspiration, which requires an invasive procedure. G-CSF has been used in liver regeneration because of its ability to increase the number of circulating BMSCs and to promote repair in the cirrhotic liver[34]. As suggested by Jin *et al*[35], G-CSF may also enhance MNC homing to the liver.

The feasibility and safety of mobilizing BM derived cells following G-CSF administration was demonstrated by Gaia *et al*[36] in eight patients with ESLD. Additionally, this study reported improved model for end-stage liver disease (MELD) scores and did not find any development of hepatocellular carcinoma or increase in alpha-fetoprotein up to eight months after G-CSF administration. A favourable effect of G-CSF administration on survival and clinical parameters in patients with liver failure has also been reported in other studies[37]. Lorenzini *et al*[38] demonstrated the safety of BMSC mobilization

and collection through leukapheresis in patients with cirrhosis, even though no improvement of liver function tests occurred. G-CSF administration can be also associated with the risk of spleen enlargement[39] or even rupture, as reported by Falzetti *et al*[40] in a healthy donor.

Other cells that have been utilized in hepatic regeneration research include foetal annex stem cells (cord blood and placenta) and embryonic stem cells[41,42]. The use of embryonic stem cells is limited to *in vitro* and animal studies because of difficulties in controlling their proliferative and differentiation potential. Another type of cell employed in animal experiments is induced pluripotent stem cells, which are embryonic-like stem cells derived from somatic cells through the expression of reprogramming factors[43].

Hypothesized mechanisms

Stem cell therapy may contribute to the improvement of liver function[44]. Although the mechanisms involved are not yet fully understood, some hypotheses have been proposed[45,46]. One hypothesis is that genomic plasticity, in response to the microenvironment, causes the trans-differentiation of stem cells into functional hepatocytes[47,48]. Another mechanism is presumably related to the cell fusion of BMSCs and hepatocytes[49,50]. Additionally, it has been proposed that stem cells may exert paracrine effects on endogenous hepatocytes to increase their ability to regenerate, through the release of proliferative cytokines and the production of matrix metalloproteinase-9[51] or by enhancing angiogenesis through the release of vascular endothelial growth factors[52]. A better understanding of the action of stem cells in the context of a fibrotic liver might allow more rational use of BMSC therapy in liver cirrhosis.

CLINICAL TRIALS

Many clinical trials have recently been published on BMSC therapy in cirrhotic patients. The results of the main prospective clinical trials are summarized in Table 1. These studies differ with respect to study design, inclusion/exclusion criteria, type and number of cells infused, route of delivery and end points. The stage of cirrhosis varied from Child Turcotte Pugh score (CTP) A to C. Although cells were harvested mainly by BM aspiration, in some studies, leukapheresis after G-CSF administration was performed. Different types of cells were infused, including MNCs, MSCs or HSCs. The number of injected cells varied from 10^6 to 10^9. The most commonly used routes of delivery were the hepatic artery or portal vein, but in some studies, peripheral vein and intrasplenic injection were also utilized.

Safety of BMSCs therapy

The majority of the clinical trials demonstrated the safety of the procedure. Couto *et al*[53] reported a case of artery dissection and a case of Tako-Tsubo syndrome after the injection of BMSCs through the hepatic artery, and Levicar *et al*[54] reported thrombocytopenia after leukapheresis. Finally, Mohamadnejad *et al*[55] reported a case of radiocontrast nephropathy that progressed to type 1 hepatorenal syndrome and caused the death of a patient. For this reason, the clinical trial was prematurely stopped, and BMSC therapy through the hepatic artery was not considered safe.

Effect of BMSCs therapy on liver histology and morphology

In a study by Kim *et al*[56], which enrolled ten patients, a significant increase in liver volume compared to baseline was documented using MRI six months after MNCs transplantation through a peripheral injection but this result has not been confirmed[57,58]. In that study, serial biopsies were performed. All biopsies at baseline showed low levels of LPC activation and differentiation. After BMSC therapy, a gradual increase in the LPC count occurred in all patients, with a peak three months after reinfusion. In contrast, no changes in the degree of stellate cell activation were observed[56].

Terai *et al*[44] demonstrated increased expression of proliferating cell nuclear antigen in liver biopsy tissue one month after peripheral MNC injection. Jang *et al*[59] performed a histological evaluation in eleven patients with alcohol-induced cirrhosis after two MSC transplantations through the hepatic artery. After five months, significant histological improvement according to the Laennec system[60] was observed, along with a significant decrease in the expression of transforming growth factor-beta1, type I -collagen and alpha-smooth muscle actin.

An interesting study by Couto *et al*[53] suggested that the hepatic retention of MNCs is fair. In that study, MNCs (MSCs and HSCs) were labelled with Tc99 and then injected through the hepatic artery in eight patients with CTP B and C. Remarkably, whole body scintigraphy at 3 and 24 h after injection showed a mean radiotracer retention of 41% and 32%, respectively. Few studies have evaluated liver histology and morphology, but the available data are consistent with histological improvement, increased LPC count and decreased expression of fibrosis markers after BMSC therapy.

Effect of BMSC therapy on laboratory parameters and prognostic scores

The efficacy of BMSC therapy in patients with cirrhosis was assessed using laboratory parameters such as International Normalized Ratio (INR), total bilirubin (TBil), creatinine (Cr), albumin (Alb) and/or prognostic scores (CTP and MELD). These results are summarized in Table 2.

Significant improvements in laboratory tests were reported at one month after BMSC infusion in one study[53], at three months in four studies[59,61-63], at six months in six studies[44,56,64-67] and after twelve months of follow up in one study[68]. In the remaining studies, the limited number of patients enrolled prevented statistical evaluation, but

Table 1 Prospective studies on bone marrow stem cells therapy in patients with cirrhosis

Ref.	Study design	No. of patients	Disease cause/stage	Cell/harvest	Infusion route/n cell infused
Park *et al*[69]	Case series	5	Mixed	MNCs (MSCs)	Hepatic artery
Cytotherapy, 2013			CTP B-C	BM aspiration	10^6-10^7/kg
Amin *et al*[64]	Case series	20	HCV	MSCs	Intrasplenic
Clin Transplant, 2013			CTP C	BM aspiration	10^7
Mohamadnejad *et al*[57]	Randomized	15	Mixed	MSCs/placebo	Peripheral vein
Liver Int, 2013	Vs untreated control	12 control	CTP A-C	BM aspiration	10^8
Jang *et al*[59]	Case series	12	Alcohol	MSCs	Hepatic artery
Liver Int, 2013			CTP A-B	BM aspiration	10^7
Salama *et al*[68]	Not-randomized	50	HCV	HSCs	Portal vein/hepatic artery
Stem Cell Res Ther, 2012	Vs untreated control	50 control	ESLD	Leukapheresis	
				G-CSF	10^9
El-Ansary *et al*[65]	Not-randomized	15	HCV	MSCs	Peripheral vein
Stem Cell Rev, 2012	Vs untreated control	10 control	CTP C	BM aspiration	10^6
Peng *et al*[61]	Not-randomized	53	HBV	MSCs	Hepatic artery
Hepatology, 2011	Vs untreated control	105 control	Mixed[1]	BM aspiration	NA
Couto *et al*[53]	Case series	8	Mixed	MNCs	Hepatic artery
Liver Int, 2010			CTP B-C	BM aspiration	10^9
Nikeghbalian *et al*[58]	Case series	6	Mixed	MNCs/HSCs	Portalvein
Arch Iran Med, 2011			CTP C	BM aspiration	10^6-10^9
Salama *et al*[66]	Randomized	90	HCV	HSCs	Portal vein
World J Gastroenterol, 2010	Vs untreated control	50 control	NA	BM aspiration	10^7
				G-CSF	
Kim *et al*[56]	Case series	10	HBV	MNCs	Peripheral vein
Cell Transplantation, 2010			MELD 7-13	BM aspiration	10^8/kg
Lyra *et al*[62]	Randomized	15	Mixed	MNCs	Hepatic artery
Eur J Gastroenterol Hepatol, 2009	Vs untreated control	15 control	CTP B-C	BM aspiration	10^8
Kharaziha *et al*[67]	Case series	8	Mixed	MSCs	Portal vein
Eur J Gastroenterol Hepatol, 2009			MELD > 10	BM aspiration	10^8
Pai *et al*[63]	Case series	9	alcohol	HSCs	Hepatic artery
AM J Gastroenterol, 2008			CTP B	Leukapheresis	10^8
				G-CSF	
Levicar *et al*[54]	Case series	5	Mixed	HSCs	Portalvein/
Cell Proliferat, 2008			CTP A-B	Leukapheresis	hepaticartery
				G-CSF	10^8
Mohamadnejad *et al*[55]	Case series	4	Mixed	HSCs	Hepatic artery
World J Gastroenterol, 2007			CTP B-C	BM aspiration	10^6-10^7
Lyra *et al*[70]	Case series	10	Mixed	MNCs	Hepatic artery
World J Gastroenterol, 2007			CTP B-C	BM aspiration	10^8
Terai *et al*[44]	Case series	9	Mixed	MNCs	Peripheral vein
Stem cells, 2006			CTP B-C	BM aspiration	10^9

[1]In this study the patients had cirrhosis or chronic hepatitis. BMSC: Bone marrow stem cell; CTP :Child Turcotte Pugh score; MNC: Mononuclear stem cell; HSC: Hematopoietic stem cell; MSC: Mesenchymal stem cells; NA: Not available; GI: Gastrointestinal; Pt: Patients.

some improvement in laboratory tests was reported[54,69,70].

A significant improvement in MELD and/or CTP score three months after BMSCs infusion in two studies[59,62], at six months in four studies[44,56,65,67] and at nine months in one study[61] has also been described.

However, the controlled randomized clinical trial performed by Mohamadnejad *et al*[57] did not show any significant difference in either INR or prognostic scores between treatment and control groups at three and twelve months after BMSCs infusion. The majority of the clinical trials showed a significant but time-limited improvement in laboratory parameters and prognostic scores, offering encouraging prospects for future trials.

Effect of BMSC therapy on clinical manifestations and quality of life

Many studies have evaluated the clinical manifestations associated with ESLD, including hepatic encephalopathy, lower limb oedema, hematemesis, ascites and jaundice. Seven studies reported an improvement in at least one of the previously mentioned clinical manifestations[44,56,63-66,68]. However, it should be noted that some clinical manifestations, such as ascites, might not accurately reflect efficacy. In fact, ascites can be over- or underestimated by physical examination and can be modified by pharmacological interventions other than BMSC therapy (*e.g.*, diuretics, albumin).

Health-related quality of life after BMSC therapy was the primary outcome in an interesting study performed by Salama *et al*[68]. One hundred patients were assigned to the treatment or control groups and completed the Short Form-36 health status evaluation. Self-reported physical and mental status significantly improved in the treatment group during the six months following BMSC reinfusion, while status significantly deteriorated in the control group; these data are also supported by another

Table 2 Studies that reported a modification of laboratory parameters and prognostic scores

Author	Results compared to	Laboratory parameters				Prognostic scores	
		INR	TBil	Alb	Cr	MELD	CTP
Amin *et al*[64]	Baseline	I	I	I	NR	NR	NR
Mohamadnejad *et al*[57]	Control group	NI	NR	NI	NR	NI	NI
Jang *et al*[59]	Baseline	I	NI	I	NI	I	I
Salama *et al*[68]	Baseline	NR	I	NR	NR	NR	NR
El-Ansary *et al*[65]	Control group	I[1]	I	I	NR	I	NR
Peng *et al*[61]	Control group	I	I	I	NR	I	NR
Couto *et al*[53]	Baseline	NR	I	I	NR	NR	NR
Salama *et al*[66]	Control group	NR	I	I	NR	NR	NR
Kim *et al*[56]	Baseline	I	NR	I	NR	NI	I
Lyra *et al*[62]	Baseline	NR	NR	I	NR	NI	I
Kharaziha *et al*[67]	Baseline	I	NI	NI	I	I	NR
Pai *et al*[63]	Baseline	NR	I	NI	NR	NR	NR
Terai *et al*[44]	Baseline	NR	NR	I	NR	NR	I

[1]In this study it was reported prothrombin concentration (PC) and not INR. I: Improved significantly; NI: Not improved; NR: Not reported; INR: International normalized ratio; MELD: Model for end-stage liver disease; CTP: Child turcotte pugh score.

recent study[56].

In addition, Salama *et al*[68] reported a significantly higher survival rate in the treatment group compared to the control group. An improved survival rate after BMSC therapy was also reported in other studies, but the data were not statistically significant[61,66]. In summary, clinical manifestations, health-related quality of life and survival rate have been reported to be improved after BMSCs therapy.

CONCLUSION

There are still many open questions concerning BMSC therapy for the treatment of liver cirrhosis. First, it is crucial to understand the homing processes of BMSCs to the liver and to elucidate the relationships that exist not only between BMSCs and hepatocytes (regeneration) but also between MSCs, myofibroblasts and stellate cells (fibrogenesis). It is essential to clarify the mechanisms by which different types of BMSCs act in the liver, as this would allow the tailoring of stem cell therapy to the specific patient. The hypothesis that BMSCs act through the delivery of specific substances (cytokines and growth factors), rather than through transdifferentiation or cell fusion, suggests that improvements in liver function might be temporary. This hypothesis is supported by the results of the majority of the clinical trials: the improvement in laboratory data and CTP and MELD scores did not persist longer than three-six months regardless of the type of BMSCs infused, the route of delivery or the aetiology of the disease. In addition, the histological evaluations support this hypothesis, as an increase in LPC count was documented, peaking three months after BMSCs infusion. These results suggest that repeated cycles of BMSC therapy could be useful to obtain a sustained benefit.

BMSC therapy, although promising, needs to be further evaluated in large randomized, controlled clinical trials with longer follow-ups because the characteristics of the study populations reported in the current literature do not allow analytic comparison between the studies. In particular, a crucial issue is the different types of stem cells used, and in this regard, it could be interesting to compare the effects of the different types of BMSCs (unsorted MNCs, MSCs, and HSCs) on objective liver function parameters.

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