Review Article

Autologous Bone Marrow–derived Cells in the Treatment of Liver Disease Patients

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ABSTRACT

Liver transplantation is universally accepted as a "cure" procedure, and yet is not universally applicable for the treatment of end-stage liver diseases (ESLD) because of the shortage of donors, operative complications, risk of rejection, and high cost. Bioartificial liver device is an option to temporarily improve the liver function and to bridge the patients to liver transplantation. However, bioartificial liver device has many problems in clinical application, such as hepatocyte allograft rejection and maintenance of hepatocyte viability and function. Another therapeutic option is stem cell transplantation. There are two broad types of stem cells: Embryonic stem cells and adult stem cells. The latter are sourced from bone marrow (BM), adipose tissue, and blood. This review will concentrate on BM-derived cells. BM-derived cell transplantation, although not ideal, is theoretically an optimal modality for the treatment of ESLD. Autologous BM-derived cells have no graft rejection, have the capability of regeneration and self-renewal, and are multipotent stem cells that can differentiate into a variety of cell types which include hepatocytes. The pathway from BM-derived cell to hepatocyte is well documented. The present review summarizes the delivery routes of BM-derived cells to the liver, the evidences of engraftment of BM-derived cells in the liver, and the possible mechanisms of BM-derived cells in liver repair and regeneration, and finally, updates the clinical applications.

Key Words: Bone marrow cells, liver disease, liver regeneration, stem cells

Liver transplantation is the gold standard treatment for patients with end-stage liver diseases (ESLD). However, the majority of patients worldwide do not receive a liver transplantation due to unavailability of the liver transplant program, inability to afford its cost, or the scarcity of liver donors, with ever-increasing waiting times on the transplant lists worldwide with all its associated significant morbidity, mortality, and cost of care.[1] Patients who are lucky enough to get a transplant often suffer from surgical complications, medication toxicities, or graft loss due to rejection or recurrence of the original disease, making this gold standard treatment modality far from perfect.[2,3]

Besides liver transplantation, artificial liver is another option for the treatment of ESLD. Nonbiologic liver support system only partially removes the toxic molecules, while bioartificial liver (BAL) seems more helpful because it not only removes the toxic molecules, but also has metabolic and synthesis functions. However, application of BAL in clinical practice still poses problems which include the difficulty of obtaining hepatocytes, hepatocyte allograft rejection, and maintaining their viability and function. Some of the BAL devices also cause coagulation of the system.[4]

To meet this huge challenge and given the rising number of patients needing treatment for ESLD, scientists all over the world have been exploring and investigating other potential options to help patients with ESLD. These options may be directed to offer a total solution for such patients or at least to bridge them until a suitable organ is available for transplantation. Stem cells (SCs) may be another option that is worth exploring. Stem cell has the capability of self-renewal and the differentiation potential. Schwartz *et al.*[5] demonstrated that bone marrow (BM) primitive cells from normal human beings, mouse, and rat can also differentiate into cells with morphologic, phenotypic, and functional characteristics of hepatocyte-like cells *in vitro*. These cells expressed

hepatocyte nuclear factor-3beta (HNF-3β), GATA4, cytokeratin 19 (CK19), transthyretin, α-fetoprotein, CK18, HNF-4, and HNF-1α; they secreted urea and albumin, had phenobarbital-inducible cytochrome p450, could take up low density lipoprotein (LDL), and stored glycogen.

In the late 19th century, Haeckel introduced the term "stem cell."[6] In 1999, Petersen first transplanted BM from a male rat to lethally irradiated female rats and found that Y chromosome was detected in hepatocytes from female recipients. Petersen's experiment suggested that the hepatocytes from recipients were derived from the BM-donor cells, and these cells continued to differentiate into mature hepatocytes.[7] Lagasse *et al.*[8] transplanted purified hematopoietic stem cells (HSCs) to fumarylacetoacetate hydrolase deficient mouse and demonstrated that HSC differentiated into hepatocytes in mice.

There are two types of SCs: (i) adult SCs and (ii) embryonic SCs. Both have the capability to differentiate to hepatocytes. The present review will focus on autologous BM-derived cells for treating patients with ESLD.

DELIVERY OF BM-DERIVED CELLS

There are four ways to deliver autologous BM-derived cells: Through hepatic artery, portal vein, intrasplenic, and peripheral vein. Five well-documented controlled clinical trials showed that cells were delivered via hepatic artery in three studies,[9-11] via portal vein in one,[12] and via peripheral vein in one.[13] Because ESLD has distortion of hepatic architecture and portal systemic collaterals, infused cells may bypass the liver.[9] Hepatic arterial route is a more specific one and more cells infused may ultimately stay in the liver. Moreover, the technique is routinely used for arterial chemoembolization of liver tumors and, therefore, is ready to be used in BM-derived cell infusion. In order to mobilize cells, granulocyte colony-stimulating factor (G-CSF) was used prior to cell collection and infusion in two studies.[9,12] Overall, the results of these studies showed positive outcomes in patients with ESLD.

EVIDENCE OF BM-DERIVED CELLS IN THE LIVER

BM transplant relies on the engraftment of donor hematopoietic precursors in the host marrow space. Kuo and colleagues transplanted BM from human being to mice with lethal fulminant hepatic failure and found that human albumin that does not cross-react with murine was detected in mice. Kuo's experiment suggested that the hepatocytes from recipients were derived from the BM donor cells, and these cells continued to differentiate into mature hepatocytes.[14] Meleshko found that when BM cells from male donor were

transplanted to female patients, the SRY gene could be detected in the liver of the recipients.[15] Terai *et al.*[16] infused the whole BM cells isolated from the femurs of syngeneic green fluorescent protein (GFP) transgenic male mice to female cirrhotic recipient mice. Four weeks later, they confirmed that GFP-positive BM cells migrated into the periportal areas of damaged liver and proliferated to form hepatic cords. Furthermore, the serum albumin levels and the survival rate were significantly increased, the liver fibrosis was significantly decreased, and the liver function was significantly improved.

MECHANISM OF BM SCS IN LIVER REPAIR AND REGENERATION

There are four aspects of the effect of BM SCs on liver repair and regeneration: Hepatocyte differentiation, modulation of immunity and anti-inflammation, anti-oxidative stress and anti-apoptosis, and improvement of blood supply and anti-fibrogenesis [Figure 1].

Hepatocyte differentiation

BM SCs develop into HSCs and mesenchymal stem cells (MSCs), which have been intensively investigated for their mechanistic contribution in liver regeneration. Although both HSCs and MSCs have the ability to transdifferentiate into hepatocytes, MSCs are reported to have the greatest potency in hepatocyte differentiation.[17,18]

The mechanism by which SCs contribute to hepatic regeneration remains poorly defined. Nevertheless, several hypotheses are available to explain this vague process.

One hypothesis suggests that liver regeneration is triggered depending on the type of infused SCs. HSCs are the
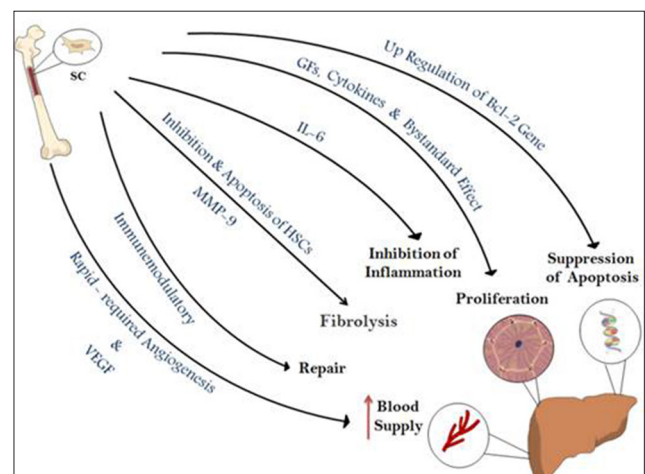

Figure 1: Role and mechanism of bone marrow stem cells in liver repair and regeneration. VEGF, vascular endothelial growth factor; MMP-9, matrix metalloproteinase-9; IL-6, interleukin-6; GFs, growth factors

predominant cell type proven to evoke the multiplication of endogenous hepatocytes, in addition to their ability to stimulate tissue-specific SCs, for example, oval cells in the liver that aid the repopulation of the target organ.[19,20] Although experiments support that transdifferentiation is fundamentally achieved by the effect of MSCs, there is growing evidence that the plasticity of both MSCs and HSCs is the major factor in liver regeneration.[8]

It is debatable whether SCs induce regeneration by cell fusion in which the SCs fuse with a local precursor or mature cell, transferring their genetic material and combining their cytosol or transdifferentiation, which is considered to be the most direct and common mechanism.[21] One study, however, reported that liver regeneration is chiefly central to cell fusion mechanism.[22] Of all the SC types used, MSCs especially have shown some potential for the treatment of liver disease, which could be explained by their promising impact on liver regeneration.[8]

Paracrine effect
MSCs stimulate mitosis of endogenous hepatocytes by the release of certain factors, collectively called as the "bystandard effect."[20] Cytokines and growth factors, in particular, enhance the intrinsic proliferative capacity of hepatocytes.[10]

Majka *et al.* revealed that CD34+ cells secreted numerous growth factors such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1). Li *et al.*[23] found that after transplantation of MSCs, the recipients' serum levels of nerve growth factor (NGF), HGF, and VEGF were significantly increased. All these factors stimulate hepatocyte regeneration.[24] All these evidences indicate that besides the transdifferentiation and proliferation of BM-derived cells engrafted in the liver after BM transplantation, the paracrine function of these cells also promotes the regeneration of endogenous hepatocytes.

Modulation of immunity and anti-inflammation
There is no direct evidence for the liver that BM-derived cells modulate immunity and render anti-inflammation. However, a renal study showed that Foxp3, a master regulator in regulator T cells, significantly increased in rats treated with BM-derived cells. BM-derived cell treatment also decreased the infiltration of macrophages and tubular interstitial injury in unilateral ureteral obstruction in rats.[25] Wang *et al.* demonstrated that pretreatment of BM-derived cells limited myocardial tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6 expression in ischemia-reperfusion (IR) injury in rats.[26]

Anti-oxidative stress and anti-apoptosis
Suppressing the apoptotic rate is another proposed mechanism, which happens as a consequence of *BCL2* gene up-regulation that is thought to be an act of SCs.[20] Jin *et al.* transplanted BM-derived cells to IR model in rats and found that the anti-oxidative factors, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), were significantly increased and malondialdehyde (MDA), a marker of oxidative stress, was significantly decreased. Furthermore, transplantation of BM-derived cells significantly decreased the levels of Bcl-2-associated X (Bax) and caspase-3 (Casp3) proteins and increased Bcl-2, an anti-apoptotic factor, and thus, IR rats transplanted with BM-MSCs had significantly fewer apoptotic hepatocytes compared to sham transplantation rats.[27]

Improvement of blood supply and anti-fibrogenesis
Another biological requirement for damage repair is sufficient blood supply which is also offered by SCs through the release of VEGF along with the repair-required angiogenesis.[8,28]

Furthermore, many studies postulated the mechanisms underlying the fibrolytic effect of MSCs. One study suggested that MSCs play a major role in blocking the synthesis of extracellular matrix (ECM) and facilitating the breakdown of ECM, leading to downgrading of liver fibrosis.[10] This study is in agreement with another one that emphasizes the influence of MSCs in attenuating collagen deposition.[29]

This significant fibrolytic effect maybe attributed to the inhibition of activation and induction of apoptosis of the hepatic stellate cells that constitute a major source of fibrillar collagens and other ECM proteins, which particularly makes them the cornerstone of liver fibrosis.[13]

Another possible antifibrotic process demonstrated by a study is the exaggerated release of matrix metalloproteinases (MMPs), particularly MMP-9.[30] In contrast, endogenous liver repair initiatives do exist even independently. One study proposed that this process is achieved by recruiting the migratory SCs from BM that can restore normal liver function and size and diminish fibrosis.[12]

CLINICAL STUDIES

Many studies were conducted to investigate the safety and efficacy of autologous BM-derived cells in treating liver disease. We will attempt to review the most important of these studies [Table 1].

Table 1: Summaries of the most important studies of autologous BM-derived cells in the treatment of liver disease

Type of stem cells	Patients	Route of infusion	Outcomes	Source
MMSCs	Hepatitis B cirrhosis (study: n=53; control: n=105)	Hepatic artery	Decreased ALT, TBIL, PT, MELD; increased ALB and survival rate	Peng et al., 2011[10]
CD34+, CD133+	ESLD (study: n=90; control: n=50)	Portal vein	Decreased AST, ALT, TBIL, ascites, CPS; increased albumin and survival rate	Salama et al., 2010[12]
MSCs	Hepatitis C cirrhosis (study: n=15; control: n=10)	Peripheral vein	Decreased encephalopathy, jaundice, bleeding tendency, edema, ascites, MELD score, BIL; increased Hb, albumin, and PC	El-Ansary et al., 2012[13]
MNCs	ESLD (study: n=15; control: n=15)	Hepatic artery	Decreased CPS, MEDL scores and BIL; increased albumin	Lyra et al., 2010[11]
MNCs	ALD (study: n=28; control: n=30)	Hepatic artery	Decreased MELD and steatosis in both study and controls, no significant difference between groups	Spahr et al., 2013[9]
MSCs	Decompensated cirrhosis (study: n=15; control: n=12)	Peripheral vein	No beneficial effect in cirrhotic patients	Mohamadnejad et al., 2013[31]
MNCs	Cirrhosis (study: n=9, no control)	Peripheral vein	Increased ALB, total protein; decreased CPS	Terai et al., 2006[32]
MNCs	Cirrhosis (study: n=10, no control)	Hepatic artery	Increased ALB, decreased BIL and INR	Lyra et al., 2007[33]

MMSC: Marrow mesenchymal stem cell, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TBIL: Total bilirubin, PT: Prothrombin time, MELD: Model for end-stage liver disease, ALB: Albumin, ESLD: End-stage liver disease, CPS: Child-Pugh score, BIL: Bilirubin, Hb: Hemoglobin, PC: Prothrombin concentration, MNC: Mononuclear cell, ALD: Alcoholic liver disease, INR: International Normalized Ratio

Controlled clinical trials

One of the earliest studies which used autologous BM-derived cells in the treatment of liver failure caused by hepatitis B included 158 patients, in which 53 patients received autologous BM transplantation while the remaining 105 patients constituted the control group.[10] Treatment with autologous BM-derived cells significantly improved albumin and bilirubin in 2 weeks and the model for end-stage liver disease (MELD) score and prothrombin time (PT) in 3 weeks. However, at this time point, alanine aminotransferase (ALT) showed no significant difference between the two groups. Self-reported symptoms improved during the 4th week in the intervention group. Long-term effects, on the other hand, among the treated patients were demonstrated by an increase in albumin levels in the 3–24 weeks interval. In addition, MELD score improvement was observed to start from 3 to 36 weeks. Improvement in both total bilirubin (TBIL) and PT was demarcated as well from 4 to 12 weeks in the treated group. Interestingly, hepatocellular carcinoma (HCC) developed in only one patient from the treated group versus nine in the controls.

Salama et al. transfused BM-derived, CD34- and CD133-positive cells via portal vein to 90 patients.[12] The results are consistent with those of Peng's study,[10] i.e. serum prothrombin and albumin concentrations were significantly increased and TBIL was significantly decreased. Furthermore, ALT and aspartate aminotransferase (AST) were significantly decreased. Compared with the control group which showed increased Child–Pugh scores, BM-derived cell treatment significantly decreased the Child–Pugh scores of the patients, which is in line with Peng's MELD score. At the end of this study, 9 out of 90 (10%) patients died in the treatment group in comparison to 13 out of 50 (26%) patients who died in the control group. Furthermore, patients' quality of life (QOL) improved as well.[12]

Lyra et al. performed a study with randomized controlled two-armed design in Austria, which included an intervention arm with 15 subjects and a control arm with 15 others.[11] The treated arm subjects were infused with BM mononuclear cells (MNCs). They found that MNC infusion via hepatic artery significantly improved the Child–Pugh score. The MELD score remained stable, whereas it increased during follow-up in the control group. Albumin levels improved in the treatment arm and bilirubin level was increased among controls, whereas the bilirubin level was decreased in the therapy arm.

All the controlled clinical studies given above demonstrated the beneficiary effects of BM-derived cell infusion in patients with ESLD.

El-Ansary et al. from Egypt investigated the differences in the groups infused with differentiated hepatocytes, undifferentiated MSCs, and controls.[13] They evaluated multiple parameters which included encephalopathic manifestations, jaundice, bleeding tendency, lower limb edema, ascites, albumin, prothrombin concentration (PC), hemoglobin (Hb), bilirubin, and MELD score. They found that the infusion of either differentiated hepatocytes or undifferentiated MSCs significantly improved these parameters compared with

controls, while no differences were found between the differentiated and undifferentiated MSC groups.

Spahr *et al.* from Geneva, Switzerland[9] first harvested the autologous BM cells into the bags containing 2500 IU heparin. They then isolated the MNCs and injected them to the liver via hepatic artery on the same day. They found that 3 months after treatment, compared with baseline, the MELD score and steatosis were significantly improved, and the hepatocyte growth factor and pro-inflammatory cytokines such as TNF-α and IL-6 were significantly decreased in both autologous bone marrow mononuclear cell transplantation (BMMCT) and standard medical therapy (SMT) groups. However, there was no significant difference between the BMMCT and SMT groups after treatment. How can these data be explained in relation to the other four studies given above? In Spahr *et al.*'s study, all the patients enrolled had alcoholic liver disease (ALD) and the MELD score was <26; thus, the patient differences might explain the inconsistency. This study at least demonstrated that autologous BM-derived cell therapy is feasible and well-tolerated in patients with ALD.

Although majority of the studies consistently demonstrated that BM-derived cell infusion significantly improved the liver function in patients with liver diseases, there are still many uncertainties:

Infusion volume and cell amount
The infusion volume is variable among studies. Lyra *et al.* aspirated 50 ml of the BM and infused 20 ml of mononuclear-enriched BM cells in saline to the hepatic artery; the average total number of cells infused was 3.78×10^8.[11] Salama *et al.* aspirated 250 ml of the BM and infused 100 ml of re-suspended cells in physiological saline to the portal vein, and the total cell number for each patient was 0.5×10^8.[12] Kim *et al.* aspirated 500–750 ml of BM and infused 100 ml of the cell suspension to peripheral vein.[2] The definitive volume of harvested BM along with the minimum effective number of infused cells is currently unclear and, hence, should be thoroughly studied in order to set the standard levels that may achieve the desirable outcomes.

Cell source
From the above-reviewed literature, it is clear that autologous BM-derived cells have received most of the attention and have probably shown most promising results. Having said that, it is still unclear if this source of cells is truly the best or whether other sources may be more effective or convenient, such as peripheral blood or adipose tissue.[34]

Cell type
Many studies used mesenchymal cells derived from BM, but it is still unclear what exact type of cells should be infused in terms of different levels of differentiation and immune characteristics. Nevertheless, MSCs, among other types, are shown to have the highest potency in hepatocyte differentiation.[17,18]

Cell identification and separation techniques
The relatively low frequency of MSCs in BM, ranging from only 0.001 to 0.01% of the total nucleated cell population,[35] necessitates further investigations regarding the best BM SC isolation procedure. Although most studies have used colony-stimulating factors to enhance the amount of harvested cells, it is still not investigated if it is absolutely necessary and how it should exactly be used. HSC and MSC cannot be isolated to absolute purity, although numerous culture methods and surface markers have been characterized that enable one to enhance the growth for MSC, with each laboratory preferring its own method of isolation. This makes the comparison of results obtained by various laboratories very difficult.[35] The cell separation and identification techniques need to be standardized.

Heterogeneity of endpoints
In addition to what we have discussed earlier regarding the heterogeneity of the methods among the available studies, it is also of major importance to take note that the end points of most of these studies are also different. Although most studies have followed some sort of liver function, the methods of assessment and their timing have been highly variable among the studies, making head-to-head comparisons very difficult.

Response durability
A careful look at the available literature leads us to believe that the positive effect of SC transfusion in ESLD patients is likely to be of short term only.[36] Most studies reported loss or reduction in the effect after the first 3 months of infusion. In this case, it seems reasonable to suggest repeated infusions in future studies to see if that will result in a more long term and durable response.

Patient candidacy
Before subjecting any patient to this or any other experimental therapy, the patients must be assessed for candidacy for liver transplantation. Although there are some positive results reported with cell therapy, it must always be emphasized that this therapy is still experimental and its results cannot be compared to liver transplantation. In addition, all standard efforts must be taken to treat the underlying liver disease and to treat its complications using standard best medical practice. Moreover, there remains an uncertainty whether the selection criteria should target the patients with advanced liver disease or the patients with early disease. This point is unclear from the literature so far.

In conclusion, infusion of BM-derived cells to the patients with liver diseases significantly improved liver function and

mental status, decreased MELD and Child–Pugh scores, and finally, improved the QOL of patients. Infusion of BM-derived cells helps the patients in liver transplantation waiting lists to gain more time and chance to finally receive liver transplantation. BM-derived cell therapy is safe, feasible, and applicable in ESLD.

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