ABSTRACT

Stem cell based therapy was very attractive in decompensated liver cirrhosis currently. The possible mechanism might be due to its potential to help tissue regeneration with minimally invasive procedures. Here we report the case of a 44-year-old man, infected by hepatitis B virus (HBV) combined with hepatitis C virus (HCV) for longer than 10 years, who eventually developed decompensated liver cirrhosis. After being infused with mobilized peripheral blood stem cells, the patient showed significantly elevated serum albumin level, cholesterol (CHO), cholinesterase (CHE) and decreased PT (prothrombin time) during the 26 months of follow-up. To our knowledge, this is the first case of transplanting mobilized PBSCs to treat the HBV combined with HCV related decompensated liver cirrhosis.

Keywords: HBV, HCV, decompensated liver cirrhosis, Peripheral blood stem cell transplantation
monocytes from patients with HBV related
decompensated liver cirrhosis could differen-
tiate into functional hepatocytes and con-tribute to liver function (Yan et al., 2007),
although this matter was still discussed
controversially by the previous reports
(Nussler et al., 2006; Hengstler et al., 2005).
Although all the preliminary results seemed
to be attractive, the follow-up time of the
treated patients was too short to fully
evaluate the safety and efficacy of stem cell
therapy in liver cirrhosis. Here, we describe
the case of one patient with decompensated
liver cirrhosis causing by HBV combined
with HCV, as a result of lasting ameliora-
tion of the clinical course with infusion of
mobilized peripheral blood stem cells.

CASE REPORT

A 44-year-old man was admitted to Xijing
Hospital in August 2005 for a detailed ex-
amination of liver dysfunction. Laboratory
data disclosed the following abnormal val-
ues: Total Protein (TP) 53 g/L (normal
60–87), Albumin (ALB) 31 g/L (37–55), To-
tal Bilirubin (TBIL) 19.4 µmol/L (6–19.2),
Cholesterol (CHO) 2.23 mmol/L (3.50-6.50),
Prothrombin Time (PT) 19.2 S (10.5-12.8),
Activated Partial Thromboplastin Time
(APTT) 49.9 S (26.8-37.5), Fibrinogen (FIB)
1.92 g/L (2.0-4.0), Thrombin Time (TT)
21.2 S (14.2-19.6), Prothrombin Activity (AT )
58.9 % (83-96%), International Normalized
Ratio (INR) 1.60 (0.92-1.11), cholinesterase
(CHE) 3021 IU/L (5300–12900). Peripheral
blood studies disclosed white blood cell count
at 1.53×10^9/L (3.5-10×10^9/L) (neutrophils
49.6 %, lymphocytes 33.3 %, monocytes
9.2 %, eosinophils 7.2 %, basophils 0.7 %),
HGB 93 g/L (115-180) and platelets
27×10^9/L (80-300×10^9/L). Virus markers
were positive for Hepatitis B surface anti-
gen(HBsAg), Hepatitis B core antibody
(HBeAb), and Hepatitis C virus antibody
(HCVAb), negative for Hepatitis B surface
antibody (HBs-Ab), Hepatitis B e antigen
(HBe Ag), Hepatitis B e antibody (HBe-Ab)
and human immunodeficiency virus (HIV);
HBV DNA was 9.5×10^6 copy/ml (< 1000).
A questionnaire revealed that the patient
was infected by HBV combined with HCV
11 years before, and had undergone an ex-
amination for liver function and was diag-
nosed with chronic hepatitis B combined
with hepatitis C. He had no history of al-
cohol abuse or blood transfusion. His
spouse was negative for HBsAg and
HCVAb. A physical examination showed
that he had mild abdominal distention,
splenomegaly, gingival bleeding, jaundice,
and edema of lower limbs. No lymphade-
nopathy or skin rash was observed. Ultra-
sound disclosed a cirrhotic liver, splenome-
galy, and mild ascites. Gastroendoscopy
revealed an esophageal varix, and a gastric
scattered congestion. Histological findings
of liver biopsy were not done for the pa-
tient’s refusal.

Liver transplant was rejected by the pa-
tients and their family members. Autolo-
gous PBSCT was carried out in this patient
after he assigned a formal written informed
consent. The patient was mobilized with
recombinant human granulocyte colony
stimulating factor (rhG-CSF, Qi Lu Phar-
aceutical Co, LTD, China) at
5-10 µg/kg/d administered subcutaneously
daily for 4 days to induce the bone mar-
row-derived stem cells into the peripheral
blood, then PBSC was collected by means
of Apheresis, using the COBE(R) Spectra
TM Apheresis System (Gambro BCT Inc,
Stockholm, Sweden). The duration of the
procedure was 3 hours until the number of
PBSC reached 10^8/ml. Then, 50 ml of the
PBSC was returned to the patients via he-
patic artery in the Imaging Department. Pa-
tients were discharged after 5 days’ bed rest.
The therapy project above was approved by
the ethics committee of Xijing hospital of the Fourth Military Medical University. The patient was followed-up to 26 months to evaluate the clinical effect of PBSCT. During the follow-up period, medication was unchanged and the patient did not receive antiviral therapies. Liver function related serum markers including albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBIL, CHO, CHE, and prothrombin time were assayed to evaluate the liver function. Liver of the patient was also examined by abdominal ultrasonography. The results of the follow-up study indicated that liver synthetic function related markers including serum albumin, CHO, and CHE were significantly increased after PBSCT (Figure 1), and prothrombin time was decreased after PBSCT (Figure 2).

**Figure 1:** After PBSCT, serum ALB, CHO and CHE were significantly increased during the follow-up.

**Figure 2:** After PBSCT, prothrombin time was decreased during the follow-up.

However, data for ALT, AST, and TBIL did not show significant changes after PBSCT, and serum HBV-DNA copy also didn’t show significant changes at all (data not shown). Abdominal ultrasonography showed that ascites was disappeared at 2 weeks after PBSCT. Taken together, the cirrhotic patient showed a lasting amelioration of clinical course after PBSCT.

**DISCUSSION**

Bone marrow-derived stem cells were known to contribute to the cirrhotic livers currently (Mohamadnejad et al., 2007; Abdel Aziz et al., 2007). HBV-related or HCV-related decompensated liver cirrhosis was very common worldwide, especially in China, because there were about more than 10% HBV carriers. Once the decompensated liver cirrhosis occurred, liver transplant provides the only definite cure; however, postoperative recurred virus related hepatitis or tumor limited is widely used. Stem cell based therapy provides one inspiring therapy for hepatitis virus related decompensated liver cirrhosis.

This is the first report about evaluating liver function of HBV combined with HCV related cirrhotic patient who underwent PBSCT. In addition, the time of follow-up was the longest compared with other reports about PBSCT contributing to liver function of decompensated liver cirrhosis. After PBSCT, the patient acquired lasting
amelioration of the liver function, which included liver synthetic function related markers including serum albumin; CHO, CHE, and prothrombin time were significantly improved after PBSCT. However, serum ALT, AST, and TBIL did not show significant changes after PBSCT, indicating that G-CSF mobilization combined with PBSCT therapy could not change the condition of virus copy. What’s more, serum HBV-DNA copy was still unchanged during the follow-up. There were two factors involved in the lasting amelioration of the clinical course, including G-CSF mobilization and PBSCT. G-CSF is a pleiotropic cytokine that plays a major role in regulating hematopoiesis and innate immune responses (Franzke, 2006). A recent study reported that G-CSF could mobilize BM stem cells into infarcted cardiac tissue and accelerates their differentiation into vascular cells and cardiac myocytes (Takano et al., 2006), and the effect of G-CSF has also been demonstrated in Crohn’s disease and ulcerative colitis (Baert and Rutgeerts, 2000). Moreover, a current report demonstrated that hematopoietic mobilization could increase the presence of bone marrow-derived hepatocytes via in vivo cell fusion (Quintana-Bustamante et al., 2006). Thus, our favorable result might be explained both by G-CSF mobilization and PBSCT. Firstly, G-CSF could mobilize a large number of PBSCs into the circulation and secret some cytokines or growth factors to promote hepatocytes functions by paracrine mechanisms. Secondly, transplanted PBSC via hepatic artery might induce the higher concentration of PBSC homing to the injured liver and contribute to the liver function by cell differentiation or fusion. To fully demonstrate the therapeutic value of this protocol, results of long-term follow-up in more patients with hepatitis related cirrhosis are needed.

REFERENCES


