Cytotherapy, 2014; 16: 1575–1583

International Society for Cellular Therapy ISCT®

Use of a transjugular intrahepatic portosystemic shunt combined with autologous bone marrow cell infusion in patients with decompensated liver cirrhosis: an exploratory study

MAOTAO HUANG[1], ZAOMING FENG[1], DAIJIN JI[1], YALING CAO[1], XIAOYING SHI[1], PING CHEN[2], PING WANG[1], MIN TANG[1] & KAI LIU[1]

[1]*Department of Gastroenterology and Endocrinology and* [2]*Department of Nursing, The 452nd Hospital of PLA, Chengdu, China*

Abstract

Background aims. Currently, there is no treatment for decompensated liver cirrhosis except for liver transplantation. The safety and effect on liver function of a transjugular intrahepatic portosystemic shunt (TIPS) with and without autologous bone marrow cell (BMC) infusion in patients with decompensated liver cirrhosis were determined. *Methods.* Ten patients who were diagnosed with decompensated liver cirrhosis during the period from September 2011 to July 2012 were enrolled in this study. The patients underwent TIPS (TIPS group) or combined treatment with TIPS and BMC infusion through the hepatic artery (TIPS+BMC group). All patients were monitored for adverse events, liver function and complications caused by portal hypertension during a period of 52 weeks. *Results.* The number of infused BMCs was $2.65 \pm 1.20 \times 10^9$. Significant improvements in the serum levels of albumin and total bilirubin and decreased Child-Pugh scores were observed in patients treated with both TIPS and BMCs ($P < 0.05$), whereas no such changes were observed in the TIPS group. Endoscopic findings showed that varices in the esophagus and the gastric fundus were alleviated after either treatment. All 10 patients showed a complete or partial resolution of ascites at 4 weeks. No major adverse effects were noted during the follow-up period for patients in either group. *Conclusions.* TIPS combined with BMC infusion is clinically safe; the treatment improved liver function and alleviated complications caused by portal hypertension; therefore, this combination has potential for treatment of patients with decompensated liver cirrhosis.

Key Words: *bone marrow cell, hematopoietic stem cell, liver cirrhosis, transjugular intrahepatic portosystemic shunt*

Introduction

Liver cirrhosis is a late stage of progressive hepatic fibrosis histologically characterized by distortion of the hepatic architecture and formation of regenerative nodules. Hepatitis B infection is one of the most common causes of liver cirrhosis worldwide. Liver cirrhosis usually progresses irreversibly into a decompensated stage, characterized by portal hypertension and liver dysfunction. Currently, there is no treatment for decompensated liver cirrhosis except for liver transplantation. Serious limitations are associated with liver transplantation including lack of donors, rejection, serious surgical complications and high cost. Therefore, novel therapeutic strategies for the treatment of decompensated liver cirrhosis are urgently needed.

In recent years, attention has been focused on stem/progenitor cells as a cell source for liver regenerative therapy. Adult human bone marrow is an accessible source of stem cells. It contains two major types of stem cells: hematopoietic stem cells (HSCs) and mesenchymal stromal cells (MSCs). HSCs are capable both of self-renewal and of differentiation into multiple hematopoietic lineages. MSCs are non-hematopoietic and represent a minute fraction (0.001–0.01%) of the total nucleated cell population in marrow [1]. Petersen *et al.* [2] presented the first report of trans-differentiation of marrow-derived cells into hepatocytes, and other researchers have shown that bone marrow HSCs are capable of differentiating into the liver cell lineage [3,4]. Previous studies have also shown that transplantation of bone marrow cells (BMCs) effectively reduces liver fibrosis, improves liver function and induces regeneration of liver in different animal models [5] through the paracrine action of BMCs as well as fusion with hepatocytes [6,7].

Correspondence: **Maotao Huang**, MD, Department of Gastroenterology and Endocrinology, 452nd Hospital of PLA, Chengdu 610021, China. E-mail: mysterioussc@qq.com

(Received 28 October 2013; accepted 4 April 2014)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2014.04.007

Injection of $CD34^+$ HSCs into the liver through the portal vein or hepatic artery increases levels of serum albumin and bilirubin in animal models or patients with chronic liver disease [8,9]. Pai *et al.* [10] reported that autologous infusion of expanded bone marrow–derived $CD34^+$ cells into patients with alcoholic liver cirrhosis through the hepatic artery decreased the serum levels of bilirubin and transaminase and lowered the Child-Pugh score.

Although BMC transplantation has been used successfully to treat chronic liver injury in animal experiments and clinical trials, it does not alleviate the increased portal hypertension in patients with decompensated liver cirrhosis. A transjugular intrahepatic portosystemic shunt (TIPS) is an artificial channel that is surgically inserted to establish communication between the inflow portal vein and the outflow hepatic vein. The procedure decreases portal hypertension and is reliable and almost non-invasive [11]. TIPS is recommended for treatment of variceal bleeding as well as refractory ascites caused by liver cirrhosis, especially during bleeding from varices in the esophagus and the gastric fundus [12–14]. Because TIPS and BMC transplantation effectively treat certain symptoms of liver cirrhosis, we hypothesized that treatment of patients with both TIPS and BMC infusion would improve liver function and reduce portal hypertension. This exploratory study was therefore designed to investigate the safety and feasibility of the TIPS and BMC infusion treatment of patients with decompensated liver cirrhosis.

Methods

Patients

Patients who were diagnosed with decompensated liver cirrhosis caused by chronic hepatitis B in our hospital from September 2011 to July 2012 were offered the opportunity to enroll in the trial. This study was approved by the Ethics Committee of the 452nd Hospital of PLA, Chengdu, China, and was registered with the identification number of ChiCTR-ONRC-12001892 (http://www.chictr.org/cn/). All patients provided written informed consent. Patients met all the following inclusion criteria: age 20–70 years, decompensated liver cirrhosis, abnormal serum albumin and/or bilirubin and/or prothrombin time, Child-Pugh score of $\geq$7 and no viable hepatocellular carcinoma shown on a computed tomography scan. The exclusion criteria were hepatic encephalopathy, variceal bleeding during the 2 months before enrollment, or evidence of extrahepatic biliary diseases, severe cardiac insufficiency or coagulation disorders. The patients were randomly assigned into two groups: patients who received TIPS treatment (TIPS group) and patients who received TIPS combined with BMC infusion (TIPS+BMC group).

Autologous BMC preparation

An aliquot of 200 mL of bone marrow was aspirated from both sides of the posterior superior iliac spine with the use of an 18-gauge myeloid puncture needle according to standard procedures. The aspirated bone marrow was anticoagulated with sodium citrate before it was collected in blood bags and sent to the center laboratory in ice boxes. BMCs were prepared within approximately 2–3 h after bone marrow aspiration. The cells were isolated by means of a Marrow and Cord Blood Stem Cells Isolation Kit (AVIC (Ningxia) Biology Co, Ltd., Yinchuan, Ningxia, China.). The cell suspensions were washed, concentrated and brought to a final volume of 10 mL. Of the final product, 1 mL was analyzed for cell number count, viability and endotoxin. The stem cell surface markers CD34-PE, CD45-FITC, CD105-PE and HLA-DR-PC5 were quantified through the use of appropriate antibodies (Becton Dickinson and Co, Franklin Lakes, NJ, USA) on a FACS (fluorescence-activated cell sorting) Calibur (Becton Dickinson).

TIPs procedure and BMC infusion

Before treatment, all patients underwent upper abdominal vascular enhanced three-dimensional computed tomography examinations to identify the spatial relationships of the portal veins and the hepatic veins and to exclude the possibility of liver tumors. After routine disinfection, the patient was given local anesthesia for TIPS treatment. The puncture was performed at the left or right internal jugular vein, and a Rupus-100 trocar needle (Cook Medical Inc, USA) was introduced into the portal vein through the internal jugular vein, guided by digital subtraction angiography. A membrane-covered stent (10 × 50 mm or 10 × 70 mm, Boston Scientific Corp, USA) was placed as guided by radiography. The BMC suspension was infused into the patient's hepatic artery through a puncture of the femoral artery under local anesthesia. Patients in the TIPS group received saline infusion instead. After the procedure, the patients were given 2500 U of low-molecular-weight heparin calcium subcutaneously every 12 h for 5–7 days. Warfarin (2.5–7.5 mg/d) was administered for 6 months. The dosage of warfarin was based on the international normalized ratio of 2.0.

Follow-up

The study protocol is shown in Figure 1. After TIPS and/or BMC infusion, patients were evaluated at 1,