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Currents Status and Prospects of Autologous Bone Marrow Cell Infusion Therapy for Liver Cirrhosis Patients

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Abstract We developed a novel cell therapy (ABM*i* therapy) using autologous bone marrow cells for liver cirrhosis patients. Our study depends on the findings from basic studies using GFP/CCl4 models. Beginning in November 2003, we started clinical trials of ABM*i* therapy and found it to be safe and effective for liver cirrhosis patients. Multicenter trials in Japan and Korea have also shown the effectiveness of ABM*i* therapy. In this review, we discuss translational research for the development of ABM*i* therapy for liver cirrhosis patients.

Key words: ABM*i* therapy, bone marrow cell, regeneration, cell therapy, liver cirrhosis

Introduction

We began clinical trials of autologous bone marrow cell infusion (ABM*i*) therapy for liver cirrhosis (LC) patients in November 2003. We then conducted a multi-center trial in Japan, in collaboration with a Korean group.[1)2)] We have now performed ABM*i* therapy in 23 LC patients, and have confirmed the safety and effectiveness of ABM*i* therapy. In this review, we discuss the current status and future prospects of ABM*i* therapy.

Basic study for development of ABM*i* therapy

Stem cells have been identified in human bone marrow (BM).[3)4)] Thus, BM is considered to be a novel source of cells for liver regenerative studies.[5)] We subsequently developed a GFP/CCl4 model that monitors the differentiation of bone marrow cells (BMC) into hepatocytes in CCl4-induced liver damage.[6)] In this GFP/CCl4 model, we found that BMC infusion is effective for improving liver damage (1. Liver function; 2. Liver fibrosis; 3. Survival rate) (Fig. 1). Infused BMC expressed matrix metalloproteinase (MMP9) and migrated into damaged areas.[7)] Finally, BMC infusion improved liver fibrosis and the liver microenvironment in cirrhotic mice.[8)] On the other hand, cell fusion is an important mechanism to explain the differentiation of BMC into hepatocytes. The phenomenon of cell fusion is important to consider in the differentiation mechanism of BMC.[9)10)] The karyotype of liver is known to be 2 N, 4 N, 8 N and 16 N. The significance of changes in liver karyotype require further analysis With regard to the differentiation of hepatocytes from stem cells, Epithelial Cell Adhesion Molecule (EPCAM) was identified as a marker of hepatic stem cells.[11)] However,

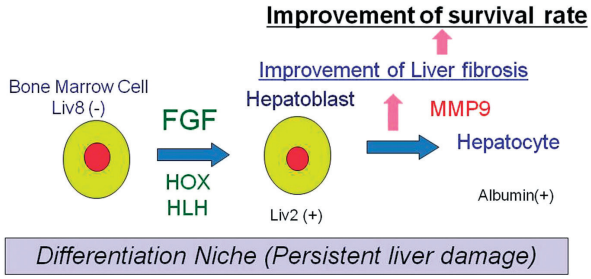

Fig. 1 Summary of basic research using GFP/CCl4 model.

Abbreviations: CCl_4: carbon tetrachloride; GFP: green fluorescent protein; BMI: bone marrow cell infusion; ABM*i*: autologous bone marrow cell infusion; EGFP: enhanced-GFP; MMP: matrix metalloproteinase; LC: liver cirrhosis; EPCAM: Epithelial Cell Adhesion Molecule; MNC: mononuclear cell; FACS: fluorescent-activated cell sorter; MMP9: matrix metalloproteinase 9

the lineage commitment of hepatocytes is not fully understood. The effects of stem cells on liver fibrosis were also analyzed by another group.[12)13)] Bone marrow cell infusion and mesemchyamal stem cell infusion were found to improve liver fibrosis in another mouse model. Based on these studies, bone marrow cell infusion appears to improve the microenvironment in the cirrhotic liver.[8)] This reparative mechanism was important for development of ABM*i* therapy for LC patients.

Clinical study: ABM*i* therapy for LC patients

We started a clinical trial on ABM*i* therapy for LC patients in November 2003 (Fig. 2). Subjects were LC patients with total bilirubin (TB) <3.0 mg/dL, platelets (Plt) >5 (10^{10}/L) and no viable hepatocellular carcinoma on diagnostic imaging. Autologous bone marrow (400 mL) was isolated from the ilium under general anesthesia. Mononuclear cells (MNC) were separated by cell washing and were infused via the peripheral vein. MNC characteristics were confirmed by fluorescence-activated cell sorter (FACS) analysis (CD34, CD45, c-kit). After ABM*i* therapy, liver function was monitored by blood examination for 24 weeks. From 400 mL of BM, we obtained MNC, and these were infused into LC patients. We then monitored liver function using ultra-sonography, computed tomography (CT) and laboratory tests.

Significant improvements in serum albumin levels and total protein were seen at 24 weeks after ABM*i* therapy ($P < 0.05$). Child-Pugh score improved significantly at 4 weeks and 24 weeks after ABM*i* therapy ($P < 0.05$). In addition, AFP and PCNA expression in liver biopsy tissue was significantly elevated after ABM*i* therapy ($P < 0.05$). No severe adverse effects were observed.[1)]

A multicenter trial of ABM*i* therapy in Japan was also carried out at Yamagata University beginning in February 2006. At Yonsei University in Korea, the Yamaguchi-Yonsei collaboration study for ABM*i* therapy started in November 2006 (Fig. 2). In these studies, the safety and effectiveness of ABM*i* therapy were confirmed. In India and Brazil, cell therapy using BMC for LC patient has also been studied, and its effectiveness has been confirmed.[14)]

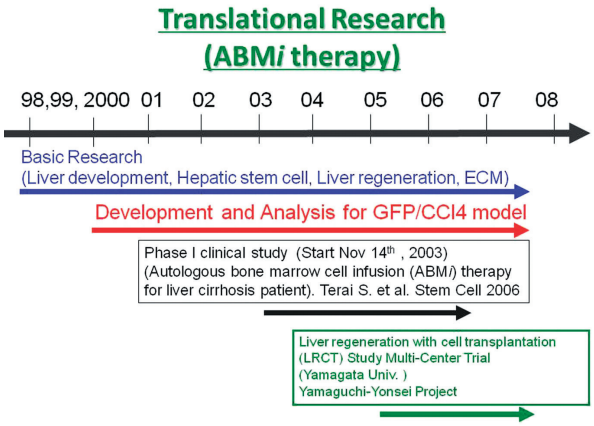

Fig. 2 Time line of translational research for ABM*i* therapy.

Future prospects

Based on previous clinical studies, we found that cell therapy using autologous bone marrow cell is safe and effective for LC patients.[1)2)] Recently, in Iran, a similar study was performed and the effectiveness of cell therapy using BMC was also confirmed.[15)16)] Although the mechanisms of stem cell differentiation within the human liver remain unclear, therapy using BMC has great potential for LC patients. A randomized multi-center clinical study is now needed for further application of ABM*i* therapy in LC patients.

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