+41 41 508 70 47
+381 62 25 61 92
www.startstemcells.com
consultant@startstemcells.com

Liver cirrhosis

Liver cirrhosis(LC) represents the end stage of various chronic liver diseases. It is accompanied by the development of liver failure and portal hypertension which lead to many serious systemic complications. Also, patients with LC have increased risk of hepatocellular carcinoma(HCC) development. It was showed that the risk of developing HCC depends on the underlying disease. In patients with autoimmune hepatitis there is low incidence rate of HCC(2.9% in 10 years)[1]. However, chronic hepatitis B is associated with high risk of the HCC development(19.8% in 13 years)[2].

There are different causes of liver cirrhosis development. It was noticed that some geographical distribution of the etiologic factors exist. For instance, in western countries the leading causes of liver cirrhosis are alcoholism, chronic hepatitis C virus infection and nonalcoholic fatty liver disease[3-5]. On the over hand, liver cirrhosis in the Asia-Pacific region mainly caused by chronic hepatitis B[6]. The other causes include inherited diseases such as hemochromatosis and Wilson's disease, primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis[7,8].

Unfortunately, liver transplantation remains the only treatment for end-stage cirrhosis. Due to the fact that transplantation is associated with many problems such as the shortage of donor organs, rejection, serious adverse effects of the long-term use of immunosuppressants and high cost the using of liver transplantation is limited for many patients[9].

Stem cell therapy of Liver cirrhosis

Stem cell therapy represents a promising alternative treatment for patients with LC. The therapeutic effects are based on the ability of stem cells to differentiate into functional hepatocytes. Thus, they promote to tissue regeneration by differentiating into the injured cells. Moreover, stem cells inhibit hepatocellular apoptosis and secrete cytokines, growth factors which enhance liver regeneration. Also, they block the production of extracellular matrix and promote to degradation of excessive extracellular matrix leading to inhibition of liver fibrosis and repair of injured liver tissues.

The first report of treating liver cirrhosis patients with autologous bone marrow derived stem cells(BMSCs) was published in 2006 by Terai S.et al. Nine patients with liver cirrhosis were enrolled in clinical trial. All of them received the infusion of autologous BMSCs. The follow-up period was 6 months. Liver function was monitored by blood examination. Significant improvements in serum albumin levels and total protein were observed at the end of follow-up period. Therefore the liver function has improved dramatically. Also, significantly improved Child-Pugh scores were noticed at 4 and 24 weeks. It is important to emphasize that infusion of BMSCs wasn't accompanied by any side effects in patients. It was the first clinical trial which confirmed the feasibility and safety of autologous bone marrow derived stem cells therapy for patients with liver cirrhosis[10].

Encouraging results were obtained in clinical trial conducted by Kim J.K. et al. in which patients with advanced liver cirrhosis were treated by autologous BMSCs infusion. There were ten patients with advanced LC due to chronic hepatitis B virus infection. After autologous BMSCs infusion liver function was improved significantly. It was noticed that median serum albumin and hemoglobin levels increased dramatically. Also, Child-Pugh scores were significantly improved at 6 months after received treatment. Moreover, all patients demonstrated improvement in quality of life. It is important to notice that there were no serious adverse reactions after stem cell therapy in any of the patients[11].

In 2011 Saito T. et al. reported the results of prospective controlled clinical trial in which positive effects of autologous BMSCs infusion were demonstrated for patients with alcoholic liver cirrhosis. Ten patients with advanced alcoholic liver cirrhosis who had abstained from alcohol intake for 24 weeks were recruited. All of them were divided into two groups of five people. Patients in first group were treated by autologous bone marrow stem cells which were injected intravenously. The second group was control. The follow-up period was 6 months. Liver function parameters and the level of the type IV collagen 7S domain as a marker of fibrosis were monitored in all patients during the observation period. The serum levels of albumin and total protein as well as the prothrombin time were significantly increased in stem cells treated patients. No changes were observed in the control group. Also, Child-Pugh scores were significantly improved in the treated group. Moreover, after stem cell therapy in four patients the serum levels of type IV collagen 7S

domain decreased indicating to amelioration of the degree of fibrosis. No serious side effects were observed after autologous BMSCs infusion[12].

In 2009 Kharaziha P. et al. demonstrated the results of clinical trial in which patients with liver cirrhosis were treated by autologous mesenchymal stem cells (MSCs). There were eight patients with end-stage liver disease. All of them received the injection of autologous MSCs. The follow-up period was 6 months. Treatment was well tolerated by all patients. No adverse effects were observed. Significant improvement of liver function was noticed. The serum levels of albumin were increased. The Model for End-Stage Liver Disease score decreased dramatically. The obtained data showed the feasibility, safety and efficacy of using autologous MSCs as a treatment for patients with end-stage liver disease[13].

Safety and positive effects of autologous MSCs therapy in liver cirrhosis were also showed in clinical trial by Peng L. et al. in 2011. It was a prospective controlled clinical study in which a total of 527 patients with liver failure caused by hepatitis B were enrolled. Among them a group of 53 patients (39 had liver cirrhosis) received autologous MSCs. No side effects related to MSCs transplantation were observed. The control group included 105 patients. The follow-up period was 24 months. It was showed that MSCs administration significantly improved the liver function. Levels of albumin, total bilirubin and prothrombin time as well as Model for End-Stage Liver Disease score were markedly improved two-three weeks after transplantation, compared with those in the control group. Also, there were no differences in incidence of hepatocellular carcinoma or mortality between the two groups over a two year follow-up period. Furthermore, among patients who received autologous MSCs therapy no significant difference was observed in the incidence of hepatocellular carcinoma or survival rate between patients with and without cirrhosis. It is established that liver cirrhosis represents one of the most important risk factors for development of hepatocellular carcinoma[6]. Therefore, obtained results provided evidence that autologous MSCs might protect the cirrhosis patients in regards to the occurrence of hepatocellular carcinoma and mortality. Also, it was confirmed that autologous MSCs transplantation is safe and effective in the treatment of liver disorder[14].

Successful application of autologous stem cells for the treatment of liver cirrhosis was showed in clinical trial conducted by Salama H. et al. in 2010. There were 48 patients with liver cirrhosis, 36 of them had chronic end-stage hepatitis C-induced liver disease and 12 others had end-stage autoimmune liver disease. All of them received autologous stem cells therapy. Treatment was well tolerated by all patients in general. The follow-up period was 12 months. A statistically significant decrease in ascites was observed in all patients. Also, it was noticed that clinical and biochemical improvement occurred in a large percentage of patients after transplantation of stem cells. Patients with hepatitis C-induced liver disease showed marked statistically significant changes in albumin, bilirubin, international normalized ratio and ALT levels. In group of patients with autoimmune liver disease significant improvement of albumin, bilirubin, international normalized ratio and ALT levels were also observed. The obtained results demonstrated that autologous BMSCs can be safely administered and represent a potential therapeutic modalities for patients with both viral and autoimmune-induced end-stage liver disease[15].

It is necessary to mention the results of randomized controlled clinical trial conducted by Lyra A.C. et al. in 2010 in which patients with advanced hepatic cirrhosis were treated by the infusion of autologous BMSCs. Thirty patients on the liver transplant waiting list were randomly divided into two groups. The first group included patients who received autologous BMSCs infusion. The second group was control. The follow-up period was 12 months. In the first 90 days it was noticed that transplantation of autologous BMCs significantly improved liver function. Albumin levels improved in treatment group compared with control group. Also, decrease of bilirubin levels was observed in the first group whereas in the control group it was increased. Moreover, Child-Pugh score improved in the stem cell therapy group. In addition, the model for end-stage liver disease score remained stable in the first group whereas it increased during follow-up in the control group. The changes observed in the clinical trial demonstrated the feasibility and efficacy of using autologous BMCs as a treatment for patients with end-stage liver disease[16].

In conclusion, according to available data from various clinical trials, using of autologous stem cells in the treatment of patients with LC is safe and effective. It was showed that stem cell therapy significantly improves liver functioning. Moreover, it has a great potential to reverse the damage occurred in the liver.

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