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Research Article

B-ultrasound-guided Intrahepatic Infusion of Autologous Bone Marrow Cells for Decompensated Cirrhosis

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Abstract

Objective: To study the therapeutic effect of B-ultrasound-guided intrahepatic infusion of autologous bone marrow nucleated cells on decompensated cirrhosis.

Methods: To observe the clinical treatment of 75 cases of decompensated cirrhosis. Among them, 30 cases received routine liver protection and diuretic treatment. 45 cases were treated by percutaneous transhepatic infusion of autologous bone marrow nucleated cells under the guidance of B ultrasound. There were no significant differences in liver function and blood routine indexes between the two groups before treatment ($p > 0.05$).

Results: The indexes of liver function and blood routine at different time periods of 1 month, 3 months, 6 months, and 12 months in the conventional treatment group did not change significantly. 6 cases died of liver failure within 1 year, the fatality rate was 20%. The indexes of liver function and blood routine of percutaneous liver transhepatic infusion of autologous bone marrow nucleated cells at 1 month, 3 months, 6 months, and 12 months under the guidance of B-ultrasound were significantly better than those of the conventional treatment group ($p < 0.05$). One case died of gastrointestinal bleeding in the group of percutaneous transhepatic infusion of autologous bone marrow nucleated cells guided by B ultrasound, with a fatality rate of 2.5%. Compared with the conventional treatment group, there were significant differences ($p < 0.05$).

Conclusion: Conventional drug therapy has no obvious effect on decompensated cirrhosis. Intrahepatic infusion of bone marrow nucleated cells can significantly promote liver function reconstruction in decompensated cirrhosis.

More Information

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Keywords: Decompensation period of cirrhosis; Bone marrow nucleated cells; Transplantation; B-ultrasound guidance; Intrahepatic infusion

Introduction

Conventional drug therapy has no obvious effect on decompensated cirrhosis. Liver transplantation is an effective treatment for decompensated cirrhosis. Due to liver strain and high cost, as well as the need to take lifelong immunosuppressive drugs, only a small number of patients choose liver transplantation. Stem cells have the potential to differentiate into a variety of cells. The bone marrow contains hematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells, and other undifferentiated cells. Transplantation of these undifferentiated cells into the liver can transform into hepatocytes in the liver microenvironment with hepatocyte damage, or secrete certain cytokines to promote the repair of damaged hepatocytes and improve liver function. Ultrasound interventional therapy is a new technique developed on the basis of ultrasound imaging to further meet the needs of clinical diagnosis and treatment. Under the monitoring and guidance of real-time ultrasound, liver puncture and infusion of stem cells were completed, and percutaneous transhepatic infusion of autologous bone marrow nucleated cells under the guidance of B-ultrasound was performed, and the clinical effect of conventional treatment was compared.

Clinical data and methods

Clinical data

From January 2020 to December 2022, a clinical study of autologous bone marrow nucleated cell therapy was

conducted in 75 cases of decompensated cirrhosis at Zigong Hospital Affiliated with Southwest Medical University, Shanghai Public Health Clinical Center, and Shandong Public Health Clinical Center. Enrolled patients were 18 years - 75 years old. Among them, 43 were males and 32 were females, aged 27 years - 74 years. CT examination indicated significant liver shrinkage, irregular morphology, cirrhosis, enlarged spleen, or splenectomy due to cirrhosis combined with hypersplenism. B ultrasound detected a small to moderate amount of abdominal fluid; the prothrombin time exceeded the normal value by more than 3 seconds. The test results of serum bilirubin, albumin, prothrombin time, WBC, hemoglobin, and platelet are shown in Tables 1-7. All patients were diagnosed with decompensated cirrhosis. Exclusion criteria: Patients with liver cancer and other malignant tumors, serious cardiovascular and cerebrovascular diseases or severe liver diseases and other serious complications, who were observed for less than 1 year in the conventional treatment group and selected liver transplantation or cell therapy, and did autologous bone marrow cell therapy for less than 3 times, and observed for less than 1 year.

Treatment methods

Among the 30 routine patients who met clinical statistics, drug treatment included antiviral drugs and hepatoprotective diuresis. In 45 patients treated with conventional therapy plus autologous bone marrow cells, 80 ml of bone marrow was collected by bone puncture at the anterior upper ridge of the iliac, and 10 ml of concentrated bone marrow nucleated cells were isolated by density gradient centrifugation. The number of nucleated cells and huge immature cells in the bone marrow were examined by an automatic blood cell analyzer. The number of concentrated bone marrow nucleated cells and the number of large immature cells in 10 ml were isolated. The autologous bone marrow nucleated cells were transfused through the intrahepatic portal vein under the guidance of B-ultrasound, and then the bone marrow plasma and red blood cells after the separation of nucleated cells were transfused back through peripheral veins. At 1 month and 3 months, the same method was used for intrahepatic portal vein infusion of autologous bone marrow nucleated cells under the guidance of B-ultrasound.

Table 1: Changes in prothrombin time before and after bone marrow cell therapy (seconds).

Group	before	1 month	3 month	6 month	12 month
Cell therapy	18.31 ± 1.59	17.13 ± 1.52	16.04 ± 1.31	14.93 ± 1.43	14.27 ± 1.65
Conventional treatment	18.73 ± 2.12	19.2 ± 2.36	20.5 ± 2.41	20.89 ± 1.90	19.42 ± 3.91
T	0.98	4.62	10.35	15.48	7.87
P	0.33	0.00	0.00	0.00	0.00

Note: Compared with before treatment, *$p < 0.05$.

Table 2: Changes in albumin before and after bone marrow cell therapy (g/L).

Group	before	1 month	3 month	6 month	12 month
Cell therapy	27.89 ± 5.54	32.49 ± 6.70	34.2 ± 7.82	35.76 ± 8.91	36.84 ± 8.42
Conventional treatment	29 ± 4.39	28.77 ± 3.13	27.75 ± 3.33	27.96 ± 2.82	26.63 ± 3.05
T	0.92	2.97	4.26	3.71	6.36
P	0.36	0.004	0.00	0.00	0.00

Note: Compared with before treatment, *$p < 0.05$.

Table 3: Changes in total bilirubin (umol/L) before and after bone marrow cell therapy.

Group	before	1 month	3 month	6 month	12 month
Cell therapy	41.87 ± 18.91	31.56 ± 13.3	28.02 ± 11.92 2	26.53 ± 10.72	23.25 ± 8.26
Conventional treatment	42.2 ± 14.51	46.2 ± 14.63	52.36 ± 14.29	49.15 ± 13.40	52 ± 12.93
T	0.08	4.49	8.00	8.09	11.76
P	0.94	0.00	0.00	0.00	0.00

Note: Compared with before treatment, *$p < 0.05$.

Table 4: Changes in white blood cells (×109/L) before and after bone marrow cell therapy.

Group	before	1 month	3 month	6 month	12 month
Cell therapy	3.21 ± 1.12	3.36 ± 1.12	3.72 ± 0.95	4.60 ± 3.75	5.68 ± 6.47
Conventional treatment	3.05 ± 0.72	3.01 ± 0.65	3.04 ± 0.65	2.78 ± 0.28	2.59 ± 0.28
T	0.69	1.55	3.42	2.65	2.61
P	0.49	0.13	0.00	0.00	0.01

Note: Compared with before treatment, *$p < 0.05$.

Table 5: Changes in platelet (×109/L) before and after bone marrow cell therapy.

Group	before	1 month	3 month	6 month	12 month
Cell therapy	45.56 ± 13.26	48.42 ± 13.37	49.33 ± 12.18	50.98 ± 13.05	54.34 ± 12.73
Conventional treatment	38.88 ± 9.68	39.78 ± 9.47	38.67 ± 9.52	38.38 ± 8.6	38.27 ± 6.89
T	2.37	3.06	4.04	4.65	6.31
P	0.02	0.00	0.00	0.00	0.00

Note: Compared with before treatment, *$p < 0.05$.

Table 6: Changes in hemoglobin (g/L) before and after bone marrow cell therapy.

Group	before	1 month	3 month	6 month	12 month
Cell therapy	98.16 ± 21.97	97.93 ± 19.37	106.24 ± 17.57	111.49 ± 15.76	114.63 ± 12.39
Conventional treatment	95.23 ± 20.97	93.73 ± 19.7	92.54 ± 17.51	91.26 ± 14.82	89.42 ± 16.28
T	0.58	0.91	3.31	5.58	7.61
P	0.57	0.36	0.00	0.00	0.00

Note: Compared with before treatment, *$p < 0.05$.

Table 7: Changes in ascites before and after bone marrow cell therapy (ml).

Group	before	1 month	3 month	6 month	12 month
Cell therapy	1577.78 ± 865.73	670.45 ± 527.64	313.95 ± 408.59	166.67 ± 325.10	87.5 ± 223.25
Conventional treatment	1716.67 ± 739.10	1950 ± 893.95	2160.7 ± 817.10	2425.93 ± 828.62	2822.22 ± 892.81
T	0.72	7.79	12.95	16.52	19.7
P	0.47	0.00	0.00	0.00	0.00

Note: Compared with before treatment, *$p < 0.05$.

Statistical methods

SPSS 20.0 statistical software was used for analysis. The chi-square test was used for counting data, and mean ± standard deviation (±s) was used for measurement data. $p < 0.05$ was considered statistically significant.

Results

There was no significant difference in liver function index and blood routine index before treatment between 30 patients in the conventional treatment group and 45 patients in the conventional treatment plus autologous bone marrow cell treatment group ($p > 0.05$). In 30 cases treated with conventional drugs, multiple indexes of liver function (prothrombin time, albumin, total bilirubin, ascites) and blood routine indexes did not improve significantly within one year, 6 cases died of liver failure, the case fatality rate was 20%. The indexes of liver function (prothrombin time, albumin, total bilirubin, ascites), peripheral blood leukocytes, and platelets were significantly improved after 1 month, and hemoglobin was significantly improved after 3 months ($p < 0.05$) in 45 patients who received autologous bone marrow nuclear cells through intrahepatic portal vein guided by B-ultrasound. Tables 1-7 lists the results. The number of huge immature cells in the bone marrow was detected by the five-classification hemocytometer. The number of nucleated cells in the 100 ml bone marrow sample with heparin anticoagulation was about 2-6 × 10^8. Among them, 3-6 × 10^6 giant immature cells were isolated by density gradient centrifugation, and 1-5 × 10^6 giant immature cells were found in 10 ml concentrated bone marrow cells. Intrahepatic portal vein infusion of autologous bone marrow nucleated cells guided by B-ultrasound does not require hospitalization or relevant examination and liver protection treatment can be completed within one week of hospitalization. The average treatment time from bone marrow collection to intrahepatic portal vein infusion of autologous bone marrow nucleated cells guided by B-ultrasound was 60 minutes. Among the 8 patients with more ascites and prothrombin time > 20 seconds after infusion of autologous bone marrow nucleated cells, real-time B-ultrasonography observed that there were cloud-like high-density images at the liver puncture site entering the low-density fluid area around the liver, indicating that the nucleated cells and blood in the liver blood sinuses entered the ascites from the liver puncture site. After an average of about 10 minutes of observation, the liver puncture site did not continue to bleed. One patient died of gastrointestinal hemorrhage complicated with liver failure within one year after B-ultrasound-guided percutaneous portal vein infusion of autologous bone marrow nuclear cells (2.5%), which was significantly lower than that of the conventional treatment group ($p < 0.05$). The indexes of liver function and blood routine of the patient returned to nearly normal.

Discussion

There are currently no particularly effective drug treatments for decompensated cirrhosis. Hypoproteinemia

and ascites are treated with transfusions of albumin and diuretic drugs. However, these treatments do not solve the underlying problem of cirrhosis, and patients gradually develop liver failure [1-5].

Liver transplantation is an effective treatment for decompensated cirrhosis. However, because of the strain on the liver, it is expensive and requires lifelong use of immunosuppressive drugs. Many patients are unable or unwilling to undergo a liver transplant. In recent years, many studies have shown that stem cells can differentiate into hepatocytes both *in vivo* and *in vitro* under suitable culture conditions. Japanese scholars used rat bone marrow stem cells and added different concentrations of HGF (hepatocyte growth factor) for induction and culture *in vitro*, and found that bone marrow stem cells can differentiate into hepatoid cells [6,7]. In 2005, German doctors reported that treatment with bone marrow stem cells in patients with cirrhosis complicated with liver tumor could promote residual liver hyperplasia after liver tumor resection [8]. Bone marrow stem cell transplantation is an effective method to treat liver cirrhosis.

In 2009, we performed splenectomy plus autologous bone marrow infusion via portal vein for AIDS patients with decompensated cirrhosis and achieved a good curative effect [9,10]. We then applied this approach to patients with hepatitis B decompensated cirrhosis without HIV infection and achieved better results [11]. However, decompensated cirrhosis usually has obvious coagulation disorders, hypoproteinemia, and ascites, and splenectomy has a greater risk. The operation of embedding the infusion port through the right gastric vein with a small incision in the upper abdomen is relatively simple, but there is still a risk of bleeding at the incision site [11]. After the operation, bed rest in the hospital is required for close observation.

From January 2020 to December 2022, 100 patients with decompensated cirrhosis were divided into 50 patients with conventional drug therapy and 50 patients with conventional drug therapy plus autologous bone marrow cell therapy. Results Twenty of the 50 patients in the conventional treatment group switched to liver transplantation or cell therapy in less than 1 year. In the autologous bone marrow cell therapy group, 5 cases underwent 1 B-ultrasound-guided intrahepatic infusion of autologous bone marrow cells, and the liver function improved and did not continue. In this study, 30 cases of conventional therapy and 45 cases of conventional therapy plus autologous bone marrow cell therapy were compared with clinical statistics.

After autologous bone marrow transplantation into the intrahepatic portal vein, bone marrow stem cells may differentiate into liver cells to improve liver function in the microenvironment with hepatocyte injury. With the improvement of cirrhosis, the hardness of the liver decreases, the portal vein pressure decreases, and hypersplenism will gradually ease. The number of white blood cells and platelets in peripheral blood increased significantly one month after autologous bone marrow cell therapy. There was no significant change in hemoglobin at 1 month ($p > 0.05$), but after 3 months, leukocyte, platelet, and hemoglobin all increased significantly. Therefore, in most patients, with the improvement of liver cirrhosis after autologous bone marrow cell therapy, hypersplenism will gradually ease. For some patients with large spleen and severe hypersplenism, splenectomy can significantly reduce the risk of surgery on the basis of improved liver function.

Five 20 ml syringes were used to collect bone marrow, each of which was prefilled with 4 ml of heparin saline. Each time 100 ml of bone marrow was collected, including 20 ml of heparin saline. About 10 ml of concentrated bone marrow cells were isolated by density gradient centrifugation. The number of nucleated cells in 100 ml bone marrow samples with heparin anticoagulation was about 2-6 × 10^8, among which 3-6 × 10^6 were giant immature cells. The density gradient centrifugation method was used to isolate 10 ml concentrated bone marrow cells with giant immature cells 1-5 × 10^6.

The lipids on immature cells are less than those on mature cells. When sulfurized amino acids are added to cell suspension, more sulfurized amino acids are bound to immature cells than mature cells due to different lipid occupy, and they are resistant to hemolysis agents. Therefore, immature cells can be kept intact, and mature cells can be dissolved, which can be detected by the impedance method. When the mature cells are broken up after the hemolysis is added to the blood sample, the immature cells can be detected by electrical resistance, while radio frequency technology is used to measure the size of the nucleus and the number of particles. A blood cell analyzer can initially detect the classification of cells in the bone marrow, the number of mature cells, mononuclear cells, and immature cells. There are almost no or very few immature cells in the peripheral blood. When there is a large amount of blood loss, mature blood cells are lacking in the peripheral blood, and immature cells in the bone marrow enter the peripheral blood. In leukemia, a large number of naive cells in the bone marrow enter the peripheral blood. So you can use a blood cell analyzer to show roughly the number of stem cells and the percentage of nuclear cells in the bone marrow blood.

We designed the intrahepatic portal vein infusion of autologous bone marrow nucleated cells under the guidance of B-ultrasound and compared the clinical effects of the conventional drug treatment group and the percutaneous transhepatic infusion of autologous bone marrow nucleated cells under the guidance of B-ultrasound. Results 30 patients in the conventional treatment group did not improve liver function for 12 months, 6 of them died of liver failure, and the mortality rate within 1 year was 20%. If no liver transplantation is performed for these decompensated

cirrhosis and only liver diuretic drugs are given, most patients may gradually develop liver failure within 3 years [10,11]. Serum albumin, prothrombin time, serum total bilirubin, and ascites were significantly improved at 1 month, 3 months, 6 months, and 12 months after percutaneous transhepatic infusion of autologous bone marrow nucleated cells guided by B-ultrasound in 45 cases (Table 1-7). Similar to relevant reports, this study suggests that portal vein infusion of autologous bone marrow nucleated cells can significantly improve liver function [12-20]. After the infusion of autologous bone marrow nucleated cells, the liver function was gradually improved, and the liver function was basically normal for a long time.

After entering the liver, bone marrow stem cells may gradually differentiate into functional liver cells in the liver microenvironment with liver cell damage, or secrete certain cytokines to promote liver function reconstruction. Generally, after about 1 week, patients feel relieved of abdominal distension, and ascites gradually decrease. The liver function improved significantly after 1 month. Autologous bone marrow stem cell transplantation will not be rejected, but after transforming into functional liver cells may not continue to prolifize, so we gave autologous bone marrow cells again through the portal vein one month later. Liver function is generally close to normal after 3 infusions. Some patients with severe cirrhosis require more transfusions of autologous bone marrow cells. With the gradual improvement of liver cirrhosis, portal vein pressure was gradually reduced, and hyplenism was gradually relieved. After re-examination, leukocytes, hemoglobin, and platelets in the peripheral blood also gradually increased significantly, and the increase of hemoglobin was slower than that of leukocytes and platelets, and the increase was not obvious until 3 months later (Tables 4-6). If the spleen is huge and there is no obvious relief of hypersplenism, splenectomy can be performed to relieve hypersplenism after liver function improves, which significantly reduces the risk of surgery compared with splenectomy at the stage of hepatic decompensation. The risk of autogenous bone marrow injection in the upper abdomen is lower than that of splenectomy. After the liver function is restored to normal, the infusion port can be surgically removed again, but permanent surgical incision scars remain in the abdomen.

Intrahepatic portal vein infusion of autologous bone marrow nucleated cells guided by B-ultrasound does not require hospitalization, and the average treatment time is 60 minutes. There is no surgical scar, and the treatment is almost noninvasive. Under the guidance of B-ultrasound, fine needle puncture directly transplanting bone marrow nucleated cells into the lesion area has many advantages, such as no operation, no perforation, safe fine needle puncture, minimal trauma, mild pain, and no need for hospitalization, which is in line with the treatment concept of modern medicine. The liver is adjacent to the diaphragm, and we usually puncture the liver through the right 5-7 intercostal space. Bone marrow nucleated cells were punctured and transfused with a No. 7 lumbar anesthesia puncture needle. Most patients did not experience any bleeding after the infusion of bone marrow nucleated cells. Even if there is a small amount of bleeding at the liver puncture site, the diaphragm slightly touches the bleeding site to help stop the bleeding. However, for patients with a large number of ascites, few platelets, and coagulopathy, the bleeding from the liver puncture site can enter the ascites after the injection of autologous bone marrow nucleated cells. We have observed in the real-time B-ultrasound detection that some patients with a large amount of ascites and coagulopathy can bleed from the liver puncture site for a long time. Therefore, for patients with decompensated cirrhosis with obvious coagulation dysfunction, more ascites, and significantly reduced platelets, abdominal catheters can be placed to release ascites, and albumin and prothrombin complex can be transfused to improve liver function, and then liver puncture can be performed to avoid the risk of intraperitoneal bleeding caused by liver puncture.

We accidentally found that autologous bone marrow nucleated cells were a better ultrasound developer by transhepatic portal vein infusion under the guidance of B-ultrasound. This may be because the syringe was pre-filled with heparin saline when the bone marrow was collected, preventing the bone marrow cells from clotting in the syringe. Nucleated cells in bone marrow combine with negative heparin charge, which prevents the aggregation of nucleated cells in bone marrow due to the mutual repulsion of negative charge. After the nucleated cells in the bone marrow are injected into the liver, the tissue density of nucleated cells is different from that of the liver, and because the negative charge forms an interface with the surrounding blood and liver tissue, ultrasonic waves will produce echo waves at the interface of different densities, which can be displayed on the B-ultrasound instrument. Therefore, the movement track of bone marrow nucleated cells in the stem can be clearly seen during the percutaneous intrahepatic puncture infusion guided by B-ultrasound. With the distribution of bone marrow nucleated cells into the liver through the hepatic sinuses, it can be seen that the brightness of the liver increases, and the brightness of the liver gradually returns to normal after about 10-20 minutes of B-ultrasonography. This may be because after the nucleated cells in the bone marrow are fixed in the liver, the nucleated cells in the bone marrow gradually fuse with the liver tissue, and gradually transform into hepatocytes, bile duct cells, intrahepatic vascular endothelial cells, and other structures needed for liver damage repair in the microenvironment with cirrhosis, so that liver function can gradually return to normal. For patients with obvious varicose veins in the lower esophagus, after autologous bone marrow cell therapy, gastroscopy ligation of varicose vessels in the lower esophagus or TIPSS intrahepatic portal-hepatic

vein shunt are still required to reduce portal venous pressure and prevent gastrointestinal bleeding.

Conclusion

From this study, it can be concluded that conventional drug therapy has no obvious effect on decompensated cirrhosis. Intrahepatic infusion of bone marrow nucleated cells can significantly promote liver function reconstruction in decompensated cirrhosis.

Authors' contributions

BL conceived and designed the experiments. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Zigong Hospital, Affiliated with Southwest Medical University. Written informed consent was obtained from all participants for the use of their samples for the detection and publication of their relevant data.

Patient consent for publication

All participants in this study provided written informed consent for the use of their samples and publication of their data.

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