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18

Treatment of the end Stage Liver Cirrhosis by Human Umbilical Cord Blood Stem Cells: Preliminary Results

Jong Yoon Bahk[1*], Zhengfu Piao[2*], Jae Hun Jung[3] and Hoon Han[4]
[1]*ChungAng University Medical School*
[2]*Beijing You-an Hospital, affiliated Capital Medical University & Beijing Institute of Liver Disease*
[3]*Gyeongsang National University Medical School*
[4]*Histostem & Huenna Ltd*
[1]*Korea*
[2]*China*

1. Introduction

The liver is a vital organ essential for life of vertebrates and other animals and plays a variety of metabolic functions, including glycogen storage, detoxification, plasma protein synthesis, the production of biochemicals for digestion and other roles. In the normal liver, hepatocytes physiologically renewed at very slow tempo. However, when injured by acute damage or drug intoxications, dormant hepatocytes re-enter the cell cycle and hepatic progenitor cells (HPCs) or oval cells are also thought to differentiate into hepatocytes, resulting in restoration of the structure and functions of the liver parenchyma (**1-2):** thus the liver has regenerative capacity. In severely overwhelmed cases, mature hepatocytes seemed to be blocked their proliferation activity, but HPCs are thought to be profoundly activated and play an important role in compensation of liver function (3, **4).** When liver injury and inflammation occur chronically, normal liver tissue is replaced by fibrosis, scare tissue, diffuse necrosis and regenerative nodules (**5)**, thus resulting in an irreversible chronic inflammation loss of liver function at the final stage: liver cirrhosis (LC) (**6, 7, 8, 9)**. Regardless of its underlying causes, the morphologic figures and complications caused by LC are similar and as disease progresses, complications develop. They include portal hypertension, varix, ascities, hepatic encephalopathy, idiopathic peritonitis and hepatic coma. The classification of LC is based on the etiology, such as alcoholics, post-hepatitic, biliary, cardiac, metabolic, inherited and drug induced cirrhosis. Incidence of the specific types of liver cirrhosis is different from area to areas. Alcoholic cirrhosis is the most common type in North America, Western Europe and South America. Abstinence from alcohol would prevent the complicating liver cirrhosis **(10).** One-fourth of the patients with repeated liver injuries and three fourth of post-hepatitic cirrhosis has the history of viral hepatitis (hepatitis B or hepatitis C). Post-hepatitic cirrhosis induced by those viruses is the

[*] Dr. Bahk and Dr. Piao are co-corresponding authors

most common cirrhosis found in South Eastern Asia and China including Korea, and second most common in America and Western Europe. In America, over 20% of patients infected chronically with HCV for more than 20 years were reported to develop post-hepatitic cirrhosis **(11)**. Biliary cirrhosis also occurs in association with injury of the biliary system or its prolonged impairment, which destroys liver parenchyme with progressive fibrosis. Billary, cardiac, metabolic, inherited and drug induced liver cirrhosis are much less common than alcoholic or posthepatitic cirrhosis (12). Avoidance of causative drugs, excessive protein intake and anti-infectious medicine were usually used as a first choice of treatment. Overall, about 75% of patients have progression and die within 5 years after the findings of the disease. Immune system is also deeply involved in the magnitude of cirrhosis. For example, in some instances cirrhosis can cause immune system dysfunction, leading to high susceptibility to infections or in other cases, autoimmune responses caused by the immunologic damage to the liver causing inflammation and eventually scaring and cirrhosis.

Until now, no simple hematologic diagnostic test for the LC has been developed **(13).** LC is diagnosed by clinical findings, such as chronic liver disease, reduced platelet count, esophageal varix, ascitis, portal hypertension symptoms, splenomegaly and changes in hematologic parameters (**14).** For the definite diagnosis, the liver biopsy is used, although invasive.

LC is the common end feature of an excessive and persistent scaring resulted from secondary fibrotic tissue remodeling followed by liver injuries and is regarded as irreversible disease.

In the rodents, both findings that carbon tetrachloride (CCl_4) treatment and bile duct ligation injury were reported to induce fibrogenesis (**15**), and spontaneous recovery from once established liver fibrosis **(16-17**), suggest that the hepatic fibrosis is a dynamic bi-directional event, and highlighted that the liver fibrosis is potentially reversible by antifibrotic therapy (**18**).

After hepatic injury, the hepatic stellate cells (HSCs), positioned in the center of the ongoing fibrogenesis of liver **(19)**, are activated to proliferate and to produce contractile elements such as α smooth muscle actin (α-sma), a major determinant of sinusoidal portal hypertension (**27**), and collagens (mainly type I and III) (**21**). This process is most likely mediated through the stimulation of cytokines, such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and endothelin (ET-1) (**20**), that are produced in a synergistic fashion of paracrine and autocrine from injured hepatic cells and inflammatory cells. The positive feedback loops between extracellular matrix and produced cytokines may also play an important roles in the acceleration of fibrosis (**22**).

Among them, TGF-β1 is thought to be the most significant factor for HSCs, because it upregulates the expression of its receptor (**23**, **32**), leading to raising the susceptibility to other mitogens such as PDGF, thrombin and angiotensin-II, etc. and eventually inducing proliferation of HSCs. It also accelerated the accumulation of HSCs in response to migration stimuli such as PDGF, vasoactive substance ET-1, and monocyte chemotatic protein (**24**). Extracellular matrix (ECM) modulates HSC functions by interacting it with PDGF, fibroblast growth factor (FGF), TGF-β, and matrix metalloproteinases (MMPs) that present in the space of Disse (**25**). Integrins expressed on HSCs play important roles in cell-matrix interactions for activation of latent TGF-β1 that modifies fibrogenesis.

In contrast, basement membrane tends to suppress the proliferation activity of HSCs and their collagen synthesis (**26**). The cirrhotic liver overexpressed the ET-1 (**28),** a stimulant of nitric oxide production from HSCs and autocrine, that plays important roles for their own proliferation. HSCs also secrete neutrophil and monocyte chemoattractants, such as colony

stimulating factors (CSF), MCP-1, and IL-8 that amplify the hepatic inflammatory response (**31**). Matrix synthesis is highly dependent on TGF β-1 and liver cirrhosis is closely related with ECM alteration in quantity and quality. Hepatic fibrosis is enhanced by synthesis of the neomatrix with type-1 collagen and the neomatrix degradation is inhibited by TIMPs (tissue inhibitor of metalloproteinases, TIMPs) (**33**). Thus activated HSCs are responsible for hepatic fibrosis. TIMP-1 inhibits apoptosis of HSCs (**33**) and induced promotion of perpetuation in hepatic fibrosis (**34**).

Prevention of the unnecessary medication is important for maintaining physiological conditions of the liver because it is very sensitive to medicines as well as microbial infection. The principle of treatment in LC is to remove such potential risk factors, and to correct the underlying invasive causes. Currently, treatments are focused on preventing complications such as ascites, esophageal varix and hepatic encephalopathy etc. Detection of serological changes at the early stage and regular follow up studies of those features are important for reducing the risky liver diseases such as LC. Usually, diet, bed rest, fluid restriction and diuretics, paracentesis and the liver transplantation are included in the treatment of the LC (**35-36**). For the treatment of decompensated LC, orthotopic liver transplantation is regarded as the only definitive therapeutic option (**36**). Several factors such as lack of available donors, combined with operative risks, complications associated with rejection, usage of immunosuppressive agents and cost-intensiveness make this strategy available to only a few people (**37, 41)**. Those problems inherent in the liver transplantation have prompted the search for alternative therapeutic methods for intractable liver diseases **(42).** Due to these problems, many LC patients die from life-threatening complications at relatively early age. Recently, along with the development of regenerative medicine, the use of pluripotent stem cells are proposed for recovering from the disease states as an alternative therapy (**38**). Fetal liver derived stem cells transplanted showed some improvement for conservative management in the end stage liver diseases (**39**). In clinical cell therapy, highly enriched cell numbers and the high repopulation potential are essential (**40**).

Liver cells obtained from the post-mortem have been also used for transplantation as the promising alternative (**43-46**). The liver cell transplantation is regarded as a less invasive, less expensive, and can alleviate the problem of organ shortage. Although there are some advantages in the liver cell transplantation over the orthotopic liver transplantation, long-term observation seems to be important for the evaluation.

Reversal of hepatic fibrosis and cirrhosis may be achieved by resolution of liver fibrosis, an increase of apoptosis of activated HSCs and collagenolysis **(47)**. In the CCl_4 rat model, the removal of CCl_4 increased the apoptosis of HSCs: 50% decrease in cell numbers at 72 hours post-removal. And antifibrotic therapy with NO donor decreased the HSCs number to 50% at 18 hours after the treatment **(48).** Induction of HSCs apoptosis degraded the matrix and recovered from the liver fibrogenetic conditions by removing the source of fibrotic neomatrix and TIMPs. **(49-50)** Biliary fibrosis was reversed after decompression of the bile duct ligation **(51**). Apoptosis of HSCs induces pro-MMP-2 activation **(52)** suggesting matrix remodeling, because MMPs specifically degrade collagens and non-collagenous substrates in matrix. The matrix degradation seems a pivotal initial step in the processes of liver fibrosis resolution. The most important event is the action of the interstitial collagenases, MMP-1, which cleaves the collagen-1 molecule **(53).** Collagenase activity resulted from the gap between activated MMPs to TIMPs. Increase of TIMP-1 expression occurs in parallel with progressive fibrosis. Sustained TIMP-1 expression means the failure in degradation of fibrosis and there is intrinsic link between HSC apoptosis and matrix degradation **(47)**. This

suggests that the proteolysis facilitates the resolution and repair of the injured liver **(54)**. The failure of degradation of fibrosis by collagenase impairs HSC apoptosis to induce the delaying or blocking the hepatocyte regenerative response **(54)**.

Recovery from the hepatic fibrosis has been reported in animal models after removal of CCl_4, which is used for induction of acute hepatitis **(55-61)** and clinical patients **(62-66).** Hepatic fibrosis, induced by several toxins **(57-59)** or ligation of bile duct **(60),** was reversed after the removal of the causes. In human, reversal of the hepatic fibrosis was reported in patients with alcoholic liver disease, hemochromatosis and other liver diseases **(62-64).** Reversal of the posthepatitic cirrhosis was also noted after improvement from the hepatitis B infection **(65).** Moreover, posthepatitic cirrhosis due to hepatitis C infection responded to the interferon treatment. **(66)**

Due to the limitation of the donor livers, the stem cell-based therapy has been suggested as a possible alternative therapy **(67).** Plasticity (trans-differentiation) and fusion activities inherent in stem cells are important for the development, regeneration and repair of liver organs **(68-70, 72)**. The stem cells produce various humoral substances (cytokines, growth factors) and factors for homing or migration, also. Those characteristics of stem cells are also important for the therapy **(71)**. **R**ecently, mesenchymal stem cell (MSC) derived from umbilical cord (UC) is regarded as a promising form for cell therapy because of their easy accessibility, MSC is much primitive than other tissue sources and do not express the major histocompatibility complex (MHC) class II (HLA-DR) antigens **(74)**. Previous studies have shown that

UCMSC are still viable and not rejected at 4 months after xenografts, without the need for immune suppression, suggesting that they are a favorable cell source for transplantation **(75-77).** UCMSC are able to differentiate into adipocytes, osteocytes, chondrocytes **(78,79)**, neurons **(80,81)**, cardiomyocytes **(78,82)** and renal tubule epithelial cells **(83)** upon cultured in induction media.

Initially, stem cell was isolated from bone marrow and characterized as plastic adherent fibroblastoid cell which has the capacity to generate some tissues **(84).** As study on stem cell has progressed, the stem cells were also found in the many other adult organs. The discovery of trans-differentiation potential **(85)** led us to use them in currently incurable or intractable diseases. Stem cells are used for two purposes: one is the trans-differentiation of stem cells into the specific cell types to replace the damaged or destroyed cells or tissues, and the other is the stimulation of the pre-existing native cellular repair mechanism in damaged organs, which may contain resident dormant stem cells. Currently, stem cell-based cell therapy is increasingly applied to the variety of diseases including cardiovascular issues **(86)**, diabetes **(87)**, musculoskeletal disorders **(88)**, renal problems **(89)**, impotence **(90)** and hepatic cirrhosis **(91)**. Stem cells can also be used for cytokine producer. Stem and other cells, which are genetically engineered for the production of cytokines, are also used as a vehicle of cytokines for targeting injury or disease sites, such as cancer sites **(92).** Stem cells, in particular committed to hepatocytes, can also be used for screening of drug toxicity **(93).**

Stem cells are classified into three, according to the differences in sources; embryonal stem cell (ESC), adult stem cell (ASC) and induced pluripotent stem (iPS) cell. ESC was developed by Thomson in Wisconsin **(94).** Fetal stem cells and amniotic stem cells may belong to this category. The differentiation potential of ESCs is great but the clinical use has been strictly limited due to the ethical problem and the tumorigenesis. The iPS cells were generated from mouse fibroblasts in 2006 by Yamanaka **(95)**, with introduction of four genes; Oct 3/4, Sox2, c-Myc, and Klf 4. The potentiality of iPS cells seems appears to be

unlimited for clinical applications, but the bio-characterization of iPS cells has not established yet, although they are under intensive study. The origin of ASCs first discovered is bone marrows (BMSC), and then, the ASCs were discovered from the many mature organs **(96-100).** Among these, bone marrow, adipose tissues (ADSC) and umbilical cord blood (UCBSC) derived stem cells are currently available for cell-based clinical therapies. BMSCs were actively applied for the treatment of hematologic diseases, already. The spectrum of clinical application of BMSCs continues to expand with the time. UCBSCs are collected from venous blood of the cord, but the cell number collected is not great. The UCBSC was applied for Fanconi's anemia **(101)** in 1986 between siblings. UCBSC seems to contain the most immature form of ASCs that have few chances to contact with environmental antigens, immunologically immature **(102)**. The UCBSCs do not raises any ethical concern at umbilical cord blood collection issues and collection can be processed without invasiveness for donors. The regenerative capabilities of UCBSC are similar to other types of ASC **(103).** Adipose tissue derived stem cell (ADSC) was first described by plastic surgeons **(104)**. The procedure harvesting adipose tissue is a common work among plastic surgeons for cosmetic or regenerative purposes, although it is somewhat invasive. The processed lipoaspirated tissues harbor abundant multipotent stem cells, which have similar potential with BMSC or UCBSC **(103).** ADSCs are permitted for autologous cell-based therapy in many countries.

The angiogenic, neurogenic and trans-differentiation potential of stem cells are the principal targets in stem cell based treatment **(105-110)**. Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet derived growth factor AB (PDGF-AB), transforming growth factor-β (TGF-β), and integrin β are stem cell angiogenic factors **(111,112).** Brain-derived neurotrophic factors, and neurotrophin-4/5 (NT4/5) **(113,114)** are stem cell neurotrophic factors. Reports on the effects of stem cells for improvement of vascular insufficiencies **(115-118)** and neuropathies **(119-121)** are accumulating these days.

Liver cirrhosis has been thought to be an irreversible disease. However, recent studies on cirrhosis of animals and humans suggest that liver cirrhosis is a potentially reversible disease. Stem cells, which are of anti-fibrotic and trans-differential potential, raised the possibility of their??? use for the treatment of liver fibrosis and cirrhosis as an alternative treatment replacing for liver transplantation.

In the present study we report our pre-clinical and clinical experiences of umbilical cord blood derived stem cell treatment for end stage liver cirrhosis, and discuss on the stem cell therapy in liver cirrhosis.

2. Materials and methods

2.1 Preclinical study

For the evaluation of the stem cell effect, we prepared the rat liver cirrhosis model with carbon tetrachloride (CCl_4). Male Sprague-Dawley rats (6weeks old, 180--200g) were used. The rats were grouped into 3, one control group (A) and two experimental groups, CCl_4 treated group (B) and CCl_4 treatment plus stem cell treated group (C). Cirrhosis was induced by intraperitoneal administration of CCl_4 (4:1 olive oil) at a dose of 0.1 mL/100 g body weights, three times a week. The same volume of olive oil only was intraperitoneally infused for control. For cirrhosis induction, CCl_4 was infused for 8 weeks. Human umbilical cord blood stem cells were infused at a dose of $1x10^6$ cells in 0.2 mL through the tail vein, and saline of same volume for control and CCl_4 only group. Rats were sacrificed at one, two

and four weeks and one pathologist evaluated the pathologic changes of liver. For pathologic evaluation, sections of approximately 4 μm thick were made and stained with haematoxylin and eosin (H&E) staining for routine histology, and Masson's trichrome (MT) staining for collagen.

2.2 Clinical study

Total 51 patients were participated in this treatment. The exclusion criteria for patient recruitment in stem cell treatment with liver cirrhosis were age limitation, over 70, and cancer. Among them, 46 patients (male 27 and 19 female) were classified as the Child-Pugh (CP) class C liver cirrhosis and 5 (four male and one female) were classified as the CP class B, finally, although they were classified as the class C from the other hospital, at the time of initiation. All participants are randomly involved in this treatment after reviewed the medical records of patients whose life expectancy were less than 6 months, evaluated by doctors in charge before involved in these treatments. 43 patients graduated from the college or upper rank school. The cause of cirrhosis was alcholic in 18 and posthepatitic in 36. Although 17 had the heart problem, it was not definite whether cardiac problem was the solitary cause of the cirrhosis or not, except two. The common clinical complications for portal hypertension were varix (41) and ascitis (34). For all patients, the explanation was made on the treatments rationale and material, and informed consents were obtained. All patients understood the treatment and no body has the opinion on baseline studies (Table 1). All participating patients were negative on cancer especially at baseline studies. They had specific conditions that could be related with liver cirrhosis and had the several complications induced from portal hypertension (Table 2).

Imaging	Ultrasound Exam. on Heart, Liver, Kidney CT on Abdomen
Endoscopic	Gastroscopy, Esophagoscopy
Blood & Serology	CBC, Serologic series 12
Urine	UA, Microscopic Examination
Cancer Marker	AFP, CEA
Others	VDRL, AIDS, Hepatitis B Ag/Ab, Hepatitis C AG/Ab., Electrolyte, C-reactive protein, ASO titer, EKG, ESR, RA factor
Coagulation	PT (INR)

Table 1. Base line studies.

The human umbilical cord blood stem cells (hUCBSC) were supplied by Histostem Co. Ltd. (Seoul, Korea) that was permitted for clinical use from the Korean government (KFDA).
The supplied stem cells were ABO, HLA-ABC, DR and sex matched for each patient, and the donor of each stem cell unit does not have any specific familial medical history. The stem cell markers of hUCBSCs were studies by flow cytometry. Total cell numbers that infused for each patient were around 1.5×10^7. hUCBSCs were infused percutaneous directly into liver parenchyma using needle under the ultrosonographic guide. All patients

were informed for usual life after one-day bed rest. Patients were followed every month from treatment at least for 6 times. At follow up check, patients were evaluated for prothrombin time, albumin, ascities and encephalopathy before and after each month from the stem cell therapy. Patients were evaluated for serological results, ascities and encephalopathy before and after each month from the stem cell therapy. The final survival was checked at November 30, 2010, 7 to 75 months from the initiation of the stem cell therapy.

Conditions manifested at initial visit	**Positive Patients Number**	**Negative Patients Number**
Alcohol Intoxication	18	33
Hepatitis History	36	15
Heart Problem	17	34
GB Problem	0	51
Varix	41	10
Ascitis	34	17
Hepatic encephalopathy	19	32
Peritonitis	1	50

Table 2. Patient condition at presentation.

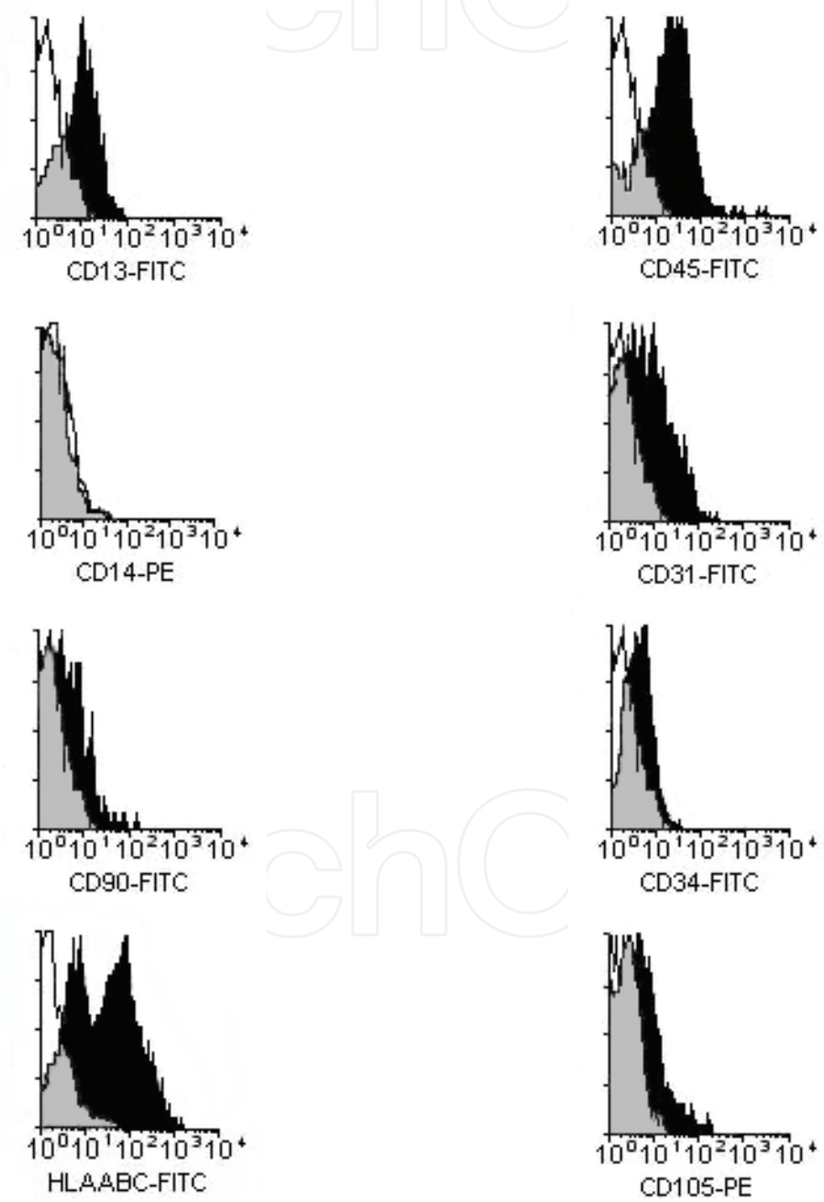
Study Items	Normal Value	Normal Patients	Range of Measure value		
			Patients Number		
Total Protein	6.3 - 8.2 g/dL	12	39		
Albumin	3.5 - 5.1 g/dL	5	1.0 - 2.0	2.1 - 3.0	>3.1
			17	26	3
ALP	38 – 126	13	38		
sGOT	5 – 40 IU/L	2	49		
sGPT	5 – 35 IU/L	1	50		
Total Bilirubin	0.2 - 1.3 mg/dL	14	<2mg/dL	2-3mg/dL	>3mg/dL
			18	16	3
Direct Bilirubin	0 - 0.3 mg/dL	17	34		
PT (INR)	<1.7	18	<1.7	1.7 - 2.3	>2.3
			18	22	11

Table 3. The results of serologic test before stem cell treatment.

3. Results

3.1 Stem cells

The flow cytometric results (Figure 1) of hUCBSCs were CD13(+), CD14(-), CD29(+), CD31(-), CD34(-), CD44(+), CD45(-), CD49e(+), CD54(+), CD90(+), CD106(-), AMSA(+), SH2(+), SH3(+), HLA-ABC(+) and HLA-DR(-).



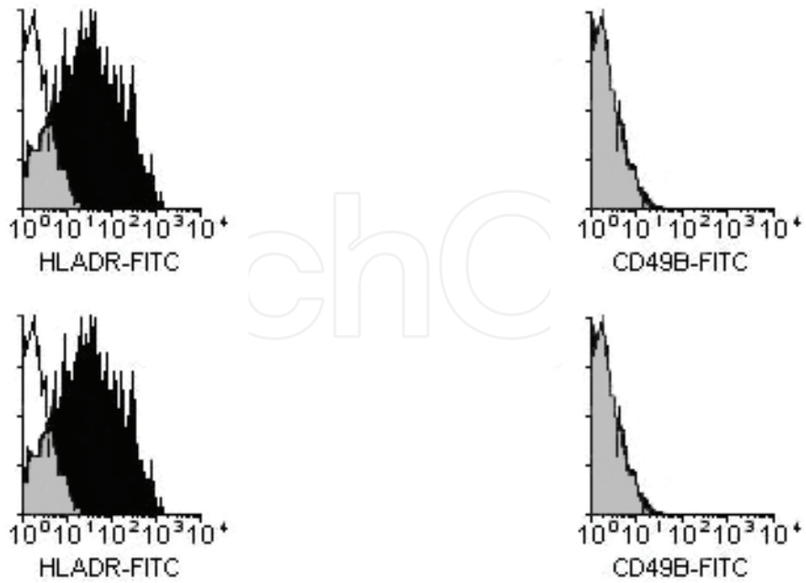


Fig. 1. Flow cytometric findings of the surface markers in hUCBSCs.

3.2 Preclinical study

The gross finding of the liver was examined (Figure 2) at 12 weeks after the starting the infusion of CCl_4. Compared to the control which have normal hepatic configuration (A), the CCl_4 infused rats (B) without stem cell treatment showed nodular surfaced distorted liver but CCl_4 infusion with stem cell treatment rat (C) showed recovered from the distorted nodular liver but much distorted compared with control (A).

The microscopic study (Figure 3), with haematoxylin and eosin (H&E) staining for routine histology and Masson's trichrome (MT) staining for collagen, were done on liver section at 1, 2 and 4 weeks after CCl_4 injection for 8 weeks. The control group showed normal

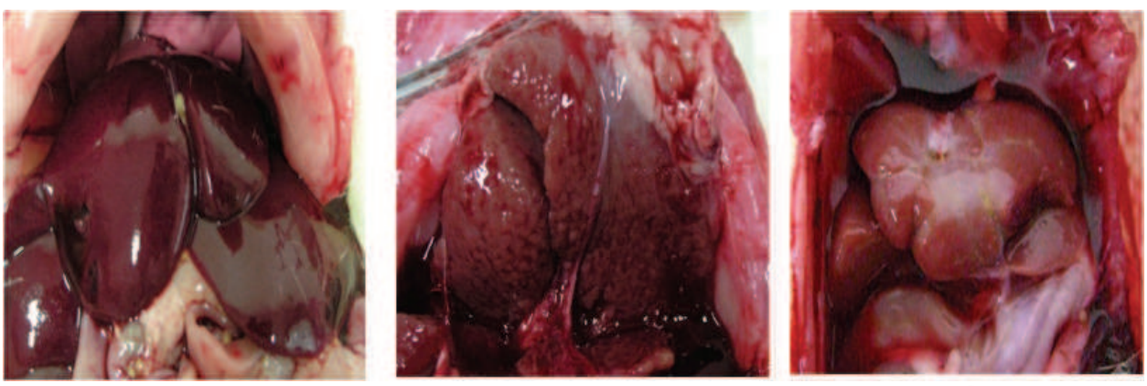


Fig. 2. Gross findings of the liver at 12 weeks after initiation of the CCl_4 intraperitoneal injections. A is control, B is CCl_4 intraperitoneal injection and C is CCl_4 intraperitoneal injection plus hUCBSC treated rat.

architecture at all livers (A). At 1 week after CCl_4 injection for 8 weeks, the experimental group showed the cirrhosis was induced in both without (B1) and with stem cell treatment group (C1), the fibrosis and deposition of collagen, separating liver parenchyma into large lobules. At 2 week after CCl_4 injection for 8 weeks, there was definite difference between without stem cell treatment group and with stem cell group. The without stem cell treatment group (B2) showed increased septa composed of fibrosis and collagen. Compared to without stem cell group, with stem cell group (C2) showed reduced septa than first week after CCl_4 injection for 8 weeks. At 4 week after CCl_4 injection for 8 weeks, the without stem cell treatment group (B3) showed much increased septa composed of fibrosis and collagen and there is new fine septa were appeared within large lobules. In with stem cell treatment group (C3), the septa composed of fibrosis and collagen were reduced and the lobules are closely approximated each other. In these pathologic findings, experimental group without stem cell therapy induced the extensive fibrosis / cirrhosis and the fibrosis was progressed as the time passing (B). These CCl_4 induced fibrosis / cirrhosis was proved by disruption of liver parenchyma architecture, extension of fibers, large fibrous septa formation, pseudolobe separation and collagen accumulation. These alterations were progressed and increased in fibrosis and collagen deposition with time passing. The histopathological findings confirmed that the cirrhosis was significantly reduced by stem cell infusion.

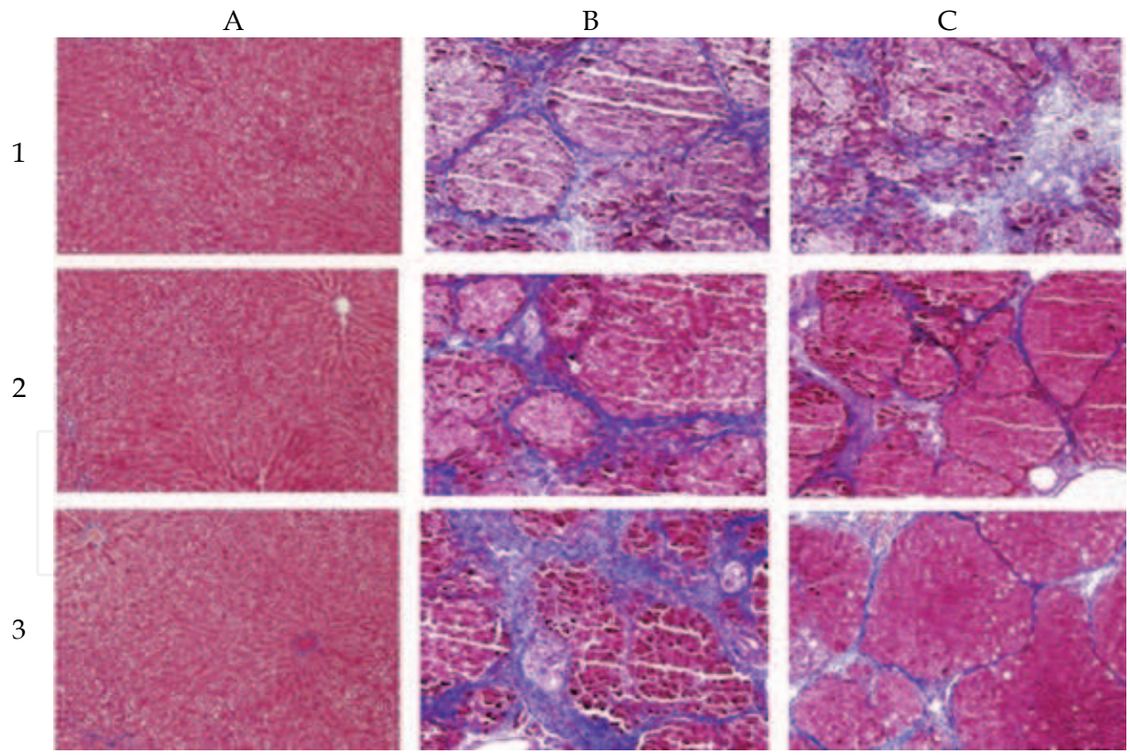


Fig. 3. Microscopic findings of the rat liver in control and experimental rats. A from control rat, B from CCl_4 intraperitoneal injection only rat and C from CCl_4 intraperitoneal injection with hUCBSC therapy rat. 1 at 9 week from CCl_4 intraperitoneal injection, 2 at 10 weeks and 3 at 12 weeks.

3.3 Clinical study

The participants' age ranged from 49 to 68 years old (mean 54.7 years). The mean age of the CP class C were 56.2 and class B were 48.9. After the stem cell therapy, there was no death within 6 months from the initiation of the stem cell therapy. There were 9 deaths from 7 months within 12 months, 19 deaths from 13 months within 2 years, 13 deaths over 2 year within 3 years, 3 deaths over 3 years within 5 years. 7 are living now, from 11 to 75 months from stem cell therapy, and among them, two are living over 5 year. During the procedure (Figure 4), the bleeding from the liver was not remarkable. Clinically, ascitis was improved in 21 and 5 did not show any ascitis within 6 months. Among 5, 2 are alive more than 5 years (Figure 5). In hepatic encephalopathy, all patients showed improvement in symptom. But there is no patient who lived more than 30 months. Serologic follow up check was done in all patients (Table 3 and 4). In serologic test, although there were some changes in the

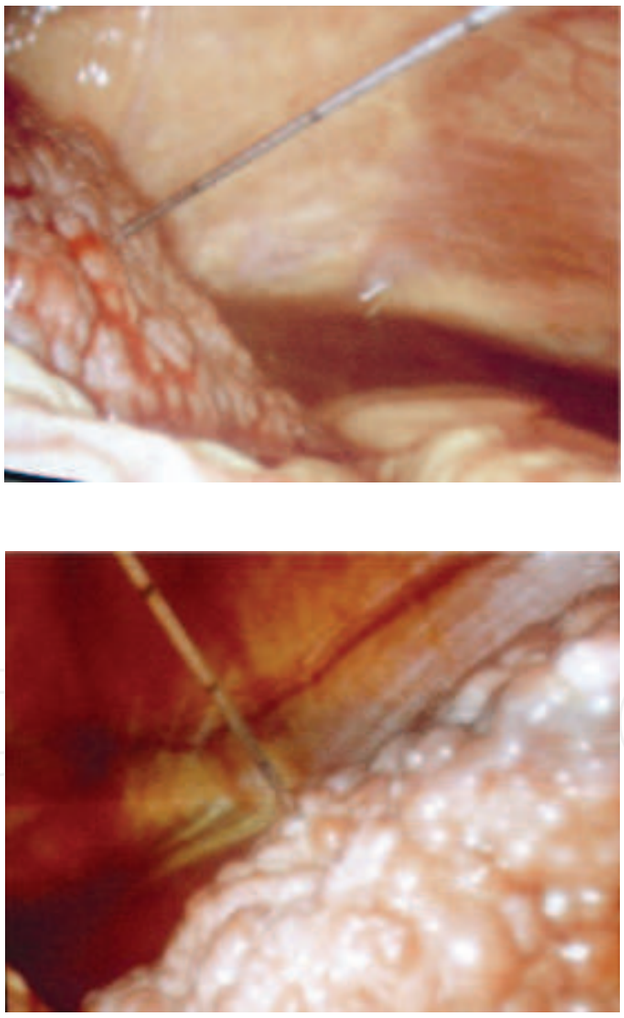


Fig. 4. Laparascopic view of percutaneous injection of the stem cells into liver. The needle is inserted into the nodular surfaced liver.

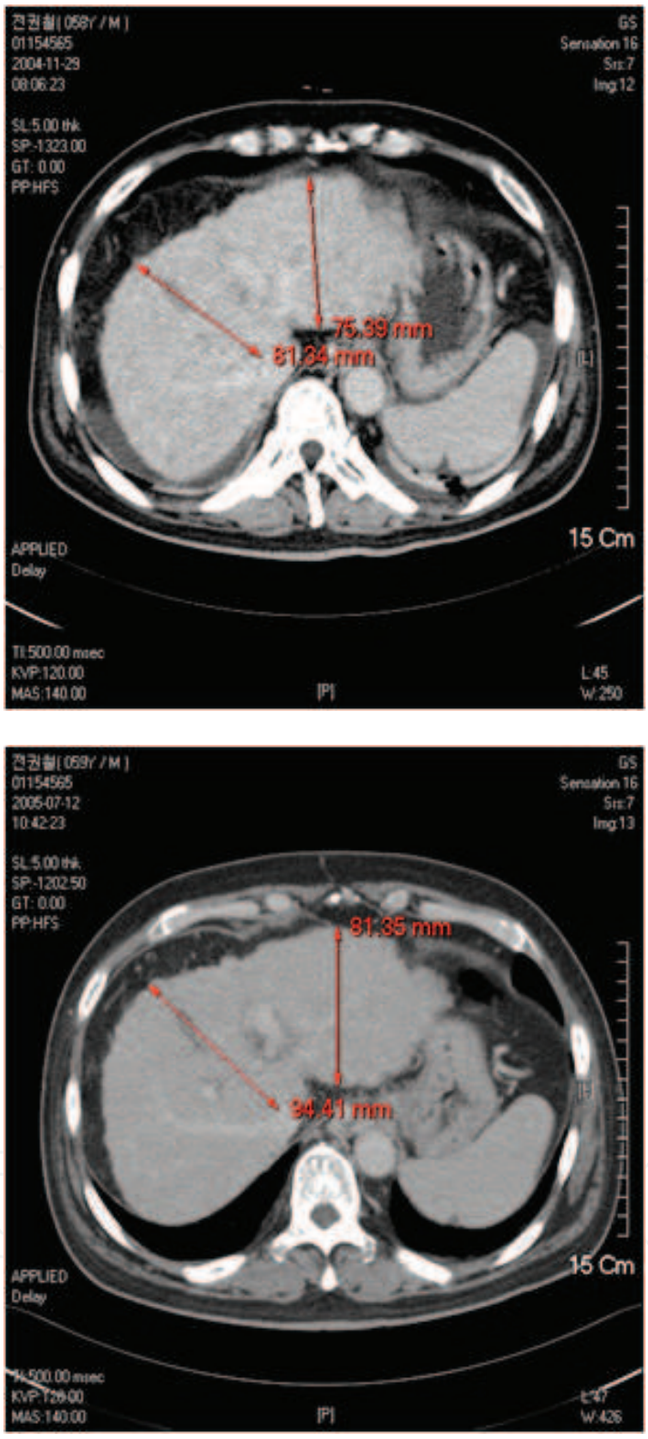


Fig. 5. CT findings from the patient who is living more than 5 years. A is CT taken just before (Feb. 21, 2005) stem cell therapy and B is CT taken was after 5 months (July 23, 2005). The measured liver size was increased from 689.98 CC to 915.36 CC and hepatic density is lowered suggesting release of fibrosis.

results, it was impossible to get the uniform information in trends of change. Among 39, those who had abnormal protein level, total protein level was normalized at 6, but among 39, only 2 were normalized in albumin. In these 2, one had normalization of total protein level but one did not, meaning some difference in improvements among sub-group.

Study Items	Normal Value	Normal Patients	Range of Measure value		
			Patients Number		
Total Protein	6.3 - 8.2	18(+6)	33(-6)		
Albumin	3.5 - 5.1	7(+2)	1.0 - 2.0	2.1 - 3.0	>3.1
			12(-5)	25(-1)	7(+4)
ALP	38 - 126	17(+4)	34(-4)		
sGOT	M: 17 - 59 F: 14 - 36	9(+7)	42(-7)		
sGPT	M: 21 - 72 F: 9 - 52	12(+11)	39(-11)		
Total Bilirubin	0.2 - 1.3	16((+2)	<2mg/dL	2-3mg/dL	>3mg/dL
			21(+3)	14(-2)	0(-3)
Direct Bilirubin	0 - 0.3	18(+1)	33(-1)		
PT (INR)	<1.7	23(+5)	<1.7	1.7 - 2.3	>2.3
			23	22	6

Table 4. Serologic test results at post stem cell treatment 6 months.

4. Discussion

Most of the chronic liver injuries, regardless of their causes, progress to liver fibrosis and eventually result in cirrhosis that is thought to be irreversible, and the liver cirrhosis (LC) results in impairment of the hepatic function becoming a massive health care burden worldwide. LC is induced by many different causes, such as chronic viral hepatitis, toxic damage including alcohol, parasitic disease, inborn errors of metabolism, and non-alcoholic fatty liver disease etc. The cause of LC has a wide geographic variation. Alcohol is the most common cause in western countries (122) and liver disease is the 5th most common cause of death in the United Kingdom (123.) Recent reports on pre-clinical and clinical studies suggested that LC could be reversible. HSCs activated upon liver injury are thought to be responsible for collagenogenesis and fibrosis in extracelluar matrix (124, 125). Modulation of HSC activity (126.), promotion of HSC apoptosis (127), blocking of matrix formation (128) or anti-proliferation measures on matrix fibrogenic and contractile response to HSC and degradation of established matrix (125,129) could be taken as potent strategies for reversal of LC. In addition to these strategies, stem cell therapy with multiple cytokine production and trans-differentiation potential would be a new option (130) for reversal of established LC.
HSCs are responsible for the production of extracellular matrix at the center of LC. Therefore, the inhibition of the activation of HSCs (131-133) or promotion of HSC apoptosis

(134-135) would be an eradicating measure for fibrogenesis. The platelet-derived growth factor (PDGF) is the most potent mitogen for HSCs, thereby inhibitors against PDGF have been tried (136-138). For the patients whose fibrosis is progressing, the matrix formation blockers (139) or anti-proliferation measures to matrix fibrogenesis (140) would be another measure for the reduction of LC. HSCs contribute to portal hypertension through multiple mechanisms including collagen deposition, vasoconstriction, and regulation of sinusoidal structure. So, the reduction of contractile response to HSC (141) would be a measure reducing critical complications induced by portal hypertension. Increasing the degradation of established matrix (125,142,142) would be an ideal strategy for reversal of LC.

Recently developed stem cell therapy (143-144) may be a promising strategy for LC, because we can expect them to trans-differentiate into hepatocytes and to stimulate the differentiation of hepatocytes from the dormant stem cells remaining in injured host liver and stem cells in bone marrow through cytokine production (145). BMSC, ADSC, and UCBSC are currently used for stem cells therapy. Unseparated bone marrow cells and purified BMSCs have been used for the treatment of the hematopoietic diseases for more than 50 years. Their application fields are expanding day by day. For advanced liver diseases such as cirrhosis, stem cell engraftment can be most promising strategy after the organ transplantation (146). In animals treated with CCl_4 intraperitoneal infusion, the percentage of lin- Sca-1+ cells in the bone marrow and peripheral blood increases twofold at twenty-four hours later (147) and this increase peaks at day one in the bone marrow and day two in the peripheral blood (147). This finding suggests that bone stem cells started to proliferate and migrate to the periphery (147). Requirement of engraftment of stem cells into the patients with the severe liver diseases are increasing. For BMSC therapy, bone marrow aspiration is inevitable and bone marrow aspiration is a invasive procedure. Differentiation potential, and maximal life span of BMSC decrease with increasing age (148-149). In post-hepatitic LC patients, the autologous BMSCs are not suitable for the treatment, because their proliferation capacity is restricted significantly in the tissue environment of end stage of the disease (150)

ADSCs were relatively recently found. Their easy isolation (151) and high differentiation potential (152) may be attractive as alternative promising stem cells in place of BMSCs. In the meantime, UCBSCs has been used for several diseases. UCBSCs have advantages over other types of stem cells, because umbilical cord blood (UCB) can be obtained without invasiveness or harm to donor. Cells from UCB have many advantages because of the immaturity of stem cells compared to other types. Moreover, UCBSCs provide no ethical barriers for basic and clinical applications (153-154). Recently, UCB banking for transplantation of haematopoietic stem cells is increasingly in many institutions (155) due to their easy availability and the ready on shelf system. All clinical papers are of autologous or allogenic stem cell therapy. Among the adult stem cells, UCBSCs are youngest stem cells and they had only few chances to contact with environmental antigens. UCBSCs have higher proliferative potential than BMSC and higher expression of the endothelial-specific markers following endothelial differentiation (156).

When we decided to attempt to treat with UCBSCs for some diseases, we carefully consider suitable cell (origin) for target organs, cell numbers, route for administration, supplementation of growth factors and post-treatment cares. In spite of increasing requirement of stem cell treatment, the protocol for stem cell treatment has not established until now. Because the preparation of the stem cells for enough quantity that has the identical or similar biology is not easy, we should consider the measure to secure the

enough number of stem cells, culture or mixing of different donors. Although many trials with stem cell were done, most of them are autologous rather than allogenic. Basically, many diseases caused by different pathogenesis, it needs different treatment. In case of LC, bone marrow stem cells from liver cirrhotic caused by chronic hepatitis B infection showed significantly lower S-phase fractions and growth factor (IGF-1, PDGF α, PDGF β) receptor expression than normal people (157). It indicates that allogenic stem cell therapy is better than autologous in LC. We suppose that allogenic stem cell therapy would be reasonable in case of the hereditary or genetic disease. The number of stem cells in specific treatment has not decided yet, too. Moriya et al. (158) used $1x10^5$ embryonal stem cells in animal study model (mice). Liu et al.(159) used $5x10^5$ endothelial precusor cells in 150 g animal study model(rat). Yan et al. (160) infuse $3x10^6$ hunman UCBSCs in mice. Although these reports are animal study, when we calculate the cell number in weight to weight (animal to human) base, the cell number for human treatment should be over $1x10^8$ cells. But Mohamadnejad et al. (161) infused 31.73×10^6 autologous bone marrow mesenchymal stem cells for four liver cirrhotic patients via peripheral vein. So, the cell number for treatment of disease should be standardized according to the disease, although there should be many trials for standardization.

In introduction part of this chapter, we mentioned on the characteristics of stem cells, homing or migration (someone uses 'targeting'). Homing in stem cell biology means stem cell moving toward injury site along the some chemotactic signal (162). So, many animal experiments localized the targeted stem cells, which were infused via tail vein (260-164) or intraperitoneal infusion(165) and sometimes via specific route such as portal vein(166). And in case of cellular cardioplasty for myocardiac infarction model, several different infusion has been used, direct intracoronary (167), intravenous with homing(168) and mobilization with homing from bone marrow or peripheral blood(169). In cellular cardiomyoplasty, according to the cell delivery system, the results are different. Least effective method is mobilization from peripheral blood or bone marrow(170-171) and most effective method is intracoronary infusion (172-173). And in case of intravenous infusion, according to the blood flow, all blood in body has to pass the lung and some proportion of infused stem cells are trapped at the lung (174-175). Some are trapped at other organs(176).

There are many growth factors which support or enhancing stem cell activities. The supplement of growth factors into stem cell culture media or coupled treatment of stem cell with growth factors was reported in vitro and in vivo, already. Supplement of growth factors in culture system has been done from long ago in culturing technique and sometimes essential job for culture, but the coupled clinical treatment of stem cell with growth factors (177-178) are in different conditions (177-178). Although we use the various growth factors for in vitro culture system, there are a few growth factors which are permitted to use for human from the health concerning governmental bureau. So, it is not easy to search the simultaneous application of the growth factor as an auxiliary measure for stem cell therapy (178-180).

Post-treatment care are difficult to mention at present time because there is no report for large sized world wide data related on the stem cell treatment on specific disease until now. Although the data on the post-treatment care for better maintenance of end result of stem cell therapy are needed, it is not proposed yet. As in the material and method, we had the clinical treatment for end-stage LC whose survival was expected to be less than 6 months. The result showed that the all patients had improved survival although their initial life expectancy was based on the doctor's experiences. Other laboratory data had some

differences among patient to patient, but most of the patients who had the hepatic encephalopathy and more than half of the ascitic patient had the improved symptoms.

In author's stem cell treatment for LC, we used umbilical cord blood stem cells (UCBSCs), only. UCBSCs produce and secrete various humoral factors (cytokine or growth factors)(261-262). They are stem cell factor (SCF), macrophage colony stimulating factor (M-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), vascular endothelial growth factor (VEGF), interleukin 1β (IL-1β), IL-6, IL-8, IL-11, IL-12, IL-15, stromal cell-derived factor 1α (SDF-1α), hepatocyte growth factor (HGF), epitehlial cell-derived protein 78 (ENA-78), Growth-related oncogene (GRO), oncostain M (OSM), monocyte chemoattractant protein-1 (MCP-1), fibroblast growth factor 4 (FGF-4), FGF-7, FGF-9, granulocyte chemotactic protein 2 (GCP-2), Insulin like growth factor (IGF), Insulin-like growth factor binding protein 1 (IGFBP-1), IGFBP-2, IGFBP-3, IGFBP-4, Interferon-gamma-inducible protein 10 (IP-10), Leukemia inhibitory factor (LIF), migration inhibitory factor (MIF), macrophage inflammatory protein 3α (MIP-3alpha), osteoprotegerin, (OPG), pulmonary and activation-regulated chemokine (PARC), Placenta growth factor (PIGF), transforming growth factor β1(TGF-β1), TGF-β2, TGF-β3, tissue inhibitors of matrix metalloproteinases 1 (TIMP-1) and TIMP-2.

Among these cytokines, some of them are favorable for antifibrosis and some are prone to enhance the fibrosis in liver. The results of balance between favorable and unfavorable effects among the various cytokines secreted from the UCBSC would predict treatment or aggravation of LC. Among above cytokines that UCBSCs secrete, HGF, IGF-1, IGFBP and interferon would be closely related with fibrolysis of liver but TGF-β1 and TIMP will promote hepatic fibrosis. Although the results of UCBSC treatment on LC patient showed much improvement on symptoms and liver function related laboratory data, we do not know the interaction between those cytokines, which has some antagonistic effects.

We injected stem cells into liver parenchyme directly under the ultrasound guide. Total cell numbers were around 1.5×10^7 hUCBSCs in each patient. Until now, there are many trials with animal model of LC but no author has presented the proper cell number for stem cell treatment on LC. Around 1×10^6 cells were infused intravascularly in rat or mouse liver cirrhosis model and they showed improvement in hepatic functions. Although the most of patients in our treatment group showed favorable effects on LC after stem cell therapy, the role of cell number in LC treatment was not definite. We infused the stem cells directly into the target organ, liver, the cell number that authors used were much less than animal experiments. In spite of our small numbered stem cells, there was some improvement in data for hepatic function.

As mentioned before, we infused the stem cells directly into the liver parenchyma. The infusion route would be closely related with results of the stem cell treatment. In systemic intravenous administration would be the easiest method in stem cell treatment but the trapping of stem cell by lung or some reticuloendothelial system, during circulation before homing, would lessen the treatment effects. Although there are several data related with homing after intravenous infusion of stem cells, it is unclear that how many portions of infused cells are homed. To increase the homed stem cells in target organ, some therapies try to infuse the stem cells via selective artery, although it is invasive. More invasive therapy would be the orthotopic infusion/transplantation of stem cells under direct of indirect visualization. Surgically exposed target lesion would be treated with high accuracy and possibly permit reduced numbered stem cell implantation with same effects. Modern developed imaging modalities enabled us target the lesions with very high accuracy with

less damage. The choice of the route for best effective targeting the lesion would be depend on the imaging modality and technique of operator.

Average life expectancy of the LC patients chose randomly by authors is expected to no more than 6 months. After stem cell therapy, no body had gone within 6 month and two of 51 patients survived more than 5 years. There would be many causes contributing to the improvement of patients' survival. Among them, the role of stem cell for improvement of survival and laboratory data should get attention. Although Kögler and Liu reported the various cytokines, which they detected from UCBSCs, there would be many unknown cytokines (humoral factors), which is secreted by the UCBSCs. We do not know the mechanisms that improved survival and laboratory data in liver function, but the HGF, INF and IGF and IGFBP would be closely related with fibrolysis and collagenolysis.

Originally HGF has mitogenic, motogenic, morphogenic and anti-cell death activities (181), and identified and cloned as a mitogen protein for hepatocyte (182-183). HGF stimulates expression and activity of proteases involved in breakdown of ECM proteins, including urokinase-type plasminogen activator and matrix metalloproteinases. In LC, HGF suppress the proliferation while promoting apoptosis of α-SMA-positive cells in the liver, that histological resolution from liver cirrhosis.(181) Growth inhibition and promotion of apoptosis in portal myofibroblasts by HGF would be an ancillary resolution for liver fibrosis/cirrhosis.(184) Mesenchymal stem cells (MSCs) can prevent the development of liver fibrosis, and hepatocyte growth factor (HGF) can also attenuate liver cirrhosis. (185) HGF/MSCs significantly inhibit the formation of liver fibrosis in rats, while MSCs and HGF had synergistic effects in the process. The antifibrosis effect of HGF/MSCs may have contributed in modulating the activation and apoptosis of HSCs, elevating the rHGF expression level, and decreasing the TGF-beta 1 secretion of activated HSCs.(185). In CCl_4-induced liver cirrhosis rat model, hBMSCs treatment results were induced by two mechanisms that work together: the differentiation of transplanted hBMSCs into liver cells that are able to restore normal liver functions, and expression by production of MMP by hBMSCs which is involved in the repair of liver fibrosis. (186).

In interferon, there are many subtypes but only a few of them are reported to be produced from the UCBSCs. Among them, interferon alpha (IFN-α) suppress the progression of hepatic fibrosis (187), and lowers fibrosis scores, tissue hydroxyproline levels, liver TIMP-1 and elevate MMP-13 levels. IFN-α has role to increases HSC apoptosis, too(188). TIMP is the representative fibrosis favoring molecule and MMP is the representative molecule for fibrolysis. IFNγ have the hepatic protective effect by inhibition of adenosine A2A receptor function in hepatic stellate cells (191). Among those cytokines, M-CSF promotes the interferone production.

Insulin-like growth factor-1 (IGF-1) and major portion of the circulating IGF-1 synthesized in the liver are hepatic origin in normal state, but in LC the plasma levels are diminished (190-191). When the deficient IGF-1 in LC was replaced by daily administration of recombinant IGF-1, it induces a significant improvement of liver function (192). In liver, the expression of IGF-1 receptor is poor (193-194) and it seems that IGF-I acts on nonparenchymal cells. IGF-1 improves the liver structures and function through the activation of tissue-repair mechanism at non-parenchyma. It seems that there is an amplification loop which are favoring the efficacy of the therapy because the IGF-1 upregulate the IGF-1R in hepatic septa (195). In liver cirrhosis, the supplementation of IGF-1 induces the antifibrogenic and hepatoprotective effects. (196) Aside from the antifibrogenic effects, patients treated with stem cell showed improved serum albumin and enzyme levels indicating liver functions and these results are supposed due to IGF effects.

This discussion reviewed the mechanism that stem cell have favoring results related with LC. But it would not be the total mechanisms that explain the favoring effect of stem cells on LC. Among the above mentioned cytokines produced by UCBSCs, there are reports for characterization of cytokins, such as SDF-1(197) IL-8 (198) M-CSF (199), RANTES (200), MIP-1α (201), IP-10 (202) and EGF (203), but the most of them are not directly related with improvement of LC.

Until now, there are several clinical papers, around 10, on the results of autologous stem cell treatments, either autologous bone marrow derived stem cells or mobilized stem cells and fetal stem cell for the end stage liver cirrhotic patients. All of them are backing further clinical application of stem cell on liver cirrhosis. Most of the reports were related with the treatment with small number of patients, less than 10 patients, except for India (204). And the routes of stem cell infusion, aside from the mobilized hepatopoietic stem cells, are portal vein or hepatic artery with a few intravenous infusions. With these data, it is practically difficult to compare the superiority of the route of stem cell infusion due to small patient number in each case. Although there are common findings are improvement of hepatic conditions.

In the clinical data that we introduced in this chapter, all patients were supposed to be gone within 6 months before they were involved in stem cell therapy, meaning terminal state LC patients. Two third in 51 had the ascitis and more than one third had the hepatic encephalopathy. After single stem cell therapy using UCBSC, most of the hepatic encephalopathy patients and more than two third of ascitic patients were improved in symptom or responded to medical therapy who were refractory to previous therapy. But other data for liver function, albumin, aminotransferases, bilirubin or prothrombin time has irregular responses. About half of patients of ascites who had the improved symptoms showed improved albumin values but difficult to pull out any reproducible protocol, requiring further study. Because we choose the patients randomly in loose exclusion criteria, it would be difficult to get the objectively reproducible data from our experience for base of any protocol in stem cell therapy. But we can get some idea of trends of stem cell therapy for LC, although we had a single treatment. The stem cell therapy improves the ascitis and hepatic encephalopathy definitely in some group of patient, although we do not characterized this group, yet. In case of hepatic encephalopathy, the most of patients showed objectively improved symptom but we do not presume the mechanism, too. At the point of patient survival, all patients survived more than 6 months, although it would be difficult to believe the patients' initial life expectancy as the objective data. The patients' survival would not be related with liver function only but would be the summation of the various indexes of life signs. The most common side reaction that related with the stem cell treatment was pain, experiencing during stem cell infusion procedures. As mentioned before, much of the stem cell biology including producing cytokines has been proven already but it would be a tip of iceberg. We treated the patients who were regarded as the hopeless condition in point of survival improvement based on the reasonable solid animal study results of stem cell therapy, but they lack objective clinical efficacy aside from trend of stem cell therapy. So, to get the further acquisition of objective clinical effects and base on proper protocol, large multicenter trial on stem cell therapy for liver cirrhosis would be needed.

5. Conclusion

The conclusion of our review and experience is that there are lots of beneficial effects of stem cells on end stage liver cirrhosis and stem cell therapy serves for prolongation of the life and

improvement of quality of life. The analysis of author's experience lacks objectivity. And if there is the more systemic multicenter large numbered study, we can make the proper guideline for stem cell therapy on liver cirrhosis.

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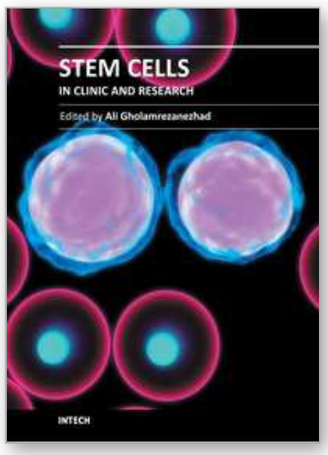

Stem Cells in Clinic and Research

Edited by Dr. Ali Gholamrezanezhad

ISBN 978-953-307-797-0
Hard cover, 804 pages
Publisher InTech
Published online 23, August, 2011
Published in print edition August, 2011

Based on our current understanding of cell biology and strong supporting evidence from previous experiences, different types of human stem cell populations are capable of undergoing differentiation or trans-differentiation into functionally and biologically active cells for use in therapeutic purposes. So far, progress regarding the use of both in vitro and in vivo regenerative medicine models already offers hope for the application of different types of stem cells as a powerful new therapeutic option to treat different diseases that were previously considered to be untreatable. Remarkable achievements in cell biology resulting in the isolation and characterization of various stem cells and progenitor cells has increased the expectation for the development of a new approach to the treatment of genetic and developmental human diseases. Due to the fact that currently stem cells and umbilical cord banks are so strictly defined and available, it seems that this mission is investigationally more practical than in the past. On the other hand, studies performed on stem cells, targeting their conversion into functionally mature tissue, are not necessarily seeking to result in the clinical application of the differentiated cells; In fact, still one of the important goals of these studies is to get acquainted with the natural process of development of mature cells from their immature progenitors during the embryonic period onwards, which can produce valuable results as knowledge of the developmental processes during embryogenesis. For example, the cellular and molecular mechanisms leading to mature and adult cells developmental abnormalities are relatively unknown. This lack of understanding stems from the lack of a good model system to study cell development and differentiation. Hence, the knowledge reached through these studies can prove to be a breakthrough in preventing developmental disorders. Meanwhile, many researchers conduct these studies to understand the molecular and cellular basis of cancer development. The fact that cancer is one of the leading causes of death throughout the world, highlights the importance of these researches in the fields of biology and medicine.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jong Yoon Bahk, Zhengfu Piao, Jae Hun Jung and Hoon Han (2011). Treatment of the end Stage Liver Cirrhosis by Human Umbilical Cord Blood Stem Cells: Preliminary Results, Stem Cells in Clinic and Research, Dr. Ali Gholamrezanezhad (Ed.), ISBN: 978-953-307-797-0, InTech, Available from: http://www.intechopen.com/books/stem-cells-in-clinic-and-research/treatment-of-the-end-stage-liver-cirrhosis-by-human-umbilical-cord-blood-stem-cells-preliminary-resu

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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No.65, Yan An Road (West), Shanghai, 200040, China
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