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Koo Jeong Kang, MD, PhD, Professor, Division of Hepatobiliary Pancreatic Surgery, Department of surgery, Keimyung University Dong-San Medical Center, Daegu 41931, South Korea

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World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, etc. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, etc.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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Stem cell transplantation for the treatment of end-stage liver disease

Dong-Bo Wu, En-Qiang Chen, Hong Tang

ORCID number: Dong-Bo Wu (0000-0003-4500-047X); En-Qiang Chen (0000-0002-8523-1689); Hong Tang (0000-0002-9790-6225).

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Dong-Bo Wu, En-Qiang Chen, Hong Tang, Center of Infectious Diseases, West China Hospital of Sichuan University, Sichuan 610041, Chengdu Province, China

Corresponding author: En-Qiang Chen, MD, PhD, Associate Professor, Doctor, Center of Infectious Diseases, West China Hospital of Sichuan University, No.37 Guo Xue Xiang, Wuhou District, Chengdu 610041, Sichuan Province, China. chenenqiang@scu.edu.cn

Telephone: +86-28-85422859

Fax: +86-28-85423056

Abstract

The past two decades have witnessed an explosion of research and clinical application of stem cells, transforming the field of regenerative medicine. Stem cell transplantation has already been performed to treat patients with cancer, liver diseases, and various types of chronic diseases. Indeed, stem cell-based therapies are effective in many diseases, and provide novel insights into the treatment of end-stage liver disease. Several clinical trials have indicated the efficacy profiles of stem cell transplantation in patients with end-stage liver disease, including liver cirrhosis, liver failure, and liver tumors. Animal models of acute liver failure have also provided important insights into the safety, mechanisms, and efficacy of stem cell therapies. Nevertheless, excitement due to this promising field must be tempered with careful and calculated research. In particular, studies on the quality, safety, and efficacy of stem cell transplantation are needed to ensure that qualified products are tested in well-designed clinical trials and approved by governments. Therefore, further investigations are required to effectively balance the safety with the innovation of stem cell transplantation research toward the effective treatment of end-stage liver disease.

Key words: Stem cell transplantation; End-stage liver disease; Clinical treatment; Efficacy; Safety

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Core tip: Stem cells have the capacity for multiple rounds of self-renewal and differentiation, and play important roles in numerous biological functions. Treatment of end-stage liver disease *via* stem cell transplantation has emerged as an effective therapeutic alternative in clinical practice. However, caution should be paid to ensuring the safety and efficacy of stem cell transplantation to avoid the use of products that are not rigorously tested that may put patients at risk.

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INTRODUCTION

Due to their capacity for multiple rounds of self-renewal and differentiation, stem cells play roles in numerous biological phenomena including immunomodulation, anti-inflammation, anti-apoptosis regulation, angiogenesis, promotion of tissue repair, and production of growth factors^[1-3]. The term “stem cells” represents cells of various origins, including mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells, hepatic progenitor cells, and hematopoietic stem cells^[1,4-8]. However, MSCs are the most common stem cell source for basic and clinical research given the lack of ethical constraints regarding their usage and availability^[4,8].

In the past few decades, stem cell transplantation has emerged as a novel and promising therapy for the treatment of patients with cancer, nervous system diseases, eye diseases, orthopedic disorders, diabetes mellitus, and liver diseases. Moreover, advances in stem cell transplantation from basic and translational clinical research have yielded improvements in the survival of patients with benign and malignant hematologic disorders^[9] and stem cell transplantation has proven to be an effective therapeutic alternative for central nervous system diseases, including Alzheimer’s disease^[10]. Moreover, stem cell therapy has been shown to delay or suppress the progression of end-stage liver disease^[4,8,11].

TREATMENT OF END-STAGE LIVER DISEASE VIA STEM CELL TRANSPLANTATION

To date, there have been numerous clinical studies on stem cell transplantation for the treatment of end-stage liver disease, demonstrating its side effects and efficacy profiles. Furthermore, there were 139 clinical trials registered, including 27 ongoing clinical trials, on the association between stem cell transplantation and liver disease in accordance with the guidelines outlined in ClinicalTrials.gov on July 01, 2018 (<http://www.clinicaltrials.gov>). Of these, 52 clinical trials were focused on liver cirrhosis (LC), nine on liver failure, and six on liver cancer.

Previous studies indicated that MSC transplantation could constitute an effective treatment for LC. In a multicenter, randomized, open-label, phase 2 trial, autologous bone marrow-derived transplantation of MSCs safely improved liver function and facilitated the quantification of fibrosis following liver biopsy in patients with alcoholic cirrhosis^[7]. Another open-label, paired, controlled study from China demonstrated that transplantation of umbilical cord-derived MSCs (UC-MSCs) also improved liver function and reduced ascites in patients with chronic hepatitis B (CHB) and in decompensated LC^[1]. MSC transplantation was also shown to improve liver function in LC patients with autoimmune diseases^[12]. However, another randomized, controlled phase 2 trial yielded no evidence to support the benefits of granulocyte colony-stimulating factor (G-CSF) administration alone or supplementation of G-CSF with stem-cell transplantation, with no significant differences in improved liver dysfunction or decreased fibrosis in LC patients after stem cell transplantation^[3]. These conflicting results may be associated with differences in LC etiology, an increased frequency of adverse events, and differences in stem cell types used in these studies.

Moreover, studies involving animal models of acute liver failure have shown strong evidence pointing to the success of MSC transplantation in improving liver function, inhibiting hepatocyte apoptosis, and promoting hepatocyte proliferation in animal models of acute liver failure^[6], suggesting that MSC transplantation may be used to treat liver failure. In 2012, Shi *et al.*^[5] performed a case-control study to evaluate the safety and efficacy of UC-MSC transplantation in CHB patients with acute-on-chronic liver failure (ACLF); and found increased survival rates, accompanied by reduced end-stage liver disease scores and enhanced liver function. Another study on MSC transplantation for the treatment of ACLF patients also achieved similar results, in which the treatment increased the 24-wk survival rate, improved liver function, and decreased the incidence of severe infections^[11].

Moreover, we recently conducted a systematic review and meta-analysis of MSC transplantation in ACLF patients, which showed that the treatment significantly reduced mortality rates, without increasing the incidence of severe complications^[13]. There were also no differences in the incidence of severe complications (*e.g.*, encephalopathy, hepatorenal syndrome, gastrointestinal bleeding) between the standard medical treatment and the MSC treatment group in ACLF patients^[5]. Nevertheless, long-term follow-up is needed to confirm the safety of MSC transplantation.

FUTURE PERSPECTIVES

Studies on stem cells and regenerative medicine have received increasing attention in the life sciences in the past 20 years. Stem cells are undifferentiated cells that undergo both self-renewal through symmetric cell division and differentiate into specialized cells, tissues, and organs through asymmetric cell division. Stem cell-based therapies have proven to be effective in many diseases, providing novel insights into the treatment of end-stage liver disease. Indeed, in recent years, numerous studies have reported stem cell-based “cures” for an extraordinary and implausible range of medical conditions.

However, research on the safety and innovation of stem cell transplantation for end-stage liver disease must be well-balanced. Some risky procedures performed without substantial evidence have led to medical accidents, leading to blindness, paralysis, or even death^[14].

Moreover, both the administration and the government must be involved in regulations and advisement to ensure the quality, safety, and efficacy of stem cell transplantation. Two finalized tenders regarding guidelines to establish a more stringent policy framework were issued by the Food and Drug Administration (FDA), which included the requirement of sponsors to document a biological license application, request permission from the agency before proceeding to FDA-supervised clinical trials, and obtain agency approval before marketing^[15]. To promote rapid yet responsible advancements in the fundamental knowledge and clinical application of stem cells and regenerative medicine, the International Society for Stem Cell Research (ISSCR) has issued three guidelines^[2]. The 2016 guidelines revise and extend two prior sets of guidelines (ISSCR, 2006; ISSCR, 2008) and address an integrated set of principles and best practices for ensuring progress in basic, translational, and clinical trials^[2]. Overall, safe and effective stem cell transplantation for treating end-stage liver disease will only be achieved from well-designed clinical trials and qualified products approved by the FDA or the government, while avoiding the high risks of unproven cell therapy products.

REFERENCES

- 1 Zhang Z, Lin H, Shi M, Xu R, Fu J, Lv J, Chen L, Lv S, Li Y, Yu S. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. *J Gastroenterol Hepatol* 2012; **27** Suppl 2: 112-120 [PMID: 22320928 DOI: 10.1111/j.1440-1746.2011.07024.x]
- 2 Daley GQ, Hyun I, Apperley JF, Barker RA, Benvenisty N, Bredenoord AL, Breuer CK, Caulfield T, Cedars ML, Frey-Vasconcels J. Setting global standards for stem cell research and clinical translation: The 2016 ISSCR Guidelines. *Stem Cell Reports* 2016; **6**: 787-797 [PMID: 27185282 DOI: 10.1016/j.stemcr.2016.05.001]
- 3 Newsome PN, Fox R, King AL, Barton D, Than NN, Moore J, Corbett C, Townsend S, Thomas J, Guo K. Granulocyte colony-stimulating factor and autologous CD133-positive stem-cell therapy in liver cirrhosis (REALISTIC): an open-label, randomised, controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2018; **3**: 25-36 [PMID: 29127060 DOI: 10.1016/S2468-1253(17)30326-6]
- 4 Tao YC, Wang ML, Chen EQ, Tang H. Stem cells transplantation in the treatment of patients with liver failure. *Curr Stem Cell Res Ther* 2018; **13**: 193-201 [PMID: 29303079 DOI: 10.2174/1574888X13666180105123915]
- 5 Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shi J, Chen L, Lv S. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Transl Med* 2012; **1**: 725-731 [PMID: 23197664 DOI: 10.5966/sctm.2012-0034]
- 6 Huang B, Cheng X, Wang H, Huang W, la Ga Hu Z, Wang D, Zhang K, Zhang H, Xue Z, Da Y. Mesenchymal stem cells and their secreted molecules predominantly ameliorate fulminant hepatic failure and chronic liver fibrosis in mice respectively. *J Transl Med* 2016; **14**: 45 [PMID: 26861623 DOI: 10.1186/s12967-016-0792-1]
- 7 Suk KT, Yoon JH, Kim MY, Kim CW, Kim JK, Park H, Hwang SG, Kim DJ, Lee BS, Lee SH. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. *Hepatology* 2016; **64**: 2185-2197 [PMID: 27339398 DOI: 10.1002/hep.28693]
- 8 Wang J, Cen P, Chen J, Fan L, Li J, Cao H, Li L. Role of mesenchymal stem cells, their derived factors, and extracellular vesicles in liver failure. *Stem Cell Res Ther* 2017; **8**: 137 [PMID: 28583199 DOI: 10.1186/s13287-017-0576-4]

- 9 **Little MT**, Storb R. History of haematopoietic stem-cell transplantation. *Nat Rev Cancer* 2002; **2**: 231-238 [PMID: [11990860](#) DOI: [10.1038/nrc748](#)]
- 10 **Kwak KA**, Lee SP, Yang JY, Park YS. Current Perspectives regarding Stem Cell-Based Therapy for Alzheimer's Disease. *Stem Cells Int* 2018; **2018**: 6392986 [PMID: [29686714](#) DOI: [10.1155/2018/6392986](#)]
- 11 **Lin BL**, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, Liu QL, Peng L, Li JG, Mei YY. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial. *Hepatology* 2017; **66**: 209-219 [PMID: [28370357](#) DOI: [10.1002/hep.29189](#)]
- 12 **Liang J**, Zhang H, Zhao C, Wang D, Ma X, Zhao S, Wang S, Niu L, Sun L. Effects of allogeneic mesenchymal stem cell transplantation in the treatment of liver cirrhosis caused by autoimmune diseases. *Int J Rheum Dis* 2017; **20**: 1219-1226 [PMID: [28217916](#) DOI: [10.1111/1756-185X.13015](#)]
- 13 **Chen B**, Wang YH, Qian JQ, Wu DB, Chen EQ, Tang H. Human mesenchymal stem cells for hepatitis B virus-related acute-on-chronic liver failure: a systematic review with meta-analysis. *Eur J Gastroenterol Hepatol* 2018 [PMID: [29727380](#) DOI: [10.1097/MEG.0000000000001156](#)]
- 14 **Charo RA**, Sipp D. Rejuvenating Regenerative Medicine Regulation. *N Engl J Med* 2018; **378**: 504-505 [PMID: [29320637](#) DOI: [10.1056/NEJMp1715736](#)]
- 15 FDA announces comprehensive regenerative medicine policy framework. November 16, 2017 ed: Food and Drug Administration, 2017. Available from: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585345.htm>.

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