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Stem cell therapy for acute and chronic liver diseases: A therapeutic challenge

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Introduction

Extensive research for the last 40 years in the area of liver regeneration, still none of the procedures represent a 'gold standard' in the clinical practice for liver diseases. Acute and chronic liver diseases are treated with palliative approach and patient morbidity and mortality is exceptionally very high. Only available treatment for end stage liver diseases is orthotropic liver transplantation (OLT) but the availability of donor organs is limited and many patients die each year waiting for liver transplants. Prevalence rates and the demand for liver transplantation are rising annually worldwide. In India, liver transplantation in India is estimated to be around 20/million population (or 25,000 per year). Unfortunately, more than 200,000 people die every year waiting for liver transplant. In this scenario, regenerative medicine or Cell-based therapies using liver stem cells is a promising new approach to this largely unmet medical need. At present, Use of alternative cell sources such as bone marrow, fetal hepatocytes, cord blood, MSCs and iPS are under investigation.

There are more than 100 different liver diseases and for the majority do not have a specific medical treatment. They can be also classified in Acute and Chronic liver diseases. For liver diseases caused by alcohol abuse or obesity can be prevented, while patients with hepatits B or hepatits C virus infection can receive antivirus medication with increased efficacy. Patients with metabolic diseases often cannot be treated and the only treatment option available is OLT.

Acute liver diseases

The common caused of acute liver failure (ALF) or fulminant hepatic failure (FHP) are viral hepatitis, idiosyncratic drug reactions, acetaminophen and mushroom ingestion. Viral hepatitis B is the most common cause of ALF worldwide, responsible for about 70% of cases and it produces significant morbidity and mortality. Another causative factor for ALF is overdose of acetaminophen that leads to excessive

production of its active metabolite N-acetyl-p-benzoquinone imine in the liver, causing depletion of the glutathione stores followed by centrilobular necrosis.

In ALF, there is rapid deterioration of hepatocyte function, which leads to hepatic encephalopathy, coagulopathy, cerebral edema, infection and multi-organ dysfunction syndrome. Orthotropic liver transplantation (OLT) is the only available treatment for ALF that gives satisfactory results. If the decision of OLT is kept on hold due to lack of patient history, rapid deterioration of the patient results in un-transplantable due to other contraindications like multi organ failure. Urgent OLT has become a standard treatment for ALF patients in USA where survival rates have shown improvement and 1-year survival exceeding 80%.

However, OLT have numerous limitations like, shortage of donor organs, the high costs, and the lifelong immunosuppressive treatments. Various alternatives to OLT have been evaluated, such as split-liver, cross circulation, plasma exchange, hemofiltration, hemodialysis, and hemoperfusion without any significant improvement. The alternatives such as stem cell transplant or artificial liver support systems can be helpful, as bridge to transplant that will increase the availability of suitable donor for patients who would otherwise have died might survive until transplantation.

Safety and efficacy of hepatocyte transplantation procedure has been studied in several animal models of ALF. These models showed replacement of about 1-5% of total hepatocyte mass, which is the limiting factor for treatment of ALF. During the study it is been observed that, animal survival rate was improved in ALF.

Chronic liver failure

The predominant reasons for Chronic liver failure (CLF) were cirrhosis due to hepatitis C, B and D viral infection, followed by HCC, and alcoholic cirrhosis with or without concomitant infection with HCV. In India, nearly 150,000 and annually about 1.4 million patient die due to CLF. Autoimmune liver diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and biliary atresia. Nonalcoholic steatohepatitis (NASH) associated with diabetes, protein malnutrition, obesity, coronary artery disease, and corticosteroid treatment. Others inherited causes are alpha-1-antitripsin deficiency, hemochromatosis, Wilson's disease, galactosemia, and glycogen storage diseases.

Study of CLF in animal models is difficult due to lack of suitable animal model that

can mimic the human situation. There are toxin-induced animal models such as carbon tetrachloride (CCl_4) cihhosis, phenobarbital, retrorsine and end to side portacaval shunt. In the animal experiments, liver toxins were injected to normal liver and four weeks after the discontinuation of liver toxins animals were subjected to cell therapy. During the experimental studies different cell types applied intrasplenic, namely fetal hepatocytes and mesenchymal stem cells. These cell therapy experimental models clearly improved liver function and prolonged survival.

Stem cell therapy for CLF patients has more limitations than acute or metabolic liver diseases. During the CLF progression there is a major loss of hepatocytes and hepatic architecture result in scar formation.

It is believed that at least 20 % of the normal hepatocyte mass is required to carry out normal physiological functions. Safety dose for hepatocyte transplantation is about 2.4×10^6 hepatocytes per gram of liver. This suggests replacement of approximately 10 % of functional liver mass. The therapeutic mass of hepatocytes required to restore adequate liver function for ALF is extremely high and CLF patient is extremely difficult to transplant cells into the fibrotic liver. In this situation, Transplantation hepatocytes into other sites such as spleen, muscle will be able accommodate the large number of therapeutic hepatocyte mass and carryout metabolic function for temporary support.

Important considerations:

- Generation of Hepatocytes: Use of different sources of stem cells to generate metabolically functional hepatocytes.
- The achievement of robust engraftment.
- Improvement of transplantation techniques that can reduce the cell loss during the transplantation.
- Extra hepatic sites of transplantation- transplantation of hepatocyte to extra hepatatic sites such as muscle, spleen is of therapeutic significance.
- Bridge to organ transplantation - Stem cells can to be used as bridge to organ transplantation.