Treating Acute Liver Failure with an Extracorporeal Liver-Assist Device

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Numerous extracorporeal liver assist devices have been developed to support acute liver failure patients to orthotopic liver transplantation or spontaneous recovery. Initial artificial liver support systems provided only detoxification through membrane filtration and column adsorption. The relative success of orthotopic liver transplantation for acute liver failure patients has led to cell-based liver support devices or bioartificial livers which provide metabolic functions to replace the functions of the failed liver. Most of these devices include liver cells of animal origins. To date, it is estimated that over 200 patients have been treated with extracorporeal cell-based liver assist devices. Preliminary results have been encouraging and currently three devices are being evaluated in a Phase I/II clinical trial and one device in a Phase II/III clinical trial.

Introduction

Orthotopic liver transplantation (OLT) is the most successful therapy for acute liver failure (ALF), a condition with an 80% rate of mortality. However, the mortality rate for ALF patients candidate for OLT continues to be almost 40%. In order to increase survival, various extracorporeal methods[1] have been developed to temporarily support patients to OLT or recovery without OLT. These methods have included detoxification (dialysis, charcoal adsorption), ex vivo liver perfusion, and cell-based liver assist (CBLA) devices. Clinical studies have shown minimal efficacy of the passive detoxification methods. The relative success of OLT led to extracorporeal liver perfusion but this method remains a challenge due to logistic issues, immune reactions and blood clotting. However, the importance of providing metabolic functions led to the conceptual development of CBLA devices. The main advantages are that the devices present a barrier between the cells and the recipient, and the cells can be stored, shipped, and tested for metabolic activity and adventitious agents prior to use. Several devices are in clinical development and preliminary patient survival rates have encouraged further work in this area.

Cell-Based Liver Assist Devices and Clinical Results

The most prevalent CBLA device design is based on a flat or hollow fiber membrane bioreactor perfused with blood or plasma.[1] In addition, with the exception of one design, CBLA systems make use of cells of animal origin.[1]

Matsumura et al[2] first successfully treated a patient with hepatic failure. The device consisted of a high-flux cellulose membrane plate dialyzer containing rabbit hepatocytes (Table 1). Shortly afterward Margulis[3] reported a controlled clinical study on ALF patients with hepatic encephalopathy (Table 1). One group received standard intensive care, and one group was treated with a system containing charcoal and porcine hepatocytes. Thirty-seven patients (63%) in the test group survived, while 27 patients (41%) in the control group survived. Li et al[4] then treated three patients with a column reactor containing glass beads and porcine hepatocytes. Two patients (67%) survived (personal communications).

Sussman[5] used a hollow fiber hemodialyzer containing a human hepatoblastoma cell line. Prior to treatment the cells were expanded in the hemodialyzer for about one month. The device was first evaluated in 11 patients with FHF.[5] Four were

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Table 1 | **Clinical Trials with Cell-Based Liver-Assist Devices for Acute Liver Failure**

Investigator	Year	Device Configuration	Cell Type	Survival Rates: Treatment % (survive/tot)	Survival Rates: Control % (survive/tot)
Matsumura[2]	1987	Plate dialyzer	Rabbit hepatocytes	100 (1/1)	—
Margulis[3]	1989	Cell suspension	Pig hepatocytes	63 (37/59)	41 (27/67)
Li[4]	1993	Packed bed reactor	Pig hepatocytes	67 (2/3)	—
Sussman[5]	1994	Hollow fiber dialyzer	Human hepatoma line	45 (5/11)	—
Ellis[6]	1996			78 (7/9)[a] 33 (1/3)[b]	75 (6/8)[a] 25 (1/4)[b]
Gerlach[7]	1997	Hollow fiber bioreactor	Pig hepatocytes	100 (6/6)	—
Demetriou[8]	1995	Hollow fiber bioreactor	Pig hepatocytes	89 (8/9)	—
Watanabe[12]	1997			94 (17/18) 100 (3/3)	— —
Mullon[11]	1999			90(35/39)	—

[a] Group not expected to need OLT.
[b] Group expected to need OLT.

To date, it is estimated that over 200 patients have been treated with extracorporeal cell-based liver-assist devices.

transplanted and a fifth recovered without OLT (Table 1). A controlled study was then initiated.[6] Patients were placed in either of two groups: those expected to need OLT to survive, and those not. Each group was subdivided into test and control groups. In each case, no difference was seen between the survival rates in the test and the control groups. For those not expected to need OLT, seven patients (78%) survived with treatment, while six patients (75%) survived with standard-of-care (Table 1). For those expected to need OLT, one (33%) survived with treatment and one (25%) without. This technology was recently transferred from Hepatix Inc the initial sponsor to Vitagen Inc. The system was modified by perfusing plasma instead of blood through the device, and a new Phase I/II clinical trial has been initiated.

Gerlach[7] developed a bioreactor containing porcine hepatocytes and multiple hollow fiber compartments. Prior to treatment the device is maintained in cultures for days to weeks. During treatment the device is perfused with plasma. In an initial clinical study, six patients (100%) treated with the device survived.

Demetriou et al[8] developed a hollow fiber bioreactor containing pig hepatocytes attached to microcarriers. Nine ALF patients were treated, eight (88%) survived; seven were bridged to transplant and one recovered without OLT. In 1993, Circe Biomedical Inc.[9] and Demetriou combined efforts to create the HepatAssist® liver support system.[10] This system is perfused with plasma and consists of a charcoal column, an oxygenator, a heat exchanger, and a cartridge containing hollow fibers, cryopreserved porcine hepatocytes, and microcarriers.[10]

A Phase I/II clinical trial of the HepatAssist® system was completed in 39 patients with acute liver failure and stage III or IV hepatic encephalopathy. Thirty-five patients (90%) survived, 29 with OLT and six without OLT.[11,12] Based on these results and on satisfactorily characterizing the safety of the system with regard to porcine endogenous retroviruses[13,14] a Phase II/III, controlled, randomized, multicenter clinical trial was initiated late in 1998 in the US and Europe. Over 100 patients have been enrolled in the study to date. The retrospective study to assess porcine endogenous retrovirus (PERV) infectivity was conducted in 29 patients treated with the HepatAssist System during the Phase I/II trial. All patients tested negative for PERV using PCR DNA analysis of peripheral blood mononuclear cells collected 1 to 5 years post treatment.[14] In vitro results also showed that the 0.15 µm pore size polysulfone hollow fiber membrane in the HepatAssist System decreased the risk of PERV transmission by a factor of 100,000.[14]

Finally, another hollow fiber device using porcine hepatocytes was recently developed at the University of Pittsburgh[15] and a phase I clinical trial has been initiated.

Considerations

In summary, early clinical results with CBLA devices are encouraging (Table 1) and suggest that

the search for an effective and safe support for patients with acute liver failure may be fruitful. However, these studies also point to areas that may need further investigation.

Most CBLA devices use animal cells as a source of tissue. However, the risk of transmission of a pathogen of animal origin to a patient may be of concern. Thus, control of the animal source to provide safe products is important. Cell storage methods (e.g., cryopreservation) may also provide time to gather all necessary quality control information[10,11] on the cells and/or the animal donor prior to treatment. Development of stable, non-tumorigenic human liver cell lines would be an alternative to provide an unlimited supply of cells and would eliminate the risk associated with zoonosis.[16]

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Cell number or mass varies among CBLA devices rendering difficult the interpretation of the results. There is a need to establish performance standards with regard to cells and devices metabolic functions.

Most CBLA devices use a selective membrane as a barrier to protect the cells from the immune system of the host, prevent the cells from being administered to the host (e.g., preventing cell microchimerism)[13] and lower the risk of transmission of infectious agents.[14] However, membrane characteristics vary among devices from very low to very high molecular weight cutoff (e.g., dialysis vs. microporous membranes). Thus, standards for membranes and devices (e.g., pore size, flux, protein passage) should be established. Finally, most systems use plasma perfusion, but blood perfusion would simplify the use and cost of the systems by eliminating the plasma separation step.

As device designs, cell sources, and patient selection criteria vary among CBLA systems controlled trials should be encouraged. The development of surrogate markers would also be helpful to differentiate the performance of the different devices and would lead to design improvements. If possible, clinical studies should also capture information to improve the understanding of liver regeneration and the pathogenesis of hepatic encephalopathy associated with ALF. Finally, future systems will need to address patient populations other than ALF.

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