Liver transplantation: Yesterday, today and tomorrow

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Abstract

With the advances in technical skills, management of postoperative complications and improvements in immunosuppressive drugs, liver transplantation is the standard treatment for many patients with chronic liver disease. Today, shortage of donor organs seems to be the major limiting factor for the application of liver transplantation. This review focuses on five issues that are challenging to clinical practice of liver transplantation and relevant to gastroenterologists. These include living donor liver transplantation, recurrent viral hepatitis, non-heart-beating donors, hepatocellular carcinoma, and ABO incompatible liver transplantation. Living donor and non-heart beating donor transplantations were initiated as a solution to increase the donor organ pool and it is expected that there will be an increase in the number of these donors. Recurrent hepatitis C and hepatocellular carcinoma following liver transplantation are among major problems and ongoing research in these diseases may lead to better outcomes in these recipients.

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INTRODUCTION

Liver transplantation is one of the most important advances in medicine. First cadaveric liver transplantation was performed by Thomas Starzl in 1963 in Denver. After this failed trial, liver transplantation was successfully performed in humans in July 1967 again by Dr. Starzl. Although rejection was a major concern, many recipients from this early era have survived for more than 20 years using immunosuppression with azathioprine, prednisone, and antilymphocyte globulin (ALG)\[1\].

For clinical transplantation, the historical beginning was Medawar's recognition that rejection is an immune reaction\[2\] (Table 1). With the advances in immunosuppression, postoperative care and surgical technique, liver transplantation has become the golden standard in the treatment of many chronic liver diseases. Since then, the number of patients on the waiting list has increased and organ shortage appeared to be one of the major problems in clinical transplantation.

Raia of Brazil performed the first living donor liver transplantation (LDLT) in 1987 as a promising method to resolve the organ shortage, but the recipient died of a transfusion reaction despite a successful operation\[3\]. After this trial, LDLT has been performed by many other pioneer surgeons in other countries. In the last decade LDLT has become a widely accepted treatment modality. The most extensive experience in LDLT was initially gained in Asia. In countries such as Japan, where the availability of organs from deceased donor is limited, LDLT seems to be the only solution in the treatment of end stage liver diseases. According to the data of Japanese Liver Transplantation Society, the adult to adult LDLT is increasing per year. Despite this increase in adults, cases in children have reached a peak around 100 cases per year. The 1 and 5-year survival rates of all recipients were reported to be 81.8%, and 77%, respectively, while those of recipients of less than 18 years old was 85.6%, and 82.6% respectively. The prognosis of adult recipients was poor when compared to children\[4\]. It was suggested that the original disease recurrence such as hepatitis C and hepatocellular carcinoma (HCC) has influenced a significant decline in the survival of adult cases.

MAJOR ISSUES RELATED WITH LIVER TRANSPLANTATION

LDLT

The shortage of cadaveric liver organs has significantly
inhibited further expansion of liver transplantation. Split liver transplantation has reduced waiting-list morality in children, but not in adults. LDLT is currently the most effective alternative to overcome the organ shortage in adults. With the efforts of transplant surgeons in the establishment and popularization of LDLT, the number of LDLT has increased dramatically not only in Japan but also in Europe and the United States as well. Major advantages of LDLT include the good viability of the liver harvested from a healthy individual, the careful selection of the timing of the transplantation, and the potential good tissue matching. The reduced waiting period for a living donor organ may decrease the risks of decompensation or death before transplantation, thereby improving the overall chances for success. Disadvantages are the risk to healthy donors and also that, this modality has a potential psychological burden on the donor.[18,19] The surgical procedures for LDLT are technically more challenging and LDLT requires a full understanding of the hepatobiliary anatomy.

A wide range of complication rates are reported in the literature in donors after LDLT. Donor safety has a major importance in LDLT. Published reports on donor outcomes indicated a wide range of complication rates that varied between 9% and 67%.[7,8] In the Kyoto University experience 50 complications in 276 right lobe grafts have been encountered, including surgical complications is 18.5% and non-surgical complications is 3.2%.[9]

On the other hand, the American Society of Transplant Surgeons reported a donor complication rate of only 10%. Thus it seems that donor morbidities have not been adequately reported and true extent of complications may be underestimated. A standardized system for reporting complications to a registry should be developed to allow meaningful data analysis. Donor mortality is also a major concern of LDLT. In the United States at least 3 deaths were confirmed. Another 3 deaths in Europe and 1 in Japan had been reported[10].

As living donation permits transplantation to take place independent of either waiting time or the severity of liver disease, the criteria required for LDLT may be modified when compared to deceased donor liver transplantation (DDLT). Estimation of liver volume needed in individual situations is an important factor in donor selection. Aged liver, steatotic liver, and special anatomic variants have the risk of a relatively poor graft quality. Recipient factors such as metabolic load, preoperative latent infections and other organ failures have negative impact on graft survival. The minimally required quantity of graft volume has not been fully clarified, which is one of the major issues of the adult to adult LDLT.

The following two methods were developed to express the graft volume: First the ratio of graft volume (GV) in the standard liver volume (SLV) of the recipient, which is calculated by the recipient's height and body weight. Second, the ratio of graft weight in the recipient's weight (GRWR: graft to recipient weight ratio). The reported safe limit of small-for-size graft is from 30% to 40% in GV/SLV, while from 0.6 to 0.8 in GRWR[11-14].

Recipients with a small-for-size graft, suffer from graft dysfunction including hyperbilirubinemia, massive ascites, poor synthetic function that leads to serious conditions such as gastrointestinal bleeding and renal failure. When a graft size is conversely too large for a recipient such as a newborn infant, the graft necrosis occurs due to insufficient blood inflow into the graft.

As pointed out by Ghobrial and Bussuttil, future application of LDLT will be based on the accurate definition of risks imposed on donors compared with potential benefits realized by recipients[15]. As an example to this statement, the number of adult LDLT declined from approximately 400 in 2001 to 280 in 2002. Such a precipitous reduction may have occurred in response to the donor death in US in 2002 which raised increasing concerns for donor safety. While the number of LDLT in the US has declined, the number in Asia as a whole has continued to increase. LDLT accounted for less than 5% of liver transplants in the US but more than 95% of the transplants in Asia excluding mainland China. The overall number of LDLT procedures performed in Asian countries and areas with well-established programs (Japan, Korea, China Hong Kong and China Taiwan) has steadily increased over years[16].

In summary, the overall results with good patient and graft survival, together with acceptable donor morbidity and mortality has led to the acceptance of LDLT in the transplant community. To maintain this procedure as a treatment modality in the future, satisfactory risk-benefit analysis and long-term morbidities imposed on living donors should be further investigated.

**Recurrent viral hepatitis**
The most common single cause of late graft loss after liver transplantation is the recurrence of the disease for which the liver transplantation has been performed[17]. Until last decade, successful long-term outcome after liver transplantation in patients with chronic active hepatitis-B has been limited because of high rate of recurrent
of recurrent hepatitis. Long-term passive immunization with high-dose intravenous hepatitis B immunoglobulin (HBIG) led to a significant improvement in the prognosis of these patients. High-dose intravenous HBIG may prevent recurrent hepatitis B virus infection, but the cost has limited its widespread use in countries with endemic hepatitis B virus infection. Low-dose intramuscular HBIG plus nucleoside analogs such as lamivudine was shown to be equally effective and safe and in the long-term prophylaxis against recurrent hepatitis B at less than 10% the cost of the high-dose regimen. Although lamivudine is effective in most of the patients, lamivudine resistance is becoming a major concern. With adeovir, a potent antiviral drug that became available in recent years, these patients with lamivudine-resistant tyrosine-methionine-asparteinate-asparteinate mutant can also be treated. Currently, liver transplantation can be safely performed in chronic active hepatitis B patients with similar survival as for patients transplanted for other indications.

The recurrence of hepatitis C is also a great concern after transplantation. Although short-term graft and patient survival rates of chronic active hepatitis C patients are comparable to those observed in other patients undergoing liver transplantation, HCV recurrence is universal and is associated with poor graft and patient survival. In contrast, survival after retransplantation for recurrent hepatitis C is poor and retransplantation for these patients is controversial. In a previous study Abbasoglu et al showed that recurrent hepatitis C was the most common cause of late graft loss in patients who had undergone liver transplantation for chronic active hepatitis C.

Treatment of recurrent hepatitis C, whether preemptive or not, is an important issue. Despite recent achievements in the treatment of hepatitis C infection with pegylated interferons and ribavirin, patients with recurrent hepatitis C after liver transplantation are difficult to treat. Virological response rates in prophylactic and therapeutic approaches of hepatitis C reinfection after liver transplantation are low compared to the pre-cirrhotic hepatitis C infection. Moreover, optimal treatment duration and dosage of recurrent infection with pegylated interferon in combination with ribavirin remains to be defined. Despite side effects, long-term antiviral maintenance therapy might be an effective approach for preventing progression to severe allograft fibrosis and thereby improving long-term survival in liver transplant recipients with recurrent hepatitis C.

Two large studies have shown that the incidence and severity of hepatitis C recurrence do not differ between DDLT and LDLT recipients; however another study has found that the incidence of cholestatic hepatitis is significantly greater in LDLT recipients. Several studies have identified a number of potential risk factors for recurrent hepatitis C infection including hepatitis C virus related factors (virus load, genotype) as well as coinfection with other viruses such as cytomegalovirus, hepatitis B virus and hepatitis D virus. There are still no well-defined parameters that would predict which patients are at risk to develop recurrent hepatitis C and those who will not. Strategies including pre- and post-transplant antiviral therapy may further improve the results.

Non-heart-beating donors

The first liver transplantation from a non-heart beating donor (NHBD) was performed by Nakayama in Japan in 1964. NHBD livers are considered as a potential for expanding donor pool. The critical problem with NHBD livers is prolonged warm ischemia time. Despite calls for the use of hepatic grafts from NHBD, there are few studies examining long-term outcome. Although metabolism is slowed 1.5- to 2-fold for every 10°C drop in temperature, considerable metabolic activity still occurs during cold preservation. In NHBD organs, the effects of cold ischemia are superimposed on the injury occurred during warm ischemia. The pattern of injury sustained during warm and cold ischemia is slightly different. Cold ischemia leads to initial injury to sinusoidal endothelial cells whereas warm ischemia mainly injures the hepatocytes. It seems that the additional injury resulting from warm ischemia in NHBD donation requires alternative preservation strategies to minimize the ischemic injury. Donor warm ischemic time may predispose hepatic allografts to an increased incidence of ischemic type biliary strictures. Although graft and patient survival has been reported to be similar to that of heart beating donor transplants, caution is urged with the use of these organs.

Despite the increased risk of graft and patient survival, NHBD livers are being increasingly used with acceptable results. Abt et al analyzed data from the United Network for Organ Sharing database. In 144 NHBDs and 16 856 heart beating donors (NHBDs) the 1-year (70.2% vs 80.4%) and 3-year (63.3% vs 72.1%) graft survival were inferior in the NHBD group. The primary non-function risk after transplantation was also significantly higher (11.8% vs 6.4%) in the NHBD group.

New strategies in organ preservation, normothermic recirculation, normothermic preservation, cytoprotection, and development of reliable markers to predict postoperative graft function may improve results in clinical transplantation with NHBD liver grafts. Based on the clinical studies and continued shortage of liver allografts, the use of NHBD organs are recommended, however, with several caveats. Careful donor (< 60 years of age) and recipient (stable, not intubated) selection, minimizing warm (< 30 min) and cold (< 8 h) ischemia, utilization of histology, and discarding organs with significant steatosis may provide acceptable results.

HCC

HCC is the most common primary liver cancer and most patients with HCC also suffer from coexisting cirrhosis. For the treatment of patients without cirrhosis, resection should be considered whenever possible. Hepatic reserve is the one of the major determinants of liver resection. When compared with resection, transplantation restores liver function and has the advantage of removing tissue with an oncogenic potential. To obtain the optimal
benefit from the limited number of organs available, strict selection criteria has been developed to offer liver grafts to patients with the highest likelihood of survival after transplantation. In 1996 Mazzaferro et al showed that when strict criteria were applied, transplantation of patients with early HCC has resulted in excellent results with a 4-year survival rate of 75%. This led to the development of Milan criteria from a retrospective analysis of 48 patients. This survival rate was achieved in patients with solitary tumor of less than 5 cm and those who have up to 3 tumor nodules each of which is smaller than 3 cm without vascular invasion or extra hepatic metastasis[33]. With the achievement of good results in HCC patients with more advanced tumors, the Milan criteria was expanded. Yao et al proposed UCSF criteria (solitary tumor smaller than 6.5 cm or 3 of fewer nodules with the largest lesion smaller than 4.5 cm or total tumor diameter less than 8.5 cm without vascular invasion) [37]. In this study the expansion of Milan criteria did not impact on survival adversely. On the other hand, this approach reduced the availability of cadaveric grafts for patients with other liver diseases. The Barcelona Clinic Liver Cancer Group has proposed expanding the Milan criteria to single tumor of 7 cm or less, or 5 tumors of 3 cm or less, in patients who showed a partial response to any treatment lasting for more than 6 mo[39]. However organ shortage, higher dropout rate, and less favorable results render these attempts to a controversial issue. With the expansion of listing criteria, liver transplantation could be performed in more advanced cancer patients but this lead in turn to poor survival rates. All patient selection criteria rely on radiological imaging to assess intrahepatic disease and exclude extra hepatic spread. It may be possible to improve patient selection by increasing the sensitivity of imaging studies and detection of micrometastasis[39].

About 50% of HCC patients who are initially candidates for liver transplantation will become ineligible, if the median waiting period exceeds 1 year[19,44]. As a result of tumor progression during the waiting period, LDLT gained popularity to transplant HCC patients in a better clinical condition without a long waiting time. Although controversial, it may be claimed that LDLT can be performed in patients with HCC that exceeds the Milan criteria as 3-year survival rate of greater than 50 has been showed in other studies[40]. In two studies it was shown that LDLT is superior to DDLT for patients with HCC meeting Milan criteria, when waiting times for organs from deceased donors exceed six months[42,43]. Despite the availability of LDLT tumor progression is still a major concern and strategies like chemoembolization and radiofrequency ablation to reduce tumor growth during waiting period have shown promising results[44]. Although many studies have shown that microvascular invasion and histological grade are significant risk factors for poor prognosis, these are difficult to know clearly before transplantation. Noninvasive markers to predict the prognosis of HCC may help better patient selection in the future[45].

### ABO incompatible liver transplantation

Two antigen systems (ABO and HLA) play role in transplantation. In liver transplantation the ABO system is important while HLA system has a minor role. Crossing the ABO barrier in liver transplantation is usually not performed except for emergency conditions and results of ABO incompatible liver transplantation have been markedly inferior with an increased incidence of vascular and biliary complications and rejection, when compared to ABO compatible grafts. In children below the age of three years, ABO incompatible liver transplantsations have been more successful[56]. In recent years, promising results with ABO incompatible liver transplantation using A2 donors (subgroup of A which is less reactive and occur in approximately 20% of group A individuals) have been reported. In a Swedish study of 10 adult blood group O recipients who received A2 cadaveric grafts, patient and graft survival was 10/10 and 8/10 respectively at 8.5 mo median follow up with tacrolimus based protocol and initial immunosuppression with antithymocyte globulin, interleukin-2 receptor antagonists or anti-CD20 antibody[46]. In 16 pediatric ABO-incompatible pediatric liver transplantation, Heffron et al reported one-year actuarial graft survival of 92% utilizing standard immunosuppression with selective post-operative plasmapheresis and without splenectomy[47]. Plasmapheresis may be useful by reducing the recipients’ antibody titers before and after transplantation. ABO incompatible liver transplantation may be the only available option in LDLT, if the patients have no ABO identical or compatible donors. According to the Japanese Registry of LDLT Across ABO Blood Type Barrier, 97 ABO incompatible LDLTs were performed in Japan before 2005 and 5-year survival rate of the patients was 38% before 2001 and improved to 63% among patients who underwent transplantation after 2002[49].

Although recent studies support the concept of ABO-incompatible liver transplantation both in adults and children, further studies are needed to draw a conclusion. More well-designed, controlled clinical trials are necessary to establish optimal pretransplantation management protocols including immunosuppressive regimens in this group of patients.

### CONCLUSION

Liver transplantation is the only definitive treatment modality of end stage liver diseases. Although LDLT has been widely performed with results similar to whole organ cadaveric transplantation, the benefits of the recipients versus the risks and long-term morbidities imposed on the donors require further studies. The overall reported donor mortality is 12 in about 6000 transplantations (0.2%)[49]. Recurrent viral hepatitis and HCC are among the major causes of late graft loss after liver transplantation. Current antiviral treatment for recurrent HCV offer limited chance of long-term success. To overcome organ shortage there is now a resurgence of interest in NHBD liver transplantation. Although ABO incompatible liver transplantation especially using A2 donors is promising particularly in children, more studies are needed to draw a conclusion.
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