

Liver transplantation in China: problems and their solutions

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BACKGROUND: The past decade has witnessed the rapid development of liver transplantation in China. The 1-year survival of liver transplant patients comes to 80% in many leading medical centers and the number of liver transplantation is increasing. However, liver transplantation in China is facing several challenges including recipient with hepatocellular carcinoma (HCC), recurrence of HCC and hepatitis B, long-term postoperative care, the bridge to liver transplantation, and shortage of liver donor. This review was to understand the status of and problems in liver transplantation in China.

DATA RESOURCES: An English-language literature search using MEDLINE (1990-2003) on liver transplantation and other related reports and review articles in Chinese from major transplant centers in China.

RESULTS: HCC is one of the main indications for liver transplantation in China but different centers adopted different criteria for selection of patients. Hepatitis B virus reinfection is a vital problem after liver transplantation in HBV-related patients. More and more attention was focused on long-term postoperative care and donor shortage. Artificial liver support system has been applied in patients waiting for a graft in many centers.

CONCLUSIONS: HCC remains to be one of the main indications for liver transplantation in China; combined hepatitis B immune globulin and lamivudine is considered effective to prevent hepatitis B virus reinfection. Apart from long-term postoperative care for the improvement of the survival rate, early steroid withdrawal is feasible in liver transplantation. Living donor liver transplantation, split liver transplantation, and marginal donor transplantation can deal with donor shortage to some extent. Artificial liver assist system serves as a bridge to liver transplantation.

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Introduction

Orthotopic liver transplantation (OLT) for end-stage liver disease continues to perform throughout the world. The past decade has witnessed the development of liver transplantation in China, with the 1-year survival rate of 80% in leading medical centers.^[1] Despite recent advances in surgical techniques, and immunosuppressive and perioperative treatment, liver transplantation in China is facing major challenges including selection of recipients with hepatocellular carcinoma (HCC), recurrent diseases, long-term postoperative care, bridge to liver transplantation, and shortage of liver donor.

Liver transplantation for malignancy

Liver transplantation is theoretically the best treatment for HCC because it results in the widest possible resection margin for the cancer, removing the remained liver tissue that is risk for the development of de novo cancer and restores liver function.^[2,3]

HCC was one of the main indications for liver transplantation in its early years in China. Technically it was easier to perform than in patients with end-stage cirrhosis, portal hypertension, and coagulopathy. The recipients were in a better physical condition and were more likely to survive the immediate postoperative period. Currently the percentage of HCC in liver recipients is decreasing to less than 40% because of the risk of tumor recurrence and poor survival after liver transplantation. The dismal early experience with transplanting patients with HCC has prompted the identification of factors for tumor recurrence. Tumor size greater than 5 cm, vascular invasion, lymph node involvement and poorly differentiated tumor histology all negatively affect the survival of patients with HCC after OLT. The recent 5-year survival of patients with HCC after trans-

plantation has been steadily improved over the past decade. It is possible that the published criteria for patient selection may have contributed to the better outcome.^[4]

At the University of Milan, a 4-year post-transplant actuarial survival of 75% was achieved in 48 recipients who had a solitary HCC less than 5 cm in diameter or up to three liver lesions sized less than 3 cm.^[5] This is the so-called Milan criteria adopted by the United Network of Organ Sharing as the selection guidelines for OLT. Another study at the UCSF, USA reported a 5-year post-transplant survival of 75% when the Milan criteria were modestly expanded to include solitary tumor less than 6.5 cm in diameter, up to three lesions sized less than 4.5 cm, and total tumor diameter less than 8 cm.^[6] The Pittsburgh modified TNM criteria further expanded the tumor size, but emphasized the effect of microvascular invasion and lymph node involvement.^[7]

In China, practical criteria should be established to choose suitable patients with HCC to receive OLT, which is considered the first line treatment for those who suffer from small HCC with Child-Pugh class C cirrhosis or with severe portal hypertension. Resection should remain the initial treatment of choice for patients with small, resectable HCC, adequate liver function, or Child-Pugh class A cirrhosis and without significant portal hypertension.^[8,9] As salvage transplantation,^[10,11] OLT can be performed in patients with large HCC limited in a lobe. Large HCC with microvascular invasion or portal vein thrombosis should be considered as a contradiction for OLT.

Prophylaxis of hepatitis B recurrence

Because hepatitis B virus infection is endemic in China, hepatitis B-related liver disease is a leading cause of end-stage liver disease and a leading indication for OLT.^[12] In the past, the results of OLT for patients with chronic hepatitis B were seriously affected by a high incidence of recurrent graft infection and subsequent graft failure. The experience with OLT for HBV-related liver disease was discouraging if no preventive measures were taken, with a reinfection rate of approximately 80%. In recent years, improved outcome has been obtained after use of specific interventions and agents including hepatitis B immune globulin and, more recently, lamivudine. Effective modalities for prophylaxis and treatment of recurrent hepatitis B have significantly improved the survival rates of graft and patient to a level comparable to those of other liver transplant recipients.

Passive immunoprophylaxis with hepatitis B immune globulin (HBIG) is the first prophylactic measure shown to be clinically effective in reducing HBV reinfection and improving graft survival after liver transplantation. In early studies, the administration of HBIG in the

anhepatic phase and the short period after transplantation did not effectively reduce the incidence of recurrent HBV infection. Only administration of HBIG for more than 6 months was shown to reduce the rate of HBV reinfection dramatically to a median rate of 20% after 2 years.^[13] The protective effect of HBIG is dose-dependent and the high-dose regimens may cost up to \$100 000 per year. Furthermore, breakthrough infection would still develop in 10%–20% of patients receiving lifelong high-dose HBIG because of selection pressure on the surface antigen leading to the emergence of mutants that lack affinity for anti-HBs.^[14]

To reduce the cost associated with the use of HBIG, one strategy was to avoid HBIG administration, but use lamivudine pre- and post-transplantation as a monotherapy.^[15,16] The overall hepatitis B surface antigen recurrence rate was about 20% one year after transplantation. The result of lamivudine monotherapy was comparable to that of long-term HBIG therapy.^[17] The disadvantage of lamivudine in prophylaxis was YMDD mutants in the HBV genome which resulted in HBV reinfection.^[18] Because of the failure with single agents of either HBIG or lamivudine, therapy using both agents was increasingly regarded as an effective approach. Various regimens of HBIG, in low or high dose, for short- or long-term administration through intravenous or intramuscular routes were proposed.^[19,20] Their effect was proved of lamivudine and high-dose HBIG for prophylaxis.^[21] The lower cost regimens of lamivudine combined with short-term high-dose HBIG or low-dose intramuscular HBIG was attractive.^[22] Adefovir was another promising antiviral agent, which could not only treat the breakthrough reinfection after lamivudine prophylaxis, but also serve as prophylactic choice.^[23]

Long-term postoperative care

Nowadays short-term survival has been improved due to modified surgical techniques and better postoperative management. Most patients and liver grafts could survive beyond the perioperative period, with a 1-year survival rate of 70%–90% and a 10-year survival rate of 62%.^[24] Therefore, long-term outcome of patients who had a liver transplant has become a major concern of clinicians. During a long-term follow-up, chronic rejection is responsible only for a small proportion of graft loss and some death, whereas immunosuppression-related complications as infection, cardiovascular disease, renal failure and de novo malignancy account for the most of the cases. In general, 3 months are something a milestone in the recovery of the majority of patients. Hence long-term postoperative care includes follow-up visits 3 months after transplantation. The problems in this stage of recovery are best divided into those related to the transplantation surgery and the graft themselves, those com-

plications arising from long-term immunosuppressant medication, and those related to the recurrence of the disease.

Abnormal findings shown by liver function test more than 3 months after transplantation are biliary tract complications, which have been found in up to 15% of cases.^[25] Surgical complications of biliary anastomosis in the early era of liver transplantation were called Achilles heel of the procedure,^[26] but the modification of surgical techniques has significantly lowered the complication rate in the anastomosis area.^[27] With the decrease of surgical stricture, ischemic stricture has become more apparent^[28] as a late complication if hepatic artery thrombosis exists. Ischemic stricture typically restricted to the donor side of biliary anastomosis is found in multiple locations, both intrahepatic and extrahepatic. Warm ischemic injury is implicated as one of the causes for ischemic stricture. It is generally held that the incidence of this stricture is increased as a result of prolonged ischemic time (over 12 hours).^[29] Regardless of the nature of the stricture, the patient would present with cholestatic signs on liver function test and a rising level of serum bilirubin. The suspected patients required urgent ultrasonography. If biliary dilation is confirmed, the whole biliary tree could be visualized by either ERCP or MRCP. The first-line therapy for simple stricture is ERCP with balloon dilation and stenting.^[30,31] If there is no sepsis, antibiotic prophylaxis at the time of biliary intervention should be considered mandatory. Early retransplantation is considered for individuals with hepatic artery thrombosis or multiple strictures insuitable for endoscopic intervention.

With regard to immunosuppression, the clinician should optimize the dose of drugs by monitoring and adjustment as indicated. The known short- and long-side effects of the immunosuppressants should be balanced with the knowledge that insufficient immunosuppression could seriously affect the morbidity and survival of the graft. The nephrotoxicity of immunosuppressive agents, tacrolimus and cyclosporin is a significant cause for morbidity and mortality of patients after the first year of transplantation. Renal function should be measured clinically. Monitoring of blood level of immunosuppressants, new formulation of cyclosporin, and maintenance of a lower level of immunosuppression help to reduce the incidence of renal impairment in patients after transplantation. In recent years, some new drugs of less nephrotoxicity such as sirolimus^[32] and FTY720^[33] have been used but their efficacy has not yet been evaluated in controlled clinical trials.

Corticosteroid which has been one of the immunosuppressive agents now is declined to use.^[34,35] The advantages of corticosteroid that has been used for immunosuppression for 50 years include lower cost, and known complications, and effectiveness in prophylactic

and therapeutic control of rejection. In contrast, the adverse effect of steroid is legion. The steroid could increase in the incidence of infection and malignancy and induce post-transplant diabetes, metabolic bone disease, wound unhealing, post-transplant hypertension, and hypercholesterolemia. Monitoring of the known cardiovascular and metabolic complications is thus necessary. The reduction and discontinuation of steroid therapy over the past several years have proven that steroid could be withdrawn in more than 85% of liver transplant recipients without the consequence of immunologic graft loss. Metabolic complications including hyperlipidemia, hypertension, diabetes mellitus, and possibly obesity after transplantation could be improved after withdrawal of steroid.^[36]

Solution to donor shortage

Donor shortage is the most important problem in organ transplantation worldwide. The success of liver transplantation in China has an increased demand on liver donor, with a marked discrepancy between the number of patients waiting for a liver and the number of available organs. With an ever-increasing number of patients on the waiting list and a stable number of available donors, the number of patients who died on the waiting list is increasing steadily. It is pressing to establish the law governing brain death as well as the national network of organ sharing. In spite of the vast territory of China, the exchange of donor organs is possible because of the convenience of transportation and long-time liver preservation. Making better use of every donor could save the life of many patients on the waiting list. Other means to deal with the donor shortage include living donor liver transplantation (LDLT) and split liver transplantation.^[37] In LDLT reported in 1990, a left lateral segment of an adult liver was resected and grafted into a child. Adult-to-pediatric LDLT is so successful that it has become a standard of care at many pediatric liver transplant centers worldwide.^[38] In adult-to-adult LDLT reported in 1994, the right lobe (segment 5 and 8), representing 60% to 65% of the liver, was resected from the donor and grafted into the recipient.^[39] This procedure is very popular in Japan and south Korea because of lack of cadaveric donors. Considering the similar culture background, we recommend LDLT in China. Unfortunately, the number of LDLT is far behind the number of cadaveric liver transplantation; but the development of LDLT could reduce the demand for cadaveric donor. In split liver transplantation a cadaver liver is split into 2 pieces, with the right lobe usually being used for an adult recipient and the left lobe or left lobe usually being used for a small adult or pediatric recipient. Only a few cases of split liver transplantation have been reported in China. In the past, older donors (over 55 years), those with fat-

ty infiltration, and those with diabetes mellitus were excluded but now they are called marginal donors.^[40] In recent years organs from marginal donors have been used with considerable success in addition to the progress in xenograft study although it is far away from clinical use.

Bridge therapy for acute liver failure

Liver failure remains to have a high mortality clinically. No specific therapy is available for patients with this fatal disease except liver transplantation. Many patients are about to die when they are waiting for a proper donor graft. It is extremely important to develop a kind of therapy to rescue such patients in the waiting period. The artificial liver support system as a bridge to liver transplantation is applicable to prevent irreversible neurologic damage and to ensure adequate time for possible regeneration of the liver. Artificial liver can be divided into biological and non-biological. In patients with acute liver failure could prevent cerebral edema, renal failure, and coagulopathy while keeping the patients survived until either a donor organ is available or spontaneous recovery takes place.^[41] Several pilot trials in humans have shown the improvement of neurologic status and that the device serves a bridge to liver transplantation.^[42]

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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