

Orthotopic liver transplantation for fulminant hepatitis B

Xiao Shun He, Jie Fu Huang, Gui Hua Chen, Qian Fu, Xiao Feng Zhu, Min Qiang Lu, Guo Dong Wang and Xiang Dong Guan

Subject headings hepatitis B; liver transplantation; lamivudine

He XS, Huang JF, Chen GH, Fu Q, Zhu XF, Lu MQ, Wang GD, Guan XD. Orthotopic liver transplantation for fulminant hepatitis B. *World J Gastroentero*, 2000;6(3):398-399

INTRODUCTION

When fulminant hepatitis progresses to deep encephalopathy, with stage III or IV coma, it is commonly irreversible with a high mortality rate (80%-100%)^[1]. Liver transplantation may be the sole treatment of choice in such circumstances. However, the early results have been disappointing, largely due to the frequency of posttransplant HBV infection^[2,3]. This recurrent disease often develops in an aggressive manner characterized by high levels of HBV replication and rapidly progressive liver graft damage. In recent years, however, as new antiviral agents, such as lamivudine came into being, the patient's survival has much been improved. The purpose of this study is to assess the effect of OLTx in a series of 7 patients with fulminant hepatitis B, and to evaluate the efficiency of lamivudine on preventing patients from HBV reinfection.

MATERIALS AND METHODS

Between October 1993 and August 1999, 7 adult male patients with hepatitis B were referred for liver transplantation. Their age at the time of operation ranged from 32 years to 49 years (median age 42.9 years). All patients were positive for HBV surface antigen (HBsAg), and 2 had evidence of viral replication. The latter was demonstrated by positive hepatitis B e antigen or/and HBV-DNA. Patient profiles are shown in Table 1.

All patients received orthotopic liver

Transplantation Surgery, First Affiliated Hospital of Sun Yat-Sen University of Medical Sciences, Guangzhou 510080, P.R.China

Dr. Xiao Shun He, MD, Ph.D., graduated from Sun Yat-Sen University of Medical Sciences, working as a visiting scholar in Australian National Liver Transplantation Unit between 1997-1998, now associate Professor and Deputy Director of Transplantation Surgery Department, majoring in liver transplantation, having 20 papers published.

Project supported by the Key Clinical Project of Ministry of Health. No. 97040230 and the Key Project of Scientific and Technological Committee of Guangdong Province No. 963003

Correspondence to: Dr. Xiao Shun He, Department of Transplantation Surgery, First Affiliated Hospital of Sun Yat-sen University of Medical Sciences, 58 Zhongshan Erlu, Guangzhou 510080, China
Tel. 0086-20-87306082, Fax. 0086-20-87306082
Email. sean@gzsums.edu.cn

Received 2000-01-13 Accepted 2000-03-02

transplantation 1 to 10 days after admission. Initial immunosuppression with cyclosporine A (CsA), and methylprednisolone was used in all cases. In the latter 3 cases, tacrolimus (FK506) was given orally when the patients resumed oral intake. Doses were adjusted in the first month to maintain 12 h trough levels of 10 g/L to 15 g/L. Prophylaxis for cytomegalovirus infection was started immediately after surgery with acyclovir or ganciclovir for 2 weeks. Lamivudine was administered orally, 100 mg or 150 mg daily in 5 patients when it became commercially available, and the treatment was not interrupted in any patient.

RESULTS

All patients in this series recovered consciousness 24 h after OLTx. Of them, five recipients were still alive and well with normal liver function during a following up period of 3-7 months. One patient with grade III hepatic encephalopathy died due to HBV reinfection 36 days after liver transplant. Another patient with preoperative esophageal varicose bleeding died of multi-organ failure 3 days after transplantation. Various medical and surgical complications occurred in two of the five survived patients. One developed recurrent onset of epilepsy necessitated continuous antiepileptic therapy. Another developed stenosis of inferior vena cava, which was successfully treated by balloon dilation and stent replacement.

No acute or chronic graft rejection occurred in any patient. In patient 1, viral replication disappeared within 1 month following OLTx and became positive thereafter. The other 6 patients had a negative HBsAg within 3 to 14 days after OLTx and all had a negative viral replication. No side effects were noted concerning lamivudine treatment.

DISCUSSION

Hepatitis B is a common disease in mainland China. It was estimated that HBsAg carriers accounted for 10% of the total population. However, the natural history of hepatitis B can be quite variable^[4]. Even once signs of portal hypertension develop, many patients can go years before complications develop that impair the quality of their lives. By contrast, others can have stable liver disease for quite some time and then deteriorate quickly, often related with bleeding or infection. Thus, it is difficult to make accurate decisions about the timing of liver transplantation. In general, once the patient's liver

disease begins to impair quality of life, the physician should consider an evaluation for transplantation. Based on this understanding, fulminant or sub-fulminant hepatitis is justifiable for liver transplantation. According to the experience of King's College Hospital in London, the selection criteria for transplantation in hepatitis B are based on the occurrence of three of the followings: a prothrombin time greater than 50 seconds; a jaundice to encephalopathy time of more than 7 days; non-A, non B hepatitis or drug-induced hepatitis; age younger than 10 years or older than 40 years; bilirubin greater than 300 $\mu\text{mol/L}$; or the finding of a prothrombin time of greater than 100 seconds in isolation^[5]. In the present series, all 7 patients met the above mentioned criteria. The overall survival rate of our series was 71.4% after a 3-7 month follow-up period. The mortality rate of those patients with fulminant hepatitis B was 29.6%. Of the two patients who died, one died 5 weeks following OLTx of recurrent fulminant hepatitis B, indicating the high risk of HBV reinfection when the serum HBeAg was positive. The other patient died of multi-system organ failure on postoperative day 3. Nevertheless, the overall outcomes were to our satisfaction and support the continued application of liver transplantation as a therapeutic measure for fulminant hepatitis B.

It has been found that nearly 100% of patients showing evidence of active viral replication, i.e. serum HBV-DNA or/and HBeAg positive, and 70%-80% of those with HBV DNA or HBeAg negative prior to OLTx and received no immunoprophylaxis, developed recurrent HBV infection of the graft following OLTx^[6]. The recurrent disease may manifest as rapidly progressive disease. In our series, patient 1

developed fulminant hepatic failure 5 weeks following OLTx. Interferon (IFN) has been used both prophylactically and therapeutically after OLTx in patients with recurrent HBV, but it has proved to be mostly ineffective and may lead to further complications^[7]. In recent years, perioperative administration of hepatitis B immunoglobulin (HBIg) has been reported to reduce the incidence of recurrence. But, it requires prolonged parenteral treatment and does not suppress viral replication. Additionally, availability of HBIg could be limited and the costs related to prolonged use of HBIg are very high^[8]. These disadvantages of HBIg prevent it from wide clinical use. Because high level viral replication seems to be important in the pathogenesis of HBV recurrence, there has been great interest in the potential role of nucleoside analogue with anti-HBV activity. The most promising are lamivudine and famciclovir. Both agents have been evaluated in both animal model of HBV and clinical trial and have been shown to rapidly suppress viral replication. Lamivudine prophylaxis after liver transplantation resulted in a complete and sustained suppression of viral replication in OLTx recipients^[9]. In our study, 5 patients received lamivudine treatment, no side effect has been identified, and the treatment was not interrupted in any patient. The doses of 100 mg daily suppressed HBV-DNA to undetectable levels in one patient. Serum HBsAg became negative and HBeAb became positive after transplantation in all the patients. No cases of HBV reinfection were noted in lamivudine-treated patients. The results indicated that lamivudine is a beneficial and well-tolerated therapy in OLTx with HBV infection. The long-term effects of lamivudine are being investigated.

Table 1 Details and results of 7 patients underwent OLTx for fulminant hepatitis B

Patients No.	Age/Sex	Medical history	Bilirubin ($\mu\text{mol/L}$)	Encephalopathy	ABO compatibility	Lamivudine regimen	Outcome	Cause of death
1	32/male		478.0	III	Identical	(-)	Died	HBV reinfection
2	44/male	Biliary surgery $\times 2$	756.1	I	Identical	(+)	Alive	
3	49/male	Nasopharyngeal carcinoma	141.3	I	Identical	(-)	Alive	
4	48/male	Epilepsy due to brain trauma, PE $\times 3$	787.1	II	Identical	(+)	Alive	
5	48/male	Hepato renal syndrome duodenal ulcer, PE $\times 4$	500.7	IV	Identical	(+)	Alive	
6	44/male	Esophageal varicosis bleeding, PE $\times 2$	937.5	III	Compatible	(+)	Died	Massive bleeding and multi-organ failure
7	35/male	Tuberculosis, PE $\times 5$	432.6	I	Incompatible	(+)	Alive	

PE: plasma exchange

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Edited by You DY
proofread by Sun SM