Long-term results of liver transplant in patients with chronic viral hepatitis-related liver disease in Singapore

Wai C T, Da Costa M, Sutedja D, Lee Y M, Lee K H, Tan K C, Isaac J, Wee A, Prabhakaran K, Lim S G

Department of Gastroenterology and Hepatology
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074

Wai C T, MBBS, MRCP, MMed
Consultant and Assistant Professor

Sutedja D, MBBS, MMed, FRCP
Consultant

Lee Y M, MBBS, MRCP
Consultant and Assistant Professor

Lim S G, MD, FRACP, FRCP
Senior Consultant and Associate Professor

Department of Surgery

Isaac J, MBBS, FRCS
Senior Consultant and Associate Professor

Prabhakaran K, MBBS, FRCS
Senior Consultant and Associate Professor

Liver Transplant Programme

Da Costa M, RN
Transplant Coordinator

Department of Medicine

Lee K H, MBBS, FRCP
Senior Consultant and Associate Professor

Department of Pathology

Wee A, MBBS, MRCPath, FRCPA
Senior Consultant and Professor

Asian Centre for Liver Diseases & Transplantation
Gleneagles Medical Centre
6 A Napier Road
Singapore 258500

Tan K C, MBBS, FRCS
Consultant

Correspondence to:
Dr Seng-Gee Lim
Tel: (65) 6772 4369
Fax: (65) 6779 4112
Email: mdclimsg@nus.edu.sg

ABSTRACT

Introduction: Liver disease from chronic hepatitis B (CHB) and C (CHC) constitutes 57 percent of adult liver transplant in Singapore. Their long-term results post-transplant may be affected by recurrence of the viral illness. This study aims to evaluate the long-term results and survival in patients transplanted for CHB- and CHC-related liver disease.

Methods: Patients transplanted for CHB- and CHC-related disease from 1990 until March 2004, which included decompensated cirrhosis and hepatocellular carcinoma (HCC), were reviewed and analysed.

Results: 25 patients were transplanted for CHB-related liver disease, with mean follow-up of 153 ± 25 weeks. Two- and four-year survival rates were 75 percent and 69 percent, respectively. Hepatitis B recurrence from YMDD mutants occurred in five patients, and four were treated successfully with adefovir dipivoxil, with resolution in transaminases and/or improvement in histology. One patient became non-compliant with follow-up and medications, and died 173 weeks post-transplant from reactivation of the wild-type hepatitis B virus. Nine patients were transplanted for CHC-related liver disease, with mean follow-up of 188 ± 40 weeks, and two- and four-year survival rates of 89 percent and 76 percent, respectively. Two patients developed hepatitis C recurrence and were treated with interferon and ribavarin. One responded with sustained response but the other remained viraemic and died of HCC recurrence two years post-transplant.

Conclusion: Long-term results from CHB- and CHC-related liver diseases were satisfactory and comparable to major transplant centres in the USA and Europe. Recurrence of viral hepatitis post-transplant is controllable with current antiviral therapy.

Keywords: anti-viral agents, chronic hepatitis B, chronic hepatitis C, hepatitis, lamivudine, liver transplantation

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INTRODUCTION

Chronic hepatitis B (CHB) is a serious liver disorder that can lead to acute liver failure, liver cirrhosis or hepatocellular carcinoma (HCC), with a high mortality and morbidity[1]. In Singapore, 4.1% of the population are carriers of hepatitis B virus and hence, complications from CHB constitute the commonest indication for liver transplant in Singapore[2]. The introduction of post-transplant hepatitis B prophylaxis, such as hepatitis B immunoglobulin (HBIG), lamivudine and adefovir dipivoxil, has allowed liver transplantation to be safely performed in patients with HBV-related liver diseases, and long-term results of liver transplant from CHB-related disease are now comparable to those of non-CHB related diseases[3]. Combination prophylaxis with lamivudine and long-term high dose HBIG appears to be the most effective strategy for preventing HBV recurrence with rates of 0-10% one year after transplant[4]. However, the cost of HBIG is prohibitively high (first year cost >US$100,000; subsequent yearly cost >US$50,000), which has limited its universal use. In Singapore, as in many other Asian countries, lamivudine monoprophylaxis has been the standard of care pre- and post-liver transplantation[5-7].

Chronic hepatitis C (CHC), on the other hand, is relatively rare in Singapore and in parts of Asia[8]. However, complications from CHC are one of the relatively more common indications for liver transplant in Singapore[2]. Although recurrence of CHC after liver transplant is common, antiviral therapy with combination treatment of pegylated interferon and ribavarin has improved response rate even in post-liver patients with hepatitis C recurrence[9]. In this study, we aimed to evaluate the long-term results of liver transplantation in Singapore for patients transplanted for complications of CHB and CHC.

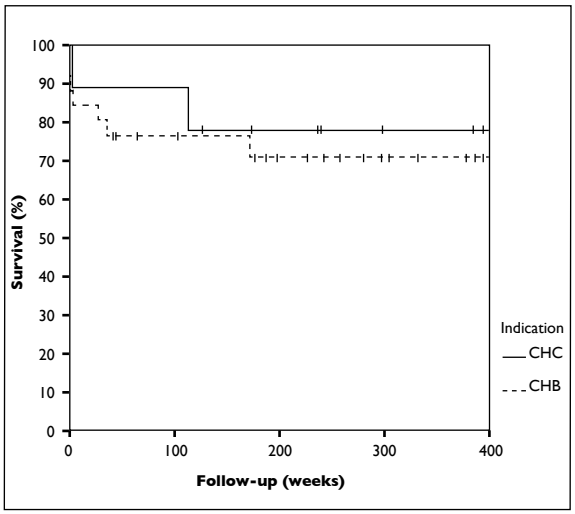

Fig. 1 Long-term survival of patients transplanted for chronic hepatitis B (CHB) and chronic hepatitis C (CHC).

Table I. Virological recurrence of all patients.

Patients transplanted for chronic hepatitis B-related liver disease (n=25)	
Follow-up period	153 ± 25 weeks
Negative HBsAg	19 (76%)
Positive HBsAg	6 (24%)
Positive HBsAg and HBV DNA	5 (20%)
Patients transplanted for chronic hepatitis C-related liver disease (n=9)	
Follow-up period	219 ± 43 weeks
Positive HCV RNA	7 (78%)
Positive HCV RNA with clinical recurrence	6 (75%)

METHODS

All adult patients with CHB- and CHC-related liver disease who underwent liver transplantation under the Liver Transplant Programme at the National University Hospital from January 1990 to February 2004 were reviewed and analysed. Patients with decompensated cirrhosis or hepatocellular carcinoma from either CHB or CHC were considered for transplantation. All CHB patients on the waiting list for liver transplant were given oral lamivudine 100 to 300 mg per day for at least four weeks prior to and indefinitely after the transplant as prophylaxis. HBIG was not given due to its cost. HBV DNA was measured three-monthly by branched-chain HBV DNA assays (Digene®, Digene Corp, USA), with a lower detection level at 100,000 copies of HBV DNA per ml. Liver transplant was performed only if the last pre-transplant HBV DNA was undetectable.

The post-transplant regime of immunosuppression consisted of weaning dose prednisolone with either tacrolimus or cyclosporineA with azathioprine. Following liver transplant, HBsAg and branch-chain HBV DNA assay (Digene®, Digene Corp, USA) were done on at three-monthly intervals. HBV DNA assay by Digene® was used as its range of 10^5-10^8 copies/ml was of clinical significance, according to the treatment guideline by the American Association for the Study of Liver Diseases[10]. Liver biopsy was performed annually. Rate of recurrence of HBV (defined as reappearance of HBsAg and HBV DNA) and its effects on patients' liver function were reviewed and analysed. Genetic sequencing of HBV DNA was not routinely performed. When HBV recurrence occurred despite being on lamivudine, lamivudine resistance were confirmed by direct sequencing, and lamivudine would be substituted with adefovir dipivoxil 10 mg daily.

All patients with CHC-related liver diseases were given the same immunosuppressive therapy as CHB patients. Pre-transplant or post-transplant pre-emptive anti-viral therapy was not routinely given. Diagnosis of recurrence of hepatitis C post transplant was defined virologically by detectable HCV RNA by PCR, as well as clinically by abnormal liver panel with compatible liver histology. Treatment of hepatitis C recurrence included ribavarin with standard (before 2002) or pegylated interferon (after 2002).

Data were expressed as mean ± standard error (SE) of mean unless otherwise stated, and were analysed using the Statistical Package for Social Sciences (SPSS) version 10.0 (Chicago, IL, USA). Survival analysis was estimated by the Kaplan-Meier method. Survival between those transplanted for different indications were compared by the log rank test.

RESULTS

Chronic hepatitis B-related liver diseases

From January 1990 to February 2004, 56 adult liver transplants were performed at NUH of which 25 (45%) were for CHB-related diseases (ten hepatocellular carcinoma, 13 decompensated cirrhosis, and two subacute liver failure from acute exacerbation of hepatitis B). Age of patients was 49 ± 1 (range 33-60) years, and all were male. Mean follow-up period post-transplant was 153 ± 25 (range 0-352) weeks. 18 (72%) were alive at their last follow-up. Mean survival post-transplant was 178 ± 27 weeks. Two- and four-year survivals were 76% and 71%, respectively (Fig. 1).

Five of the 25 (20%) patients developed hepatitis B recurrence (i.e. positive for both HBsAg and HBV DNA) after 104 ± 48 (range 14-260) weeks post-transplant. All were proven to harbour the YMDD

Table II. Mortality post-liver transplant for patients with CHB- or CHC-related liver diseases.

Indications	Cause of mortality	Time of death post-transplant
Hepatitis B-related diseases		
1. Acute liver failure from reactivation	Post-operative bleeding	1 day
2. Decompensated hepatitis B cirrhosis	Sepsis following retransplant	35 weeks after first transplant and 2 weeks after retransplant
3. Hepatocellular carcinoma	HCC recurrence	28 weeks
4. Decompensated hepatitis B cirrhosis	Sepsis	10 days
5. Hepatocellular carcinoma	Hepatitis B recurrence	173 weeks
6. Hepatocellular carcinoma	Primary non-function	1 day
7. Decompensated hepatitis B cirrhosis	Cardiac failure	2 weeks
Hepatitis C-related diseases		
1. Hepatocellular carcinoma	Hepatic artery thrombosis	2 weeks
2. Hepatocellular carcinoma	HCC recurrence	114 weeks

mutants and were started on adefovir dipivoxil for 101 ± 27 (range 4-155) weeks. Four patients remained well with serum creatinine at 144 ± 21 uM at their last follow-up. One patient was non-compliant with immunosuppressive and antiviral drugs and died of subacute liver failure from reactivation of wide type hepatitis B virus 173 weeks post-transplant, and 135 weeks post-commencement of adefovir dipivoxil.

One patient became HBsAg positive 62 weeks post-transplant but remained HBV DNA negative with normal liver panel till his last follow-up 159 weeks post-transplant. The other 12/18 (67%) patients without hepatitis B recurrence were all negative for HBsAg with undetectable HBV DNA level (Table I). Causes of mortality for the other CHB patients are listed in Table II. None of the patients died of hepatitis B-related complications, except for one patient who was non-compliant with medication.

Chronic hepatitis C-related liver diseases

Since 1990, nine (16%) patients were transplanted for CHC-related diseases (six HCC and three decompensated cirrhosis). The mean age of patients was 59 ± 1 (50-64) years, and eight (89%) were male. Seven (78%) were alive at follow-up of 219 ± 43 (range 2-393) weeks. Two- and four-year survivals were 89% and 78%, respectively (Fig. 1). One patient died of sepsis two weeks post-transplant. Another patient developed hepatitis C recurrence both virologically and histologically with bridging fibrosis eight months post-transplant, but died of HCC recurrence 14 months post-transplant (Table II).

Among the eight patients who survived the immediate post-transplant period, seven (88%) developed virological recurrence with detectable HCV RNA post-transplant, of which six (75%) developed clinical recurrence with elevated transaminases and compatible histology. Five patients received anti-viral treatment but three stopped treatment after one, 14 and 20 weeks respectively, due to adverse effects in two, and recurrence of HCC in one patient. Two patients completed 12 months of standard interferon and ribavarin and both achieved end of follow-up virological response, representing a cure of their HCV. When comparing the survival between those with and without chronic viral hepatitis, the two- and four-year survival rates between those transplanted for chronic viral hepatitis B or C were 81% and 81%, respectively, which was similar to those of adult patients transplanted for other indications (76% and 70%, respectively, p=0.42).

DISCUSSION

Our study showed that CHB- and CHC-related liver disease constituted 57% of all indications for adult liver transplants in Singapore. The high prevalence was not surprising, as chronic hepatitis B is endemic in Singapore with 4.1% of carrier rate, and complications develop in 10-40% of patients with chronic hepatitis B[11]. Long-term survivals for both conditions post-transplant are reasonable at 68% and 76%, respectively, and are comparable with results in major centres in the USA and Europe[12,13].

Our results showed that our current strategy of antiviral prophylaxis of lamivudine monotherapy pre- and post-transplant, followed by adefovir dipivoxil when lamivudine resistance occurs, is effective. With the use of prophylactic lamivudine, none of the liver transplant recipients developed fibrosing cholestatic hepatitis after liver transplant.

Five patients developed post-transplant recurrence of hepatitis B from YMDD mutants but all had their hepatitis B viral load controlled by salvage therapy with adefovir dipivoxil. One patient, unfortunately, became non-compliant post-transplant and stopped taking his immunosuppressants and antiviral treatment. He also defaulted follow-up despite repeated reminders, and subsequently died of subacute failure from reactivation of hepatitis B. Virological analysis revealed his reactivation was from a wild-type of hepatitis B virus, indicating that he deteriorated due to non-compliance rather than ineffectiveness of adefovir dipivoxil.

Long-term adefovir dipivoxil is considered safe, as less than 5% of patients develop renal toxicity and less than 4% develop adefovir resistance after three years of follow-up[14]. Our favourable results are comparable to results from Hong Kong, where HBV recurrence was only 2.7%, with HBV prophylaxis being lamivudine with/without adefovir dipivoxil[15]. Despite our policy of not using HBIG peri- or post-transplant, which is considered the standard of care in the West[16], our results show that viral relapse is easily controlled with adefovir dipovoxil, thus saving about S$10,000 per patient per year, without affecting adverse outcomes.

Our experience contrasted sharply with those of Multimer et al from the United Kingdom[17]. In their study, they reviewed the clinical course of four liver transplant patients who developed graft infection with lamivudine-resistant virus. Lamivudine-resistant HBV developed after a mean duration of 36 (range 32-44) weeks post-transplant. Liver function abnormalities occurred at a mean duration of 24 (range 12-48) weeks after the emergence of lamivudine-resistant virus, with three of the four patients dying 20-80 weeks later. As hepatitis B is prevalent in Singapore and complications of liver cirrhosis are the tenth most common cause of death in Singapore, our results are especially encouraging[18].

Unlike published reports from USA and Europe where post-transplant hepatitis C recurrence was almost universal[19], recurrence is uncommon in our population. All other patients transplanted for CHC-related liver diseases remained well with normal transaminases. This could be due to different patient background, and further studies are necessary to evaluate differences in recurrence rates between Caucasian and Asian patients.

In summary, our results are encouraging to many Asian countries like Singapore, where HBV is endemic[20,21]. Patients with HBV-related liver diseases can achieve satisfactory long-term survival. Prophylactic lamivudine monotherpay pre- and post-transplant appeared to be effective in preventing graft reinfection of HBV and graft failure. Lamivudine-resistant HBV post-liver transplant occurred in 28% of patients but was treatable with substitution with adefovir dipivoxil. Long-term outcome of patients transplanted for CHC-related diseases is also satisfactory. Further studies on better prophylaxis and treatment of HBV reinfection as well as studies on the optimal timing of treatment of CHC-related liver diseases, would further improve the long-term results. The era of long-term survival of patients with end-stage liver disease due to viral hepatitis has now arrived, with effective combined treatment comprising successful liver transplantation and anti-viral therapy.

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