Original Paper

HCC Influence on Patient Survival After Liver Transplantation for HDV Cirrhosis

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ABSTRACT

Background/Aims: The effect of hepatocellular cancer (HCC) in patients transplanted for hepatitis B and D virus (HB/DV) cirrhosis is not well studied. Our aim was to study the long-term survival outcomes of patients who underwent liver transplantation for HB/DV cirrhosis with and without HCC.

Methodology: A total of 231 primary, adult, single-organ liver transplants were performed from 1990 to 2007. HB/DV was the cause of cirrhosis in 36 patients. Nine patients died during the first 3 postoperative months from surgical complications. The study group comprised the remaining 27 patients. The median follow-up was 1515 days.

Results: The mean patient survival was 3760 days (95% CI: 3013-4507). Six patients were diagnosed with HCC. The mean patient survival was 3011 days (95% CI: 2344-3679) and 4036 days (95% CI: 3002-5070) for recipients without and with HCC, respectively. For the same groups, the incidence of microbial infections was 61.9% and 33.3%, respectively (p=0.219). HCC has not recurred in any of the six patients.

Conclusions: The mean long-term survival after liver transplantation for HB/DV and HCC surpassed 11 years. The superior survival of HCC patients is difficult to explain. The increased number (almost double) of microbial infections in the non-HCC population might be held accountable.

KEY WORDS: Liver transplantation; Patient survival; Hepatitis B and D virus co-infection; Hepatocellular cancer; Outcomes

ABBREVIATIONS: Hepatocellular Cancer (HCC); Hepatitis B and D Virus (HB/DV); Orthotopic Liver Transplantation (OLTx); Hepatitis B Virus Infection (HBV); Hepatitis D Virus Infection (HDV); Anti-HB Immunoglobulin (HBIg); Model for End-stage Liver Disease (MELD); Acute Cellular Rejection (ACR); Cytomegalovirus (CMV)

INTRODUCTION

In immunocompetent patients, hepatitis B virus plus hepatitis D virus co-infection (HB/DV) is associated with worse patient outcomes. In fact, HB/DV results more often in chronification of liver disease (1) and is associated with a higher risk of hepatic decompensation and an elevated risk of hepatocellular carcinoma (2). On the other hand, the results of orthotopic liver transplantation (OLTx) in patients with HB/DV are superior than those of recipients with single hepatitis B virus infection (HBV) (3,4). Indeed, in a recent comparative study, HB/DV mean recipient survival was 13.3 years, whereas HBV mean patient recipient was only 8.2 years (5). It seems that hepatitis D virus infection (HDV) improves the outcomes of HBV after OLTx due to lower re-infection rates (6-8). The use of single immunoprophylaxis with anti-HB immunoglobulin (HBIg) after OLTx for HB/DV, yielded an average re-infection rate of approximately 17% (4,8-11). Combined prophylaxis against the recurrence of HB/DV with HBIg and nucleos(t)ide analogs appears to be even more beneficial (12).

Approximately 25% of liver graft recipients with HBV are co-diagnosed with HCC. Presence of HCC is a significant prognostic indicator of an inferior 5-year patient survival after OLTx (13). However, that might not be the case for recipients with HB/DV. Recurrence of cancer after OLTx for HB/DV and HCC ranges from 0% to approximately 20%, 3 years post-transplant (8,12). Data of longer follow-ups are lacking.

The aim of this study was to evaluate the long-term survival outcomes of patients who underwent OLTx for HB/DV and HCC.

METHODOLOGY

A total of 231 consecutive, primary, single-organ OLTx were performed from 1990 to 2007 in our institution. All the recipients were adults. Their records were retrospectively collected for analysis. HB/DV was the cause of cirrhosis in 36 patients (15.6%). Nine patients died during the first 3 post-operative months from surgical complications. The study group comprised the remaining 27 (10 females, 17 males) patients with a median age of 45 years (range, 18-63 years). Median, minimum and maximum follow-ups for the study group patients were 1515, 365 and 4626 days, respectively.

No induction immunosupression was used. Maintenance immunosupression included cy-

closporine, mycophenolate mofetil and methylprednisolone. Cyclosporine C_0 levels were kept between 120-160μg/mL for the three first postoperative months and between 80-120μg/mL thereafter. Mycophenolate mofetil was quickly (over two-weeks time) tapered down to 1000mg *per os*/day. Methylprednisolone was either tapered to 4mg *per os*/day or completely discontinued by the sixth postoperative month.

Twenty-five patients had no traceable HBV DNA before transplant. Two patients had between 200-100,000 copies/mL of HBV DNA. No patient with >100,000 copies/mL of HBV DNA was transplanted. Post-transplant prophylaxis against HBV recurrence was achieved by HBIG administration so as to maintain a titer of >500IU/L for the first 2 postoperative months and >100IU/lL thereafter. Prophylaxis was always supplemented by analogues (one or combination), *i.e.* lamivudine, adefovir, entecavir or tenofovir, depending on the era of treatment and the clinical scenario.

The study group was split according to the presence of HCC in the explant in two sub-groups. Subgroup A' (n=21, 77.8%) was free from HCC whereas sub-group B' (n=6, 22.2%) was diagnosed with HCC. All sub-group B' recipients were within Milan criteria both by radiology and pathology (in the explant) studies.

The patient survival was analyzed. Recipients' and donors' demographics (gender and age) and other characteristics (donor's length of stay in the intensive care unit, cold ischemia time, model for end-stage liver disease (MELD) score at the time of transplant, duration on the waiting list, renal impairment and diabetes mellitus diagnosis) were studied and compared between the two sub-groups. The incidence of acute cellular rejection (ACR), cytomegalovirus (CMV) infection, microbial infection, HBV recurrence and HCC recurrence was also recorded and compared. Renal impairment was defined as serum creatinine ≥1.7mg/dL. Diabetes mellitus was defined as the need for hypoglycemic agents or insulin. ACR was diagnosed by liver biopsy. CMV infection was diagnosed by PCR. In order for the diagnosis of a microbial infection to be placed, besides the clinical picture (fever and/or white count abnormalities), a positive culture was required. HBV recurrence was diagnosed by the return of HBsAg seropositivity. HCC recurrence was always diagnosed by biopsy.

Data entry and statistical analysis were performed using the SPSS statistical software, version 16.0.1 for Mac (SPSS Inc., Chicago, IL, USA). For continuous data description mean values (± standard deviation) were utilized and Mann Whitney U was employed to identify statistical significance. For categorical data, because of the small size of the study group (n=27), absolute numbers were always provided with percentages only in brackets. Statistical significance was tested by the χ^2 test (Fisher's exact test). Kaplan-Meier analysis was employed to calculate and compare the recipients' actuarial survivals, which were presented by mean values and confidence intervals.

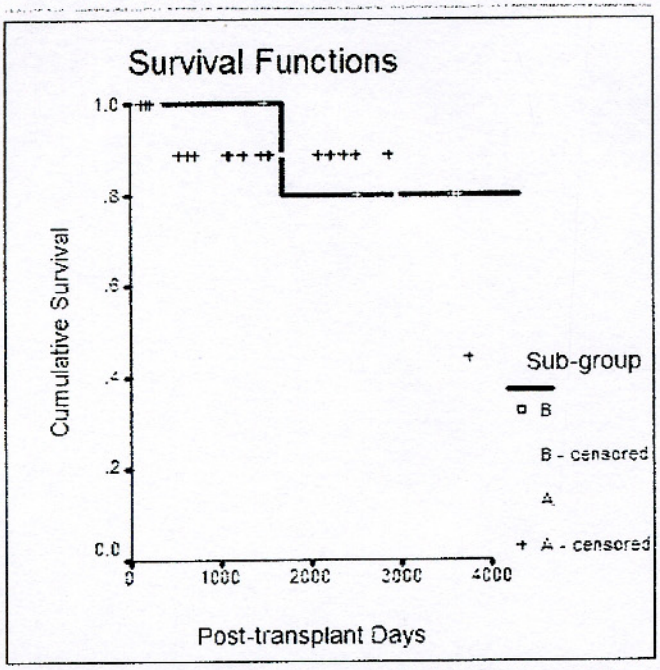

FIGURE 1 Actuarial patient survival after liver transplantation for HB/DV cirrhosis, categorized by absence (sub-group A) or presence (sub-group B) of HCC in the explant. The 10-year recipient survival was 45% and 80% for sub-group A and B, respectively (p=0.570).

RESULTS

The study group mean patient actuarial survival was 3760 days (95% CI: 3013-4507). Mean patient actuarial survival was 3011 days (95% CI: 2344, 3679) and 4036 days (95% CI: 3002-5070) for sub-group A' and sub-group B' respectively (**Figure 1**). Three deaths (one from intra-abdominal sepsis due to chronic ischemic cholangitis, one from microbial pneumonia and one from a heart attack) were recorded in sub-group A. On the other hand, one death (from a heart attack) was observed in subgroup B.

The study group mean recipient age was 43.7 (±11.5) years, the mean duration on the waiting list was 269.8 (±255.7) days and the mean MELD score at the time of transplant was 15.7 (±5.9). No recipient was diagnosed with renal impairment or with diabetes mellitus. On the other hand, mean donor age was 40.7 (±15.9) years, mean donor's length of stay in the intensive care unit was 7.2 (±2.1) days and the mean cold ischemia time was 7.8 (±2.0) hours. When recipients' and donor's demographics and characteristics were studied separately for the two sub-groups, no statistically significant differences were identified, except for recipient age (**Table 1**).

Three patients in sub-group A (14.3%) and one patient in sub-group B (16.7%) had at least one episode of acute cellular rejection. All rejection episodes

	Sub-group A (No HCC)	Sub-group B (Yes HCC)	*p*-value
Recipient age (years)	41.3 ± 11.3	52.2 ± 8.0	0.042
Duration on the list (days)	262.0 ± 232.3	297.2 ± 350.8	0.842
MELD at the time of transplant	16.8 ± 5.8	11.6 ± 5.1	0.088
Donor age (years)	40.3 ± 16.0	42.3 ± 17.2	0.887
Donor length of ICU stay (days)	7.1 ± 2.1	7.2 ± 2.3	0.977
Cold ischemia time (hours)	8.0 ± 2.1	7.0 ± 1.9	0.195

The values are given in means ± standard deviation.

Incidence of	Sub-group A (No HCC)	Sub-group B (Yes HCC)	p-value
Acute cellular rejection	14.3%	16.7%	0.659
CMV infection	19.0%	33.3%	0.404
Microbial infection	61.9%	33.3%	0.219
HB/DV recurrence	9.5%	16.7%	0.545

Actual numbers (not percentages) are given in the Results section of the text. Notice that, despite big numerical differences, there is no statistical significance in any of the parameters that were studied.

were treated successfully with steroid boluses. Four patients in sub-group A (19.0%) and two patients of sub-group B (33.3%) were diagnosed with a CMV infection. In sub-group A, the infection manifested as pneumonia (2 cases), as hepatitis and as enteritis. In sub-group B, the infection manifested as pneumonia and as hepatitis. Thirteen patients in sub-group A (61.9%) and two patients of sub-group B (33.3%) were diagnosed with a microbial infection. In sub-group A, the infection manifested as urinary tract infection (4 cases), as pneumonia (4 cases), as intra-abdominal sepsis (3 cases) and as wound infection (2 cases). In sub-group B, the infection manifested as pneumonia and as intra-abdominal sepsis. No statistical significance was identified between the two sub-groups for any of the observed complications (**Table 2**).

In 2 patients in sub-group A (9.5%) and in 1 patient in sub-group B (16.7%) recurrence of HBV was diagnosed. This was not statistically significant (**Table 2**). In all 3 cases, HDV was reactivated too. In these patients, hepatitis was diagnosed within 4 months after serum HBsAg reappearance. One of the 3 recipients (sub-group A) developed chronic active hepatitis, still without cirrhosis at 61 months post-transplant. The other two recipients spontaneously cleared serum HBsAg at 7 months post-transplant. No *de novo* HBV infection was diagnosed in either sub-group A or sub-group B patients. No HCC recurrence was diagnosed in sub-group B patients. No *de novo* malignancies were diagnosed in either sub-group A or sub-group B patients.

DISCUSSION

The long-term survival of OLTx in patients with HB/DV is superior to that of recipients with single HBV (3,4). In this study, the 10-year patient survival was 68%, a number higher by almost 20% than the ten-year patient survival for all the recipients transplanted in our center (14). This high long-term survival rate may be due to several factors: i) the low HBV recurrence rate of 11.1%; ii) the fact that in the three cases of HBV recurrence, no patient developed cirrhosis or severe liver failure requiring re-transplantation; and iii) the absence of HCC recurrence in patients that were transplanted for HB/DV and cancer. Lower HBV recurrence rates in transplanted patients for HBV/DV have frequently been reported (5,8-12,15) and are attributed to the HDV inhibitory effect on hepatitis B virus replication (15). On the other hand, the less severe evolution of HBV re-infection in patients transplanted for HB/DV, proving that HDV is beneficial to the natural course of HBV after OLTx not only due to prevention of HBV recurrence, has been noted in previous studies (4,10,11). However, no study has pointed out the fact that the presence of HCC in the explant might not be a predictor of inferior mortality of patients transplanted for HB/DV, although relevant observations have been made at least indirectly. For example, Samuel *et al.* (8) presents no mortality from HCC in five patients transplanted for HB/DV and cancer, within 4 years of follow-up. In another study, Rifai *et al.* (5) report a mean patient survival of 13.3 years after OLTx for HB/DV; when HCC patients are excluded, the mean survival is increased (not statistically significant) by a mere 0.4 years.

In the present study, long-term survival after OLTx for HB/DV is not affected by the presence of HCC in the explant. In fact, the 10-year survival for recipients with HCC is higher (80%) than for the recipients without HCC (45%). Despite the high numerical difference, there is no statistical significance due to the small size of sub-group B (n=6). However, it is tempting to assume that this is a type II error and that patients with HB/DV and HCC have at least equal, if not better, long-term survival than patients without cancer.

Looking for an explanation of why liver recipi-

ents with HB/DV and cancer might fare better than those without HCC, we compared patient and donor demographics and other characteristics (**Table 1**). The only parameter with statistical significance was recipient age; however it was in favor of the patients without HCC. On the other hand, MELD score was numerically (but not statistically) higher for the patients without HCC. However, since we have excluded from the study all patients that died during the postoperative period, the possible difference in MELD score cannot explained the difference in long-term survival (16).

Two of the secondary end-points of this study might explain why liver recipients with HB/DV and cancer fare possibly better than those without HCC.

Firstly, the incidence of microbial infections is double in recipients without cancer. Again, despite the high numerical difference, there is no statistical significance due to the small size of sub-group B. However, there is a definite trend, and since three out of four deaths in sub-group A occurred due to severe microbial infections, it is tempting to assume that this is one of the main reasons why liver recipients without HCC had an inferior survival. The explanation for this observation is difficult. Perhaps, the fear of HCC recurrence dictated a less "intense" immunosupression. This fact might have resulted in reduction of the incidence of microbial infections, leading to the improved 10-year patient survival. Indeed, median cyclosporine C_0 levels, 12 months post-transplant, were 118ng/mL and 92ng/mL for recipients in sub-group A and B respectively. Although this difference in levels was not statistically significant and no specific studies were performed to evaluate patients' real immune state, it might be an indirect indication of decreased host defense and therefore increased probability of infection occurrence.

Secondly, the absence of HCC recurrence in patients transplanted for HB/DV and cancer despite a median follow-up of almost five years, when most of tumor relapses occur within the first two post-transplant years (17). It is tempting to assume that since the hepatitis B virus is tumorigenic (18-20), the HDV inhibitory effect on hepatitis B virus replication (12) leads to less tumor recurrences. In addition, the less "intense" immunosupression (see previous paragraph) might be responsible for the complete absence of HCC recurrences.

In conclusion, it appears that the improved patient survival observed after OLTx for HB/DV when compared with OLTx for single HBV is due to many reasons. The observation that the presence of HCC in the liver explant might not have a detrimental effect in recipient survival is one of them. Of course, the small size of the population precludes the drawing of any definite conclusions. Perhaps, a single-center study from a bigger (than ours) institution or a meta-analysis of the already published data will help verify or reject the findings reported in this paper. We believe that any research done regarding outcomes after OLTx for HB/DV should include simultaneous studies of recipients' state of immunity (*i.e.* immunophenotyping, T- and B-cell sub-populations, *etc.*).

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