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Increased mortality after liver transplantation for hepatocellular carcinoma in hepatitis B-associated cirrhosis

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Abstract Transplant patients suffering from hepatocellular carcinoma in cirrhosis are selected according to tumor nodule number and diameter. Vascular invasion and histopathological grading are predictive of outcome. The prognostic influence of hepatitis B-cirrhosis has been investigated after resection and after local tumor treatment, but not after transplantation. Of the 1,188 transplantations performed between 1989 and 2000, 120 were on patients with hepatocellular carcinoma in cirrhosis (HCC) (follow-up: 57 months; 1–140 months). Within this group, 25 patients (21%) suffered from hepatitis B. Pre-transplant selection criteria were a maximum diameter of 5°cm in uni-nodular tumors, or 3°cm for two to three tumor nodules. The rate of tumors with 2–3 tumor nodules was increased in the hepatitis-B group (52% vs. 29%; $P < 0.05$). Other tumor characteristics did not differ. In the hepatitis-B group, more patients died post-transplantation (44% vs.22%; $P < 0.05$). This difference was due to unspecific causes, not to tumor recurrence or re-infection. These findings may be indicative of a more complicated course in patients suffering from hepatitis B in general.

Keywords Hepatocellular carcinoma · Liver transplantation · Cirrhosis · Hepatitis B · Tumor recurrence

Introduction

Vascular invasion and histopathological grading of hepatocellular carcinoma have been reported to be the most significant determinants of post-transplant patient survival [3]. Moreover, in our experience, an influence of underlying primary disease on the outcome cannot be ruled out for the first years after transplantation if the cirrhosis was due to a hepatitis-B infection [6]. However, this difference represented a trend and was not statistically significant. To date, it is uncertain whether hepatitis B-associated liver cirrhosis has additional prognostic impact, and, if this is indeed the case, whether it is due to the cirrhosis itself or to the characteristics of a tumor rising within the cirrhosis.

Data obtained after liver resection or in situ ablation by local treatment suggest a strong prognostic influence [8, 15]. Intra-hepatic recurrence rates at a site different from the primary lesion at 4 years after treatment were 100% in a hepatitis-B group, 57% in a hepatitis-C group, and 28% in patients with non-B non-C hepatitis [8]. Moreover, various mechanisms of tumor development with a more aggressive tumor potential in hepatitis

B than that of the primary disease have been suggested [12, 13, 14]. In this study we report on the differences of tumor characteristics according to hepatitis-B as the underlying liver disease.

Patients and methods

This study comprises all 120 patients with a non-fibrolammellar hepatocellular carcinoma in cirrhosis that had undergone liver transplantation from 1989 to 2000. Minimum follow-up of the surviving patients is 10 months. Among these 120 patients, 25 (21%) suffered from hepatitis B. Two of these patients were positive for the δ antigen. In the other 95 patients, the underlying diseases were hepatitis C-associated liver cirrhosis ($n=47$; 39%), alcohol toxic liver cirrhosis ($n=24$; 20%), cryptogenic liver cirrhosis ($n=17$; 14%), hemochromatosis ($n=3$; 3%), and, in one patient each, primary biliary cirrhosis (PBC), porphyria cutanea tarda, and autoimmune hepatitis.

Liver transplantation was performed because of the underlying liver cirrhosis or a presumed irresectability of a tumor due to impaired functional hepatic capacity. Selection criteria regarding the tumor were a maximum diameter of 5°cm in solitary tumors, and of 3°cm in the case of two or three tumor nodules [9, 10]. Pretransplant diagnosis of vascular invasion resulted in the exclusion of the patient.

The transplantation technique is described elsewhere [4]. There was no donor age limit throughout the entire study period. Steatotic livers were accepted if the degree of steatosis did not exceed 30%. Donor selection was mainly based on the harvesting surgeon's personal impression of a potential liver graft. If the assessment of a graft was considered to be critical, the decision was objectified with a frozen section biopsy. Primary malignancy of the donor – except for selected cases of primary cerebral neoplasia – was an exclusion criterion [5].

Immunosuppression was achieved with cyclosporine and tacrolimus as the primary agents. Concomitant and immunosuppressive treatments were implemented as described elsewhere [11]. Since 1989, all patients with hepatitis B undergoing liver transplantation have undergone long-term passive immunoprophylaxis with HBs-hyperimmunoglobuline (Hepatect, Biotest, Dreieich, Germany) with titers aimed at over 100 U/l.

The explanted livers were sliced and examined by an experienced histopathologist. Vascular invasion relates in this study mostly to microscopic, but also to pre-transplant undetected macroscopic, infiltrations. The tumor stages according to the International Union against Cancer (UICC) followed the 5th edition of the TNM classification [2]. Statistical comparison was achieved by means of the log-rank test and the χ^2 test for patient survival and categorical variables, respectively.

Results

Demography, follow-up, Child–Pugh stage at transplantation, and primary immunosuppressive drug did not differ between patients suffering from a hepatocellular carcinoma in a hepatitis B-associated cirrhosis and patients suffering from other types of underlying liver cirrhosis (Table 1). The follow-up period was the same for the group of patients with a hepatocellular carcinoma in an alcohol toxic cirrhosis (1,395 ± 906 days).

A total of 24 patients (20%) had tumors not fulfilling the selection criteria due to diagnostic inaccuracy or progression thereafter. This rate tended ($P=0.07$) to be higher in the hepatitis-B group ($n=8$; 32%) than in all other patients with a hepatocellular carcinoma ($n=16$; 17%).

Of the eight patients in the hepatitis-B group, six presented with two or three tumor nodules that exceeded the limit of 3 cm for the maximum diameter (median 4 cm; range 3.5–7 cm). The hepatitis-B group had a significantly higher rate of hepatocellular carcinomas with two or three tumor nodules than all other patients with a hepatocellular carcinoma (52% vs. 29%; $P<0.05$; Table 2). None of the other tumor-associated variables differed significantly between both groups, and the rates of vascular invasion were identical (40%; Table 2).

No patient with cryptogenic or alcohol toxic liver cirrhosis died during the first year post-transplantation. One-year survival of patients with hepatocellular carcinomas in a hepatitis B-associated liver cirrhosis was 84%. Though this difference did not reach statistical significance, we detected a trend towards impaired survival when comparing patients suffering from hepatitis B-associated hepatocellular carcinoma in cirrhosis with the subgroup of hepatocellular carcinoma in a cryptogenic liver cirrhosis at 5 years post-transplantation (survival rates: 59% vs 92%; $P=0.08$).

Significantly more patients died in the course after transplantation in the hepatitis-B group (44% vs. 22%; $P<0.05$; Table 3). The rates of death from tumor recurrence did not differ significantly and were 20% ($n=5$) among patients suffering from hepatitis B and 14% ($n=13$) in all others. In the hepatitis-B group, death

Table 1 Patients' characteristics according to a hepatocellular carcinoma arising in hepatitis B-associated or other types of liver cirrhosis ($P<0.05$) (*HBV* hepatitis B-virus-associated liver cirrhosis)

Characteristic	HCC in HBV cirrhosis $n=25$ (21%)	HCC in non-HBV cirrhosis $n=95$ (79%)
Male	23 (92%)	83 (87%)
Female	2 (8%)	12 (13%)
Age (years)	53 ± 6	55 ± 8
Post-transplant follow-up (days)	1,407 ± 1,205	1,437 ± 1,054
Child-A cirrhosis	6 (24%)	26 (27%)
Child-B cirrhosis	12 (48%)	44 (46%)
Child-C cirrhosis	7 (28%)	25 (26%)
Tacrolimus-based primary immunosuppression	12 (48%)	56 (59%)
Cyclosporine-based primary immunosuppression	13 (52%)	39 (41%)

Table 2 Tumor characteristics of hepatocellular carcinomas arising in hepatitis B-associated or other types of liver cirrhosis (*HBV* hepatitis B-virus-associated liver cirrhosis)

Characteristic	HCC in HBV cirrhosis $n=25$ (21%)	HCC in non-HBV cirrhosis $n=95$ (79%)
UICC stage I	5 (20%)	12 (13%)
UICC stage II	8 (32%)	33 (35%)
UICC stage IIIa	6 (24%)	20 (21%)
UICC stage IVa	6 (24%)	30 (31%)
Highly differentiated (G1)	11 (44%)	29 (30%)
Moderately differentiated (G2)	12 (48%)	48 (51%)
Poorly differentiated (G3)	2 (8%)	18 (19%)
One tumor nodule	10 (40%)	49 (52%)
Two to three tumor nodules	13 (52%)*	28 (29%)*
> Three tumor nodules	2 (8%)	18 (19%)
< 3 cm	16 (64%)	61 (64%)
3–5 cm	6 (24%)	21 (22%)
> 5 cm	3 (12%)	13 (14%)
Vascular invasion	10 (40%)	38 (40%)
Non-compliance with pre-transplant tumor criteria	8 (32%)	16 (17%)

*$P < 0.05$

Table 3 Cause of death after liver transplantation for hepatocellular carcinoma in cirrhosis associated with hepatitis B or other types of liver cirrhosis (*HBV* hepatitis B-virus-associated liver cirrhosis)

Cause of death	HCC in HBV cirrhosis $n=11$ of 25 (44%)*	HCC in non-HBV cirrhosis $n=21$ of 95 (22%)*
Tumor recurrence	5	13
De novo tumors	1	4
Cardiac failure	–	2
Intracranial bleeding	2	–
Sepsis	1	1
Rejection	–	1
Initial non-function	1	–
Recurrence of primary liver disease	1	–

*$P < 0.05$

from recurrence always occurred in the first 2 years post-transplantation, compared with a rate of 21% of the other patients dying from recurrent tumors after 5 to 7 years. The second most common cause of death was non-hepatocellular de novo cancer, occurring with an identical rate of 4% in both groups. Exclusion of tumor recurrence as well as de novo tumors resulted in a significantly increased rate of non-tumor deaths in the hepatitis-B group (20% vs 4%; $P=0.02$; Table 3). The difference also remained significant after further exclusion of one patient who had died from a hepatitis-B re-infection (16% vs. 4%; $P<0.05$). One patient in each group had died during the immediate postoperative course, i.e., within 120 days after undergoing transplantation. This accounts for an overall postoperative mortality of 1.7% (hepatitis-B group: 4%; others: 1%; not significant). Hepatitis-B re-infection was also the only underlying liver disease resulting in retransplantation ($n=2$).

Discussion

The present study indicates that application of the current tumor selection criteria for liver transplantation results in an even distribution of tumor-associated parameters, also in the case of hepatitis B-associated liver cirrhosis. In terms of tumor nodule number and non-adherence to pre-transplant criteria, the observed differences represent a selection error. Vascular invasion, as the most important prognostic parameter, nevertheless occurred at an identical rate of 40% in hepatitis-B and non-hepatitis B-associated cirrhosis. Several factors may demonstrate that this finding cannot be expected unequivocally. For example, the protein encoded by the X gene within the reading frame of the hepatitis-B virus has an oncogenic potential of its own, in addition to liver cirrhosis itself as a risk factor [12]. Similar tumor size and tumor nodule number do not necessarily indicate identical biological behaviour of hepatocellular carcinomas. Recently, the proportion of small hepatocellular carcinomas quickly developing aggressive features, such as vascular invasion or poor differentiation, has been reported to be 15% [7]. However, data concerning a correlation with primary diseases were not reported. The discrepancy of an impact on tumor recurrence of the primary disease after liver resection and missing influence on the post-transplant course may be best explained by cirrhosis remaining a risk factor after resection but being treated by transplantation [1].

Interestingly, significantly more patients died after undergoing transplantation in the hepatitis-B group. This finding was not related to the most common causes of death, recurrence of hepatocellular carcinoma or de novo tumors. Only one patient died from a hepatitis-B re-infection, which almost rules out the fatal potential of the underlying liver disease as a major prognostic determinant. However, two patients underwent retransplantation after a hepatitis-B re-infection. This may be indicative of a more complicated post-transplantation course in patients suffering from hepatitis B in general, which can eventually result in causes of death appearing non-specific. So far, possible explanations are not at hand. Though these findings are still based on small patient numbers in the hepatitis-B group, further investigation and analysis appears warranted.

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