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Transplantation for alcoholic cirrhosis: How does recurrence of disease harm the graft?

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Abstract Many transplant centres are reluctant to accept alcoholic patients because of their supposed potential for alcoholic recidivism, resulting in graft failure and recurrence of alcoholic liver cirrhosis. From May 1982 to January 1993 80 patients received orthotopic liver transplantation (OLT) at our institution either for alcoholic cirrhosis exclusively ($n = 58$) or for a hepatoma in an alcoholic cirrhosis ($n = 22$). The outcome of these patients was analysed with particular attention to recurrence of liver disease. Overall survival in this group was 67% and 49% at 1 and 5 years, respectively, with a median follow-up of 45 months. Actuarial survival of patients transplanted since January 1989 ($n = 46$) and 84% and 82% at 1 and 2 years (median follow-up 31 months). Non-fatal clinical endpoints were analysed in those patients surviving for at least 3 months ($n = 61$). Return to alcohol abuse was documented in 16 patients at routine short-term out patient check-ups. All patients except one admitted to taking alcohol and showed changes in their laboratory test results. A specific pattern of liver function test values related to alcohol abuse was not detected and at the end of a relapse the liver function values usually returned to pre-event values. Only in one case was toxic injury of the liver related to alcoholic recidivism diagnosed on percutaneous liver needle biopsy or post-mortem examination. Complicance with the required immunosuppressive regimen and social rehabilitation after OLT were excellent. Unwillingness to offer OLT to individuals with alcoholic liver disease because of failure to demonstrate 100% long-term abstinence appears difficult to defend in the face of results showing good survival, compliance and social rehabilitation. The hypothesis of a higher sensitivity of the transplanted liver to a drinking episode and the redevelopment of alcoholic diesease in the new liver was not confirmed in our study population.

Key words Liver transplantation
Alcoholic liver cirrhosis
Alcoholic recidivism

Introduction

Orthotopic liver transplantation (OLT) is a therapeutic option for patients with end-stage liver disease that no longer responds to medical treatment [5, 11]. Alcohol-induced cirrhosis is one of the most common forms of fatal liver disease seen in the western world [4] and can be treated by OLT. Although the incidence is lower, the commonest benign indications for OLT in Europe are primary biliary cirrhosis and virus-induced cirrhosis [1]. Few centres, however, are willing to provide transplants to individuals with alcohol-induced liver disease. The major reason for this reluctance is the fear of a high rate of recidivism and poor compliance with the required immunosuppressive regimen, both resulting in graft failure. In contrast to patients suffering from other forms of liver cirrhosis, alcoholic cirrhosis is the fault of the individual. The reluctance to transplant alcoholic patients is further underlined by the supposed probability of recurrence of the pretransplant liver disease because of a higher sensitivity of the new liver to exogenic noxes. This hypothesis has been proved for virus-induced cirrhosis [13] but has only been assumed for alcohol-induced cirrhosis. Although this theoretical concern appears important, only scarce or inconclusive data relating to alcoholic recidivism and redevelopment of alcoholic liver disease after transplantation are available. The present study attempts to identify the significance of these two issues in this subset of liver transplant recipients. Furthermore, we evaluated survival rates, compliance with the required immunosuppressive regimen and social rehabilitation.

Patients and methods

From May 1982 to January 1993 80 patients (12 women, 68 men) with end-stage alcoholic liver disease underwent OLT at the Department of Transplant Surgery of the University of Vienna. Preoperatively 77% were classified as Child's score C and 23% score B. The indications for OLT were alcoholic cirrhosis exclusively in 58 cases and hepatoma and alcoholic cirrhosis simultaneously in 22 cases. Analysis of factors other than survival rate was restricted to patients surviving for more than 3 months. Thus 61 patients were available for analysis of non-fatal clinical endpoints. The diagnosis of alcoholic liver disease in each case was based on a history of habitual and excessive alcohol consumption in the absence of other causes of liver cirrhosis, compatible clinical and laboratory findings and the results of examination of the resected diseased liver after transplantation.

Patients had routine short-term outpatient check-ups at which they were personally contacted by a member of the transplant team to determine their current alcohol and illicit drug consumption, health status, compliance with the imunosuppressive regimen employment status (full-time employed, homemakers, unable to work), marital status (married, living together with a partner, single) and social status (regularly activities, no or occassional activities). A complete laboratory investigation (haematology, liver parameters, coagulation, electrolytes, total protein, renal parameters, electrophoresis, lipid profile) as well as the cyclosporine HPLC whole blood trough level (target level 100–150 ng/ml) were determined at every check-up. The follow-up intervals were usually once weekly during the first months after leaving the hospital, twice monthly during the second and third month, monthly during the first half year and thereafter every 2 or 3 months, and at every attendance personal contact might be necessary. For the purposes of this study, harmful drinking was defined as more than one drinking episode and moderate drinking as only one episode. Diagnosis was made by at least one of the following: patient admitted drinking, pattern of liver function test values (increase of serum gamma-glutamyl transpeptidase, serum alkaline phosphatase, erythrocyte mean cell volume, bilirubin and serum transaminase levels) or in some cases percutaneous liver needle biopsy.

Biopsies were performed when clinically indicated. The severity of acute graft rejection on biopsy was graded as mild, moderate or severe rejection. Anti-rejection treatment was started for the presence of moderate or severe rejection on histology. Rejection requiring treatment was classified as a clinically relevant rejection episode. The incidence of rejection episodes and the proportion of cyclosporine HPLC whole blood trough level above and below the target range were assessed as an approximative indicator of drug compliance.

Recurrence of alcoholic liver disease was assessed by histological examination either from a percutaneous needle biopsy specimen of the liver or from a post-mortem examination.

Patient survival and the alcoholic recidivism rate were calculated by the Kaplan-Meier method [6]. The Mantel [8] and Breslow [2] tests were used to test differences between proportions and the significance of associations. Differences in pre- and postoperative employment marital and social status were calculated by univariate Chi-squared analysis. A probability value of $P < 0.05$ was considered to be significant.

Results

Survival analysis

Of the 80 patients who received liver transplants, 44 (55%) were alive in June 1993. The overall survival rate at 1 and 5 years was 67% and 49%, respectively; median survival time at the time of this survey was 45 months. Actuarial survival of patients transplanted since January 1989 ($n = 46$) was 84% and 82% at 1 and 2 years (median follow-up 31 months). Survival of patients suffering from alcoholic cirrhosis exclusively ($n = 58$) versus those with hepatocellular carcinoma in an alcoholic cirrhosis ($n = 22$) was 71% versus 59%, and 66% versus 47% at 1 and 2 years, respectively (Fig. 1). The difference was statistically significant (Mantel $P = 0.043$) in the early period but not in the late period (Breslow $P = 0.220$). Of the 36 patients who died, 3 expired intraoperatively, 15 died in the early postoperative period (< 3 months) and 18 died subsequently (Table 1). Most of the patients (83%) who died after OLT were preoperatively Child's score C.

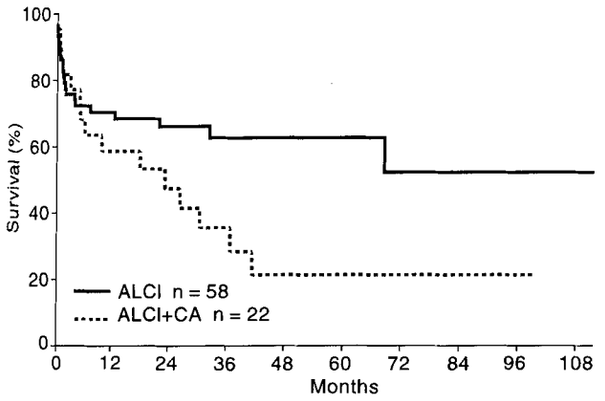

Fig. 1. Probability of patient survival for alcoholic cirrhosis (—) exclusively ($n = 58$, standard error > 10% at 66 months) and hepatoma in an alcoholic cirrhosis (---), $n = 22$, standard error > 10% at 6 months). P (Mantel) = 0.043, P (Breslow) = 0.220

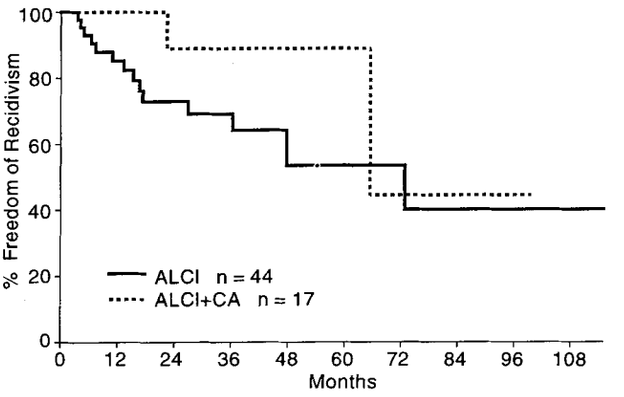

Fig. 2 Probability of freedom from alcoholic recidivism for alcoholic cirrhosis (—) exclusively ($n = 44$, standard error > 10% at 45 months) and hepatoma in an alcoholic cirrhosis (---, $n = 17$, standard error > 10% at 22 months). P (Mantel) = 0.178, P (Breslow) = 0.087

Table 1 Deaths after OLT

Cause	Intra-operatively (< 1 day)	Early post-operative (1 day to < 3 months)	Late post-operative (> 3 months)	Total
Bleeding	2			2
Sepsis		11	5[a]	16
Brain		2	1	3
Primary non-function		2		2
Other	1		4[a]	5
Carcinoma recurrence			8	8
Total	3	15	18	36

[a] One death related to alcoholic recidivism

Table 2 Alcoholic recidivism

	Alcoholic cirrhosis	Alcoholic cirrhosis + hepatoma	P-value (Mantel/Breslow)
Harmful	7	1	
Moderate	7	1	
	14 (32%)	2 (12%)	0.18/0.09

Alcoholic recidivism

Of the 61 recipients surviving for at least 3 months, 16 (26%) resumed alcohol consumption during the observation period (Table 2). Of these, eight (13%) returned to harmful drinking and eight (13%) reported only one episode of drinking. The rate of recidivism was 32% (14 of 44) in individuals who had alcoholic cirrhosis as the only indication for OLT as compared with 12% (2 of 17) in individuals where the indication for OLT was a hepatoma and the second diagnosis alcoholic liver disease (Fig. 2). This difference was not statistically significant (Mantel $P = 0.178$, Breslow $P = 0.087$). Of all recidivism events, 69% ($n = 11$) occurred during the first 2 years after transplantation with a median follow-up of 37 months.

Recurrence of disease

All patients except one admitted to taking alcohol and showed changes in their laboratory test results, but a specific pattern of liver function values related to alcohol abuse was not detected. Concerning the pre-event values, serum gamma-glutamyl transpeptidase varied between no increase and a 9-fold increase, serum alkaline phosphatase between no increase and a 3-fold increase, bilirubin between no increase and a 7-fold increase and serum transaminase levels between no increase and a 12-fold increase. The values of erythrocyte mean cell volume also showed inconclusive alterations. Increases were partially dependent on low red blood cell count, partially related to an alcoholic relapse, but mostly the reason remained unknown. At the end of the relapse liver function values usually returned to the pre-event value.

The one patient who did not admit alcoholic relapse but presented a suspect pattern of liver function values at least had a percutaneous needle-biopsy of the liver for exclusion of rejection. The histology demonstrated a mild form of non-specific injury of the liver parenchyma and, after informed being about the inconclusive histological diagnosis, even this patient admitted a drinking episode.

Out of the 16 patients with alcoholic recidivism 3 died. Two of these deaths were related to harmful alcoholic recidivism (Table 1). In the first patient liver function tests returned to pre-event values after a drinking episode but finally, 22 months after OLT, they remained highly pathological and the patient was admitted at our department. A percutaneous needle biopsy of the liver was performed and a massive nutritive-toxic injury and fibrosis of the transplanted liver were diagnosed. Harmful alcoholic recidivism was the reason for this massive damage to the liver, leading to sepsis and death. A second patient who was also known to have returned to harmful drinking, died 68 months after OLT as a consequence of a fall after excessive drinking. This patient demonstrated up to her death acceptable liver function tests and at post-mortem examination no alcohol-induced damage of the transplanted liver was found. The death of the third patient in this subset was not related to alcoholic recidivism. He suffered four drinking episodes and only at the time of alcoholic abuse could a pattern of liver function values be determined. This patient died 34 months after OLT from a cerebral insult. At post-mortem examination no alcohol-induced injury of the transplanted liver was found.

Compliance

Clinically relevant acute rejection occurred in 31% of patients during the observation period. None of the 61 patients surviving for at least 3 months had an episode of chronic rejection at any time. Furthermore no graft lost or death related to rejection occurred. A total of more than 2000 cyclosporine HPLC whole blood trough levels were performed in the study population with 93% of measurements within the target range.

Rehabilitation

Before OLT 34 (55.7%) of the 61 patients living longer than 3 months were unemployed and completely unable to work. Of these, only 5 remained unable to work and 29 classified themselves either as homemakers ($n = 26$) or obtained full-time employment ($n = 3$) postoperatively (Chi-squared $P = 0.001$). With regard to marital status, 34 patients (56%) were married preoperatively and 39 (64%) were married after OLT. Of the 12 unmarried patients before OLT, 4 remained single and 8 were currently living with a partner. All of the recipients had an equal or better marital status postoperatively (Chi-squared $P < 0.001$). Of the 11 patients with no or occasional social activities preoperatively, 10 improved to regular activities after OLT (Chi-squared $P < 0.001$).

Discussion

The major argument against the widespread use of OLT for alcoholic patients is a possible high rate of alcoholic recidivism that would prevent long-term survival and lead to redevelopment of the original liver disease in the allograft. Alcoholic patients would therefore have only a poor chance of successful social rehabilitation. Thus the major factors determining the candidacy of patients with alcohol-induced liver disease for OLT have been related to aspects other than medical issues. Furthermore, the screening process for those suffering from alcoholic cirrhosis is required to be especially rigorous because of medical factors affecting survival, particularly assumed accompanying multiorgan disease, which are themselves influenced by a history of heavy drinking and even more by its resumption [3].

In our series the potential risk of previous alcohol abuse did not affect long-term transplant success. The survival rate of our study population (OLT for alcoholic cirrhosis exclusively or OLT for a hepatoma in an alcoholic cirrhosis) did not differ from that of patients receiving transplants for indications other than alcoholic cirrhosis [9, 10, 13].

Concerning compliance with the immunosuppressive regimen, we expressed compliance as the incidence of rejection and measurements of cyclosporine trough levels. It is of great significance that no chronic rejection occurred in our study population and acute rejection episodes occurred no more frequently than in patients receiving OLT for other indications. Furthermore, non-compliance can be discounted because out of more than 2000 cyclosporine HPLC whole blood trough measurements, 93% were within the target range. Five retransplantations were performed in four patients, but none of the grafts failed because of acute or chronic rejection. We also found encouraging results concerning the employment, marital and social status of the patients.

In contrast to these good outcomes, the study population demonstrated a rather high alcoholic recidivism rate in comparison to rates reported by other transplant centres [7, 12]. The reason might be the very close follow-up of recipients after OLT at our department that may contribute to a more accurate detection of drinking episodes. Also changes in the liver function values and other laboratory test parameters were documented early

and in a short-term manner. Despite the large number of laboratory investigations a specific pattern of liver function values could not be detected. In general, after OLT many patients suffered from recurrent episodes of general infections or cholangitis, had other problems with the bile duct system or suffered clinically non-relevant rejection episodes. Therefore, in many recipients the pattern of liver function values were often a result of various overlapping effects. This circumstance is also reflected in patients transplanted for alcoholic cirrhosis. The extent of deviation of the separate liver function parameters in cases of a drinking episode demonstrated a non-specific reaction even if the liver function values were considered in relation to the pre-event values. The alterations may have been the result not only of alcoholic recidivism but also of non-alcohol-related problems existing simultaneously.

The susceptibility of a transplanted liver to alcoholic injury seems to be equal to that of the original non-transplanted liver as in both cases the pattern of liver function values usually returned to the pre-event values after a drinking episode. In contrast, after OLT for cirrhosis with persistent hepatitis B virus infection, a higher sensitivity of the transplanted liver to recurrence of disease has been demonstrated [13]. Todo et al. reported 11 deaths in 38 patients who were hepatitis B virus infected at the time of transplantation and survived for more than 60 days because of multiorgan failure related to recurrent hepatitis B virus infection. In an additional seven patients a retransplantation was necessary for recurrent hepatitis B virus infection. In patients who underwent a second retransplantation it was found that the second graft was even more vulnerable than the first. A similar behaviour of the graft after recurrent alcohol injury was assumed but was not found in our study population. Each of the 36 patients who died after OLT had a post-mortem examination. In none of these, in none of the retransplanted grafts and only in one of the percutaneous needle biopsy specimens was injury to the graft related to alcohol abuse.

Liver transplantation results in this series confirm that alcoholic patients with advanced liver disease can be transplanted successfully with a reasonable expectation of subsequent abstinence, social rehabilitation and quality of life. The experience of 10 years indicates that the survival rate does not differ from that of patients receiving transplants for other indications. Unwillingness to offer liver transplantation to individuals with alcoholic liver disease because of a failure to demonstrate 100% long-term abstinence, particularly in view of great risk of death without OLT, appears difficult to defend. The hypothesis of higher vulnerability of the transplanted liver related to alcoholic recidivism and redevelopment of alcoholic liver disease was not found in our study population.

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