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Repeat orthotopic liver transplantation in the 1990s: is it justified?

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Abstract Repeat orthotopic liver transplantation (ReOLT) is controversial because of limited donor organ availability and increasing health care costs. The purpose of this study is to analyse and compare the outcome of reOLT in the 1990s and the 1980s. Prospective data of 1077 adult OLT from the Liver Unit database were used for the study. The log-rank test was used for statistical analysis. Between January 1982 and December 1996, a total of 1077 adult OLTs were performed including 107 reOLTs. The proportion of retransplants decreased from 13 % in the 1980s to 9 % in the 1990s. There was a significant improvement in outcome; the overall 1-year graft and patient survival for reOLT was 60 % and 74 % in the 1990s compared to 29 % ($P < 0.0001$) and 51 % ($P < 0.0001$) in the 1980s. In the second half of the study between January 1990 and December 1996, 732 adult OLTs were undertaken including 70 (9 %) reOLTs which consisted of 62 second, 7 third and 1 fourth grafts. The main indications for retransplantation were chronic rejection (31 %), hepatic artery thrombosis (30 %), primary non-function (16 %), ischaemic injury (11 %), recurrent disease (6 %) and biliary complica-

tions (6 %). During this period, the 1-year graft survival for all reOLTs was significantly lower than for primary OLTs (67 % vs 78 %, $P < 0.001$). The timing of reOLT was found to be associated with graft survival; 1-year graft survival for early reOLT (< 30 days) was 50 % compared to 73 % for late reOLT ($P < 0.001$). The worse outcome associated with early reOLT is explained by the poor preoperative medical condition of patients who were retransplanted from intensive care. Subgroup analysis of indications for reOLT revealed 1-year graft survival of 81 % for late vascular complications, 75 % for early vascular complications, 69 % for chronic rejection and 30 % for primary non-function. One-year graft survival rates for third and fourth grafts were 42 % and 0 %, respectively. Graft survival and resource utilisation in patients who received a late regraft for the first time is now comparable to that for primary OLT. The favourable overall results should not preclude this group of patients from consideration for reOLT.

Key words Repeat orthotopic liver transplantation · Early regraft · Late regraft · Marginal donor liver

Introduction

Retransplantation offers the only chance of survival for patients whose grafts fail following primary transplantation [1, 2]. However, it has been suggested that allocation of donor livers to this group of patients constitutes inefficient utilisation of resources because of an inadequate supply of donor organs and a poor outcome following repeat orthotopic liver transplantation (reOLT) [3]. In the 1990s, new developments in organ preservation, perioperative management, immunosuppression and recipient selection have resulted in improved survival following primary OLT; however, it is not clear if these changes have also altered the outcome of reOLT during the same period. This study compares the outcome of retransplantation performed in the 1990s with that in the 1980s and identifies some of the risk factors associated with poor graft survival following reOLT in the 1990s.

Patients and methods

Patients

Between January 1982 and December 1996, a total of 1077 liver transplantations were performed on 970 adults at the Liver and Hepatobiliary Unit, Birmingham, UK. Actuarial patient and primary graft survival in the 1980s was 62% and 57% vs 83% and 78% in the 1990s. The study population consisted of 107 (10%) reOLTs of which 93 (9%) were second, 12 (1%) were third and 2 were fourth grafts. There were 238 (87%) first, 31 (11%) second, 5 (2%) third and 1 fourth liver allografts in the 1980s and 732 (91%) first, 62 (8%) second, 7 (1%) third and 1 fourth liver allografts in the 1990s. The minimum follow-up period was 6 months.

Analysis

The primary end point of the study was graft failure following reOLT resulting in either further retransplantation or patient death. The secondary end point was the cause of graft failure. A number of variables were analysed in association with graft outcome following reOLT in the 1990s. Recipient characteristics were age, sex, aetiology of primary liver disease, indication for reOLT, time to reOLT, number of transplants, need for pretransplant mechanical ventilation, pretransplant creatinine, bilirubin, prothrombin time and AST; donor characteristics were age, sex, cold and warm ischaemic times. Graft survival was analysed by the Kaplan-Meier method and the log-rank test was used to compare survival between different groups.

Results

A total of 107 reOLTs were carried out on 93 patients. The main indications for retransplantation were chronic rejection (31%), hepatic artery thrombosis (30%), primary non-function (16%), ischaemic injury (11%), recurrent disease (6%) and biliary complications (6%).

The aetiology of primary liver disease was primary biliary cirrhosis in 37 (40%), fulminant liver failure in 14 (15%), primary sclerosing cholangitis in 12 (13%), chronic active hepatitis in 11 (12%), viral hepatitis in 4 (4%), cryptogenic cirrhosis in 4 (4%), metabolic in 3 (3%), alcoholic cirrhosis in 3 (3%), neoplasm in 2 (2%), Budd-Chiari in 1 (1%) and other causes in (2%) patients. There were no ABO mismatches in any of the reOLTs.

The overall 1-year graft and patient survival for reOLT was 60% and 74% in the 1990s compared to 29% ($P < 0.0001$) and 51% ($P < 0.0001$) in the 1980s. The median time that elapsed between retransplantation and the preceding transplant was 35 days in the 1980s and 61 days in the 1990s. Analysis of recipient characteristics between the two study periods did not reveal any significant differences in terms of age, need for pretransplant ventilation, serum bilirubin, AST and time to reOLT. Significant differences were detected for the following recipient characteristics between the 1980s and the 1990s: female: male ratios 28:9 vs 38:32 ($P = 0.03$), median serum creatinine 175 vs 126 $\mu\text{mol/l}$ ($P = 0.02$) and median prothrombin time 26 vs 19 s ($P = 0.01$). In addition, significant differences in donor factors between the two groups were also identified: median age 21 vs 36 years ($P = 0.003$) and cold ischaemic time 363 vs 683 min ($P = 0.0001$).

In the 1990s, 732 (91%) first, 62 (8%) second, 7 (1%) third, and 1 fourth liver allografts were performed. The 1-year graft survival was 78% for primary OLT, 67% for second, 42% for third, and 0% for fourth grafts during this period. Subgroup analysis of indications for reOLT revealed 1-year graft survival of 75% for late (> 30 days) hepatic artery thrombosis, 73% for chronic rejection, 55% for early (< 30 days) hepatic artery thrombosis and 35% for primary non-function/ischaemic injury. Thirty-one of 70 reOLTs have failed for the following reasons: sepsis/multiorgan failure in 12 (39%), rejection in 4 (13%), primary non-function in 4 (13%), hepatic artery thrombosis in 3 (10%), biliary complications in 3 (10%), ischaemic injury in 2 (6%), recurrent disease in 2 (6%) and intraoperative complications in 1 (3%). The 1-year graft survival for all early (< 30 days) reOLT ($n = 30$) was 50% compared to 73% for all late reOLT ($n = 40$; $P < 0.001$). Graft survival analysis stratified according to timing and transplant number revealed a 1-year survival of 80% for late second grafts. Significant differences in recipient characteristics were detected between the early and late retransplants: the need for preoperative mechanical ventilation 57% vs 3% ($P = 0.0001$), serum creatinine 204 vs 101 $\mu\text{mol/l}$ ($P = 0.0001$), prothrombin time 29 vs 17 s ($P = 0.0001$) and serum AST 920 vs 168 U/l ($P = 0.0001$). There were no differences in terms of age, sex ratio and serum bilirubin levels of recipients who were retransplanted early or late.

Multivariate analysis of recipient characteristics revealed that the need for pretransplant mechanical ventilation ($P = 0.001$) and renal impairment ($P = 0.0001$) were associated with poor graft survival following reOLT. Paradoxically, the median cold ischaemic time was 585 min for grafts that survived less than 6 months compared to 743 min for grafts that survived more than 6 months ($P = 0.001$). Recipients' age, serum bilirubin, prothrombin time and AST, and donors' age and sex were not associated with graft outcome.

Discussion

This study confirms that the overall 1-year survival for reOLT has improved significantly in the 1990s compared to the 1980s. The poor outcome in the 1980s may be partly explained by a significantly higher proportion of patients who had renal impairment and more severe liver failure prior to retransplantation. In addition, more reOLTs were carried out for early graft failures as reflected by more than half the patients being retransplanted within 30 days of their previous graft. The 60% 1-year graft survival for all reOLTs in the 1990s is comparable to other series reporting 48–54% 1-year survival for reOLT [1, 2].

Consistent with the findings of other studies [1, 2], retransplantation performed within the first 30 days of the

preceding transplant was associated with a poor outcome. This is explained by the fact that patients in this group tend to require mechanical ventilation and have renal impairment, both of which are risk factors associated with poor graft survival following retransplantation. We have previously reported that the use of marginal donor livers did not affect the outcome of primary liver allografts [4]. Patients who require an early reOLT are generally more ill and tend to be given priority according to the donor allocation policy. With an expanding marginal donor pool and an urgency to retransplant early graft failures, it is likely that more marginal donor livers will be used for early reOLT. However, the impact of marginal donor livers on the outcome of early reOLT is not known and the number of early regrafts involved in this study is not sufficient for meaningful statistical analysis.

In conclusion, reOLT for patients with early graft failure who require ventilatory or renal support is associated with a poor prognosis and it is debatable as to whether they should continue to be given superurgent priority. However, this study clearly demonstrates that in a subgroup of patients who received a late regraft for the first time the 1-year graft survival is comparable to that following primary grafts. There is sufficient evidence to suggest that this group of patients should not be precluded from consideration for reOLT.

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