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LIVER TRANSPLANTATION

Selection of Patients and Results

Late Mortality and Morbidity After Liver Transplantation

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SINCE THE INTRODUCTION of cyclosporine (Cs)-steroid therapy in 1980, 665 patients received orthotopic liver transplantation by the end of June 1986 at the University Health Sciences Center of Colorado (in 1980), the University Health Center of Pittsburgh (since 1981), and the Pittsburgh-affiliated Baylor University Medical Center of Dallas (since 1985). One- to 5-year actuarial survival rates of these patients were 70%, 65%, 62%, 61%, and 61%, respectively, as of July 31, 1986. With these good survival rates, liver transplantation has been accepted as a therapeutic modality for end-stage liver disease, and >50 medical centers worldwide have started liver transplantation in the last few years. This report summarizes the long-term mortality and morbidity after liver transplantation to provide some useful guides in managing liver recipients after the first posttransplant year.

CASE MATERIAL AND METHOD

During the 5-year period between 1980 and 1984, 313 patients received orthotopic liver transplantation under Cs-steroid therapy at the University Health Sciences Center of Colorado (14 patients in 1980) and at the

University Health Center of Pittsburgh (299 patients between 1981 and 1984). Two hundred sixteen (69%) of the 313 patients survived at least 1 year after transplant. Medical records of these 216 1-year survivors are reviewed to study late mortality and morbidity. The follow-up period ranged from 18 months to 75 months with a median follow-up of 30 months as of June 30, 1986.

The age of patients ranged from 7 months to 54 years. Ninety-six patients were aged <18 years, and 120 patients were >18 years. The three most common liver diseases among pediatric recipients were biliary atresia, inborn errors of metabolism (α -1-antitrypsin deficiency disease, Wilson's disease, tyrosinemia, etc.), and postnecrotic cirrhosis; those most common in adult recipients were postnecrotic cirrhosis, primary biliary cirrhosis, and sclerosing cholangitis.

Survival rates were calculated by life-table analysis of Kaplan-Meier. The 1-year survival rate was actual and 2- to 5-year survival rates were actuarial figures.

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RESULTS

Survival After Liver Transplantation

The 1-year survival rate of 313 patients who received liver transplantation between 1980 and 1984 was 69%; and 2- to 5-year survival rates were 64%, 62%, 60% and 60%, respectively, as shown in Fig 1. Survival rates of the 216 1-year survivors after the first year were 93%, 90%, 87%, and 87%, respectively, at 2 to 5 years after transplant, as shown in Fig 2. Thus, the chance of dying between 1 and 5 years after liver transplant was only 13% of 1-year survivors.

Deaths >1 Year After Liver Transplantation

Thirteen patients died between 1 and 2 years after liver transplantation. Four patients died of recurrence of primary liver malignancy (one example each of epithelioid hemangioendothelioma, hepatocellular carcinoma, cholangiocarcinoma, and bile duct carcinoma). A fifth patient died of myocardial infarction with recurrence of hepatocellular carcinoma. Another patient died of disseminated oat cell cancer of the lung diagnosed >1 year after transplant. Thus, 6 of the 13 deaths were caused by or related to cancer.

Two of the other seven deaths were due to liver failure caused by graft rejection after retransplantation. Another patient died of septicemia following chemotherapy for myeloproliferative disorder that caused recurrent

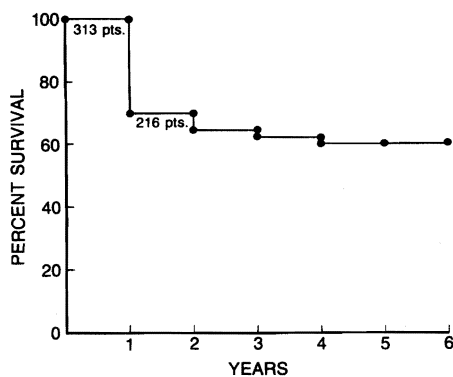


Fig 1.

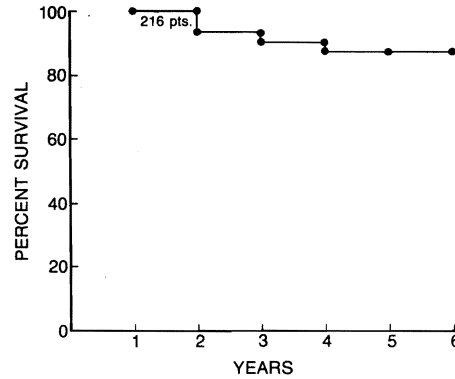


Fig 2.

Budd-Chiari syndrome. Single deaths were caused by liver failure due to recurrent hepatitis B and septicemia, recurrent pancreatitis and abdominal abscess, gastrointestinal bleeding and liver failure due to rethrombosis of the portal vein, seizures of undetermined cause, and cardiopulmonary arrest.

Between 2 and 3 years after transplantation, 4 patients died: 1 of recurrence of fibrolamellar hepatocellular carcinoma, 1 of liver failure due to rejection, and 2 of graft rejection and infectious complications 4 months and 8 months, respectively, following retransplantation for primary graft failure.

Two patients died between 3 and 4 years after transplant. One patient died of graft failure due to rejection; the second patient died of lymphoma and aspergillosis. The diagnosis of lymphoma was unduly delayed for several months.

There has been no death after 4 years—as of June 30, 1986.

Rejection and Retransplantation >1 Year After Liver Transplantation

Twenty-five of the 216 1-year survivors experienced moderate to severe graft rejection >1 year after liver transplantation. Rejection episodes of 18 patients occurred between 1 and 2 years after transplant, those of 5 patients occurred between 2 and 3 years, and those of 2 patients occurred between 3 and 4 years.

Two of the 25 patients died from graft liver failure before retransplantation could be performed. Eleven of the 25 patients underwent transplantation—8 after 1 to 2 years, and 3 between 2 and 3 years. Four of the 11 died after retransplantation. The deaths occurred intraoperatively 2 weeks later because of liver graft failure, 4 months later because of systemic herpes virus infection, and 8 months later because of graft failure and bacterial and fungal infection. Seven of the 11 patients who received retransplantation >1 year after the initial grafting were alive from 4 months to >3 years after retransplantation as of June 30, 1986.

Of the 25 patients who underwent late rejection, the remaining 12 still have their original grafts. The liver function tests of seven patients have returned to normal or near normal after antirejection therapy. These tests have improved but remain abnormal in four patients, and they are worsening in one patient who is waiting for retransplantation.

Posttransplant Malignancy

Six of the 216 1-year survivors developed de novo malignancy >1 year after liver transplantation. Five of the six patients developed posttransplant lymphoma or lymphoproliferative lesions, and another patient developed oat cell cancer of the lung. Two of the six patients died from malignancy as previously described: one from lymphoma in the fourth year and another from lung cancer in the second year posttransplantation. The remaining four patients who developed lymphoma in the second year have been cured of lymphoma by drastic reduction or temporary discontinuation of immunosuppression therapy; and they all were alive with good liver function as of June 30, 1986.

Late Bile Duct Complication

Seven surgically corrected biliary duct strictures occurred among 216 1-year survivors. Five of the seven biliary strictures developed after end-to-end choledochocholedo-

chostomy, and two developed after end-to-side choledochojejunostomy in Roux-en-y. None of the strictures after choledochocholedochostomies occurred at the anastomosis. Three of the five choledochocholedochostomies were strictured at the recipient distal common duct, and two of them were strictured at the donor hepatic duct just below the bifurcation. All five strictures were corrected by hepaticojejunostomy in Roux-en-y 1 to 6 years after transplant. Two choledochojejunostomies were strictured at the anastomosis and were corrected by revision of the anastomosis in the second and fourth posttransplant year.

Two other patients had surgically uncorrectable intrahepatic biliary strictures similar to those of primary sclerosing cholangitis. These strictures were successfully treated by transhepatic biliary catheter and balloon dilatation, but both patients were suffering from occasional bouts of cholangitis.

Renal Impairment

Serum creatinine levels of 120 adult (aged >18 years) 1-year survivors were 1.7 ± 0.5 , 1.7 ± 0.5 , 1.8 ± 0.6 , 1.6 ± 0.5 , and 1.3 ± 0.5 mg/dL (mean \pm SD), respectively, at 1 to 5 years after liver transplantation; those of 96 pediatric 1-year survivors were 0.7 ± 0.3 , 0.7 ± 0.3 , 0.7 ± 0.3 , 0.8 ± 0.5 , and 0.8 ± 0.4 mg/dL (mean \pm SD), respectively, at 1 to 5 years. Only 6 adult recipients had serum creatinine levels that remained persistently >2.0 mg/dL, and only 3 pediatric recipients had creatinines levels that remained >1.0 mg/dL during 1 to 6 years of follow-up. No patients required chronic maintenance dialysis after liver transplantation; in two patients, however, Cs had to be discontinued because of nephrotoxicity of the drug; azathioprine (Aza) was substituted.

Other Major Complications

Seventeen other nonfatal major complications developed in 15 of the 216 1-year survivors 1 to 4 years after liver transplantation. Eight of the 17 complications were infectious:

2 bacteremia due to urinary tract infection, 1 toxic shock syndrome caused by *Staphylococcus pneumoniae* in a splenectomized child, 1 *Candida* brain abscess, one cryptococcal meningitis, 1 acute gangrenous appendicitis, 1 acute pancreatitis associated with Epstein-Barr virus infection, and 1 non-A, non-B acute viral hepatitis. Two patients developed orthopedic complications, one of which was a tibial fracture that occurred when the patient fell. The other was aseptic necrosis of the hip, which required a prosthesis. Two major gastrointestinal hemorrhages occurred: one caused by a gastric ulcer that was successfully managed medically, and another caused by esophageal varices due to portal vein thrombosis that was successfully treated by distal splenorenal shunt. One patient developed hypertensive crisis with a systolic pressure >200 mm Hg. The patient's hypertension was finally controlled after discontinuation of Cs. The last complication was idiopathic thrombocytopenic purpura which developed during the fourth posttransplant year. The platelet depression was refractory to steroid therapy and was successfully treated by splenectomy.

DISCUSSION

Since the introduction of Cs for clinical transplantation, survival rates after liver transplantation have improved to 1-year survival of 70% and 5-year survival of 60%.¹ Our long-term follow-up of 216 1-year survivors showed that the chance of dying each year after the first year was <3% when the deaths from recurrent hepatic malignancy were excluded.

The most common cause of death after the first year was late graft failure due to rejection before or after retransplantation. Therefore, continuous monitoring of liver function is essential for long-term survival. We usually obtain a monthly checkup in the second year and every 2 to 3 months thereafter. Closer follow-up is necessary when immunosuppressive therapy is changed or liver function tests become abnormal.

The second most common cause of death was recurrent hepatic malignancy. More than two-thirds of patients who received liver transplantation for the treatment of conventionally unresectable hepatic malignancy died from recurrence within two years.² To prevent tumor recurrence, we recently instituted adjuvant chemotherapy soon after successful liver transplantation for patients whose indication for transplant was hepatic malignancy.

Six patients developed new malignant tumors >1 year after liver transplantation. Five of the six malignancies were lymphomas or lymphoproliferative lesions related to immunosuppression and viral infection as previously reported.³ We believe that the lymphomas developed after transplantation are almost always induced by immunosuppression therapy and viral infection such as Epstein-Barr virus and that the treatment of choice is drastic reduction of immunosuppression rather than cytotoxic chemotherapy.³ Four of the five patients with lymphoma so treated are alive and well with good liver function. Only one patient, whose diagnosis of lymphoma had been delayed for several months, died of disseminated lymphoma and aspergillosis in the fourth year. Another patient developed disseminated oat cell cancer of the lung and died in the second year.

Although most bile duct complications are identified within the first 6 months of transplant,⁴ surgically correctable bile duct complication can occur late after liver transplantation in patients whose clinical course has been stable over years. Clinical manifestation of late bile duct complications are often atypical for bile duct stricture and cholangitis; furthermore, laboratory abnormalities are similar to those of graft rejection. A high index of suspicion is important if abnormal liver function tests that are unresponsive to antirejection therapy develop. Although histological evidence of mild graft rejection may be present, direct visualization of the biliary system may identify partial bile duct obstruction. Liver biopsy and ultrasonography have not been

accurate in diagnosing late bile duct complications in our experience. After partial biliary obstruction was relieved, liver function tests of all seven patients with late reintervention returned to normal.

The etiology of intrahepatic biliary stricture in our two patients is unknown. Four others developed this peculiar biliary stricture within the first 12 months after liver transplantation. All these patients had had moderate to severe graft rejection prior to the development of intrahepatic biliary strictures. It is possible that intrahepatic biliary stricture within liver grafts is either the result or a form of graft rejection.

The nephrotoxicity of Cs must be surmounted to maintain good liver graft function chronically. Although we have not yet used chronic maintenance dialysis in our liver recipients, Cs had to be withdrawn and substituted by Aza in two patients. With careful adjustment of dosage, Cs can be used as a maintenance immunosuppressive agent for at least 5 years without causing clinically significant renal impairment in most patients.

After 1 year, infectious complications occur less frequently than during the first year. Orthopedic complications such as aseptic necrosis are rare in long-term survivors, probably because maintenance steroid doses are significantly lower with Cs than those previously commonly used with Aza. Life after a year of liver transplantation has been quite satisfactory for most of the recipients and >85% of 1-year survivors are expected to live at least 5 years. The quality of life in chronic survivors has greatly improved since the issue was last formally examined at this same meeting 8 years ago.⁵

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