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Decline in Survival After Liver Transplantation

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Abstract

Twenty-three recent cases of orthotopic liver transplantation were individually reviewed in an effort to determine why survival had declined from the 50% one-year survival rate of an immediately precedent series. In the series of 23, only six (26%) achieved one-year survival. Faulty case selection, technical complications, the use of damaged organs, and complications of immunosuppression were the main causes of death. Attention was directed to the possible use of preoperative lymphoid depletion to improve the effectiveness and safety of immunosuppression.

Our total experience with orthotopic liver transplantation up to January 1978 has been reported[1] with a minimum potential follow-up of at least one year for every recipient. As these 141 cases were compiled there was a slow improvement in the one-year survival rate, which in the last 30 patients reached the 50% level.

We report here a subsequent, less encouraging experience in 23 more consecutive cases. An analysis of these recent patients was undertaken to determine the reasons for the recent increase in mortality, and to consider further policy changes in case selection and management from which to mount renewed efforts.

CASE MATERIAL AND METHODS

Underlying Liver Disease

The Table gives information on the 23 cases. There were 12 adults and 11 children. Among the adults the most common diagnosis was chronic aggressive hepatitis (six examples). Two patients with sclerosing cholangitis had had previous operations, and one (orthotopic transplant [OT] patient 149) had a residual duodenal fistula. There was one example each of protoporphyria, secondary biliary cirrhosis from an old choledochal cyst, primary biliary cirrhosis, and alcoholic cirrhosis.

Of the five children with biliary atresia, three had undergone unsuccessful Kasai procedure. Four children had alpha$_1$-antitrypsin deficiency and one had congenital hepatic fibrosis. The final pediatric patient was a 15-year-old girl (OT 150) whose duct system had been excised five years previously during right hepatic lobectomy for trauma. Repeated attempts at duct

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reconstruction had failed. At the time of transplantation, a large unsuspected, retrohepatic abscess was found and excised along with the contiguous liver remnant.

Donor Sources

Donor ages are given in the Table. All donors had suffered acute irreversible brain injury, usually from trauma. When the livers were obtained from Colorado donors, graft removal and preservation with chilled lactated Ringer's solution were performed at the Colorado General Hospital, Denver, in an adjacent operating room. Consequently, the cold-ischemic times were short (Table). Organs removed elsewhere were preserved in Collins' solution for six or more hours (Table) since they had to be flown to Denver from cities as far away as 1,500 miles.

Immunosuppression

In all cases, standard treatment was started on the day of operation with azathioprine and prednisone. Eleven of the patients were also given intravenous antithymocyte globulin. Seventeen of the 23 recipients had concomitant splenectomy and one other had splenectomy 2½ months after transplantation because of persistent leukopenia. The five exceptions were patients OT 149, 158, 160, 162, and 163. Splenectomy was omitted only when the preoperative WBC count was more than 5,000/cu mm and when the spleen was small.

Thoracic duct drainage (TDD) as described elsewhere[2] was performed in 21 patients. The lymph depletion was begun on the day of operation in 17 patients, ten and 18 days before transplantation in two others, and two and four weeks after transplantation in the final two. The duration of TDD was seven to 80 days.

All patients received livers from donors who had three or four HLA mismatches. There was donor/recipient blood-type compatibility in all but case OT 148 in which the first graft was B to A. Three of the donors had positive cytotoxic cross matches with the recipient sera. The resistance of the liver to hyperacute rejection, despite the presence of preformed antidonor antibodies, has been described previously.[1]

Other Management Practices

The complicated postoperative care of these patients has been thoroughly described,[1] including the need for frequent postoperative diagnostic studies to rule out all causes other than rejection for postoperative hepatic malfunction. T-tube or transhepatic cholangiography and results of repeated liver biopsies were commonly used to guide adjustments in immunosuppression.

RESULTS

Mortality and Survival

As in the past, the overwhelming mortality was early. Within one month, eight of the 18 patients died, and between 30 and 90 days there were six more deaths. Three more patients died after 4, 6½, and almost 12 months.

A final patient died 386 days after transplantation. Five remain alive with present follow-ups of 390 to 612 days (Table). All are presently well. The one-year survival rate was six of 23 (26%), of whom one subsequently died.

Causes of Failure

Individual cases are documented in the Table. The deaths could be classified as follows:

Insurmountable Preexisting Problems—Liver transplantation was fundamentally difficult in most of the patients. However, three of the recipients had such severe preexisting pathologic conditions that in retrospect the attempt at transplantation was futile. One (OT 153) had a portal thrombosis that precluded normal revascularization of the liver. The second (OT 149) had a preexisting duodenal fistula that was repaired but that reopened postoperatively and was responsible for fatal intraperitoneal infection. The third (OT 152) had so many previous procedures that it was almost impossible to remove her diseased liver. Postoperatively, she died of infection that was made uncontrollable by an enteric fistula. The deaths were after 21, 90, and 19 days.

Intraoperative Calamities—Three of the patients (OT 145, 148, and 156) received livers that never functioned properly. All three donors were thought to be satisfactory; two of the organs were removed at Colorado General Hospital, while the third had been preserved and shipped from Los Angeles. Bleeding diathesis, perturbed clotting studies, and failure of other liver functions were immediately evident. Two (OT 148 and 156) were given second organs. One did not function. The other retransplant was a technical success but the patient already had sustained profound neurologic injury. Eventually her second graft failed, and at autopsy six months later the hepatic artery was thrombotic.

The foregoing clinical assessment of ischemic graft injury was not reflected in the histopathology of the allografts (Table). Acute rejection undoubtedly occurred with the first transplant of patient OT 148. Transplant patients OT 145 and 156a both showed changes suggestive of bile duct obstruction in spite of the fact that T tubes for transhepatic cholangiograms had provided no evidence for this possibility. Patient OT 156a also had cholangitis.

A fourth patient (OT 160) was profoundly hypotensive when taken to the operating room. A later report from a blood culture revealed enteric organisms. A technically satisfactory transplant was performed. However, the cardiovascular state of the patient remained so poor that an intraaortic balloon support to maintain the blood pressure was required for a week. He subsequently died of disseminated candidiasis. A fifth patient (OT 162) who received a liver too large to be accommodated in the abdomen died five days later of respiratory failure.

Delayed Technical Complications—One patient each had delayed thrombosis of the portal vein (OT 157) and of the hepatic artery (OT 154) at some distance from the vascular anastomosis. Results of serial biopsies of patient OT 157 had revealed progression from acute to chronic rejection and the eventual portal thrombosis may have been secondary to these events (Table). In two patients enteric fistulas developed from the Roux-en-Y reconstruction, leading to early (OT 147) or late (OT 143) death.

Acute Viral Infection—Two patients (OT 161 and 163) had almost identical courses after initially satisfactory graft function. After almost a month, fulminating liver failure developed in both children, with SGOT level rises of 2,000 to 3,000 IU. They died so quickly that their bilirubin levels rose to only 2.6 and 1.1 mg/dL, respectively. Adenovirus had been previously grown in cultures taken from the throat and rectum of one patient; and in the other, adenovirus was grown in cultures taken from the allograft at autopsy. The graft of patient OT 161 had contained evidence of acute cellular rejection at day 16 (Table). At autopsy, multiple focal areas of necrosis were seen in case OT 163. There were basophilic nuclear inclusions in the hepatocytes bordering the necrotic foci, and electron microscopy revealed that these inclusions were composed of adenovirus particles. This graft also contained colonies of candida (Table).

In addition, a 5-year-old child (OT 151) who had had an untroubled recovery was discharged from the hospital. Systemic chicken pox with pneumonitis and acute liver failure then

developed, with an SGOT level of 5,000 IU. At autopsy, chicken pox and cytomegalovirus grew from cultures taken from the consolidated lungs but not from the liver allograft. However, herpes group viruses were seen by electron microscopy in the necrotic hepatocytes in the central and middle zones of the lobules of the liver allograft. The portal vein contained a fresh thrombosis that was thought to be only one or two days old.

Acute Rejection—By clinicopathologic correlation, only one patient (OT 158) was lost solely because of acute uncontrolled rejection of the graft. The histopathologic rejection was equally severe in the first graft of patient OT 148, but this organ had never functioned, and the failure was ascribed by the clinicians to ischemic injury.

Miscellaneous—A 9-year-old girl (OT 159) with a seemingly perfect result died 56 days postoperatively of massive pulmonary emboli that had come from the collateral Retzius' veins.

A 31-year-old man (OT 141) had a liver transplantation for chronic aggressive hepatitis, hepatitis B surface antigen (HBsAg) positive. In spite of postoperative treatment of the patient with specific hyperimmune globulin, the results of his HBsAg tests became positive again after several weeks. He died of liver failure 355 days postoperatively. The differential diagnosis of rejection vs recurrent hepatitis was evaluated from several biopsy specimens and from the autopsy allograft. These showed rejection progressing until only isolated nodules of hepatocytes remained at autopsy. Investigations with immunoperoxidase and electron microscopy showed no evidence of recurrent hepatitis.

Allograft Histopathology

Biopsy and autopsy changes for individual cases are given in the Table. The autopsy allografts were remarkably free of rejection, this being an autopsy diagnosis in only five (29%) (OT 141, 149, 156b, 157, 158) of 17 retrieved livers. Such findings may have understated the role of rejection in lethal clinical events since results of prior biopsies confirmed episodes of acute rejection in three more allografts (OT 159, 161, 163). Acute rejection at some time was found in 12 (52%) (OT 141, 142, 146, 148a, 149, 150, 155, 157, 158, 159, 161, 163) of the 23 grafts from which tissue was obtained. Chronic rejection, as defined by intimal thickening and rupture of the internal elastic lamina of small intrahepatic arteries, was present in five (22%) (OT 141, 142, 149, 156b, 157) of the 23 grafts. Changes suggestive of chronic bile duct obstruction were present in three allografts (OT 143, 145, 156a). Viruses were responsible for widespread liver necrosis in three livers; the organism was varicella in one (OT 151) and adenovirus in two (OT 161, 163). *Candida* abscesses were present in two cases (OT 147, 163). Nonspecific fatty change was present in six livers (OT 143, 147, 148b, 149, 160 162) mostly in association with disseminated bacterial or fungal infections. The hepatocytes had atrophied in one liver (OT 150) that had been deprived of an adequate portal blood supply.

COMMENT

The development of liver transplantation has been hampered by the poor condition of almost all recipients, by the technical demands of the operation, by lack of effective liver support techniques with which to prepare patients for operation or to tide them over if initial graft function is poor, and by difficulties in defining exactly the reasons for postoperative hepatic dysfunction. Nevertheless, a slow but steady improvement in survival was reported at our institution from 1963 through early 1978[1] in 141 consecutive cases. The expectation that these gains could be maintained was not realized in the 23 subsequent patients herein reported. Although the recent sample was a small one, we slowed our liver program almost to a halt in order to assess the reasons for the deterioration in results.

Faulty case selection played a role. Three of the patients had such serious anatomical problems that success was virtually precluded, and in addition, some of the other patients were so ill and so progressed in the course of their liver failure that the final measure of transplantation may have been inadvisable.

Three otherwise suitable recipients were given poorly functioning livers. At present, there is no good way to identify such flawed organs in advance. The ischemic injury was not clearly related to the time of cold preservation. Two of the three organs were removed in distant cities and shipped to Denver with a total cold ischemic period of several hours. However, the third graft was removed at Colorado General Hospital and immediately transplanted.

Similarly, a need to eliminate technical misadventures was evident from this recent series as it has been in the past; but how to achieve this is less definable. The enteric and vascular complications occurred at the hands of experienced surgeons whose record under more favorable circumstances in patients who did not undergo immunosuppressive treatment or in kidney recipients who had received immunosuppression has been good.

With such a spectrum of management problems, it has been difficult to assess the additional roles of rejection and of the immunosuppressive treatment used to prevent this process. Recent publications,[3] including some from our center,[1] have questioned whether rejection is a major factor in the unsatisfactory results and have drawn attention to the possible error of overimmunosuppression, especially with steroids. The occurrence of three deaths from acute viral infections of the liver in the present series, as well as the high incidence of other infectious complications, could be viewed as support for such a contention.

The issue has not been settled, although there is no doubt that hepatic allografts at autopsy are usually free of histopathologic signs of acute rejection. The liberal use of biopsies hag provided a fuller picture. The biopsy specimens obtained during life often contained evidence of rejection to which the appropriate response at the time was increased immunosuppression. However, the penalties, including the development and persistence of enteric fistulas, ranged from serious to lethal. Thus, the clinician has been faced with a situation in which there is little or no margin of safety.

Dissatisfaction with “standard” antirejection therapy has prompted us to reevaluate TDD as an adjunct to classical immunosuppression, realizing the importance of developing treatment principles with the simpler clinical model of renal transplantation. At first, TDD was instituted on the day of renal transplantation, as was done in many of the liver recipients of the present series.[2] It became evident that this was a suboptimal use of TDD, since renal rejection was common during the first three weeks before an immunosuppressive TDD effect was established. In the liver recipients herein reported, there was no demonstrable benefit from TDD. Although TDD was not responsible for the death of any patient, it may have contributed to the delayed infectious complications while at the same time providing little or no prophylaxis against rejection during the critical first two or three postoperative weeks. We now recommend pretreatment with TDD for four weeks or more, the exact duration being strongly influenced by the presence or absence of different kinds of antibodies in the recipient serum. Using this approach, early rejection has been greatly reduced in cadaveric kidney recipients.[4]

Such an improvement in immunosuppression should be applicable to transplantation of other organs, but there may be special problems in liver recipients. Prospective liver recipients are so fragile that a month of TDD pretreatment may impose great risks. For one thing, the lymph drainage in a patient with hepatic disease tends to be voluminous, particularly if ascites is present. In our experience, the output may exceed 1 L/hr. Nevertheless, as our liver program reopens, we are attempting to provide pretreatment with TDD or with the removal of peripheral blood lymphocytes (lymphapheresis).

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References

1. Starzl TE, Koep LJ, Halgrimson CG, et al. Fifteen years of clinical liver transplantation. Gastroenterology 1979;77:375–388. [PubMed: 376395]
2. Starzl TE, Weil R III, Koep LJ, et al. Thoracic duct fistula and renal transplantation. Ann Surg 1979;190:474–486. [PubMed: 384943]
3. Calne RY, Williams R. Liver transplantation. Curr Probl Surg 1979;16(1):3–44.
4. Starzl TE, Weil R III, Koep LJ, et al. Thoracic duct drainage before and after cadaveric kidney transplantation. Surg Gynecol Obstet 1979;149:815–821. [PubMed: 388702]

Table 1

Consecutive Recent Orthotopic Liver Transplantations (OT)							
OT NO.	**Diagnosis**	**Donor/Recipient Age, yr**	**Ischemia Time, hr, min**	**Survival, Days**	**Last Bilirubin, Level, mg/dL**	**Cause of Death, Clinical and Autopsy**	**Graft Histopathology**
141	Chronic aggressive hepatitis, hepatitis B surface antigen positive (HBsAg +)	17/31	2,46	355	28	Liver failure from chronic rejection and recurrent hepatitis	End-stage chronic rejection; Biopsy (bx,) results at 147 and 179 days had shown progressing rejection; no evidence of recurrent hepatitis B infection
142	Alpha$_1$-antitrypsin deficiency (with hepatoblastoma)	3½/5	3,42	612	0.8	Alive	Bx results at 166 days and 1 yr, 57 days showed continuing low-grade rejection
143	Sclerosing cholangitis	17/31	1,45	386	16	Intraabdominal infection; liver failure from chronic rejection; and (?) cholangitis	Diffuse fatty change and some centrilobular necrosis; no evidence of rejection or sclerosing cholangitis
144	Alcoholic cirrhosis (previous shunt)	19/39	6,15	563	0.8	Alive	No bx
145	Chronic aggressive hepatitis (previous shunt)	15/22	7,18	20	16	Acute liver failure from ischemic graft injury; candidiasis	No ischemic injury in bx results at 14 days, only evidence of biliary obstruction; same at autopsy
146	Primary biliary cirrhosis	21/49	1,23	502	0.8	Alive	Bx results at 30 and 111 days showed cellular rejection; no evidence of hepatitis despite being HBsAg +
147	Biliary atresia	2½/5½	7,26	42	3.7	Peritonitis from enteric fistula; candidiasis	Diffuse fatty change; multiple small foci of *Candida* infection
148	Chronic aggressive hepatitis	(a)13/29 (b)18/29	1,17 1,29	16	34	Acute liver failure from (?) ischemic graft injury, 1st graft; Gram-negative septicemia, 2nd graft	(a) Acute cellular rejection; (b) Fatty change and some cholestasis in centrilobular hepatocytes ____
149	Sclerosing cholangitis	18/38	1,34	80	10.6	Peritonitis and persistent duodenal fistula; pneumonitis	Centrilobular fatty Change; arteriolar narrowing from past rejection ____
150	Biliary cirrhosis (secondary to trauma)	7/15	2,2	472	0.8	Alive	Bx result at 33 days showed acute cellular rejection
151	Biliary atresia (previous Kasai procedure)	2/5	8,51	72	3.3	Chicken pox; fresh portal thrombosis	Herpes group viruses seen by electron microscopy in

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							necrotic tissue and in some of adjacent cells
152	Biliary cirrhosis (secondary to choledochocyst)	1½/29	2,5	19	8.3	Peritonitis from enteric fistulas; questionable candidiasis; no autopsy	No bx or autopsy
153	Chronic aggressive hepatitis	16/28	2,30	21	1.8	Acute hemorrhage from esophageal varices*	Some atrophy of hepatocytes because of lack of portal blood; no evidence of rejection
154	Alpha$_1$-antitrypsin deficiency	4/6	8,23	54	11	Liver failure with intrahepatic arterial thrombosis; regional liver infarctions and Gram-negative septicemia	Intrahepatic arterial thromboses and infarcts in bx results at 29 days and at autopsy; no evidence of rejection in surviving liver; (?) primary thrombosis due to endothelial damage caused by eight hr ischemia .
155	Alpha$_1$-antitrypsin deficiency	8/11	1,24	395	0.5	Alive	Bx result at six mo showed acute cellular rejection
156	Chronic aggressive hepatitis	(a) 8/24 (b) 24/34	7,20 5,23	194	6	Acute liver failure from Ischemic injury, 1st graft; arterial thrombosis, 2nd graft, neurologic invalidism	(a) Cholangitis, centrilobular cholestasis and marked centrilobular and midzonal fatty change; did not look like Simple ischemic damage (b) Bx results at 69 and 124 days showed acute and chronic rejection, respectively, with arterial involvement; at autopsy at 179 days there were multiple large areas of old and recent ischemic necrosis and atrophy of hepatocytes caused by arterial lesions of chronic rejection
157	Chronic aggressive hepatitis	19/21	2,10	120	35	Liver failure from portal thrombosis and (?) chronic rejection	Bx results at 14, 62 and 109 days showed progression from acute cellular rejection to chronic rejection with narrowing and obliteration of intrahepatic artery branches and portal vein tributaries; at autopsy large areas of hemorrhagic necrosis from recent main portal vein thrombosis predominated

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158	Congenital hepatic fibrosis	2/2	1,45	21	15.4	Acute rejection	Acute cellular rejection with necrosis of centrilobular and midzonal hepatocytes
159	Alpha$_1$-antitrypsin deficiency	3/9	7,39	56	0.8	Pulmonary emboli	Little fat in hepatocytes; mild mononuclear cell infiltration of portal tract
160	Protoporphyria	9/21	8	26	10.8	Cardiac insufficiency; candidiasis	Fatty change and some cholestasis
161	Biliary atresia (previous Kasai procedure)	1/2	7,12	28	1.1†	(?) Adenovirus hepatitis; Gram-negative septicemia	Bx results at 16 days showed acute cellular rejection; no autopsy tissue available
162	Biliary atresia (previous Kasai procedure)	1/2½	6,26	5	3.4	Respiratory insufficiency from oversized graft	Focal areas of centrilobular and midzonal hemorrhagic necrosis; fatty change, cell cholestasis and moderately dense mononuclear cell infiltration of portal tracts
163	Biliary atresia	1½/3	1,23	30	2.6†	(?) Adenovirus hepatitis	Multiple focal areas of necrosis; some of these contain large candida colonies; nuclear inclusions in the hepatocytes bordering the necrotic foci; by electron microscopy these are found to consist of adenovirus particles

*At operation, portal cavernous transformation found. Graft portal vein anastomosed to vena caval which subsequently clotted.

†Last SGOT values more than 2,000 IU/L.