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LIVER TRANSPLANTATION WITH USE OF CYCLOSPORIN A AND PREDNISONE

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THE difficulties in consistently prolonging survival after orthotopic liver transplantation have been documented by us[1] and by Calne.[2] In this report we describe a new trial of orthotopic liver transplantation in 14 patients who were scheduled to be treated with cyclosporin A and prednisone. Two patients died during the operation. Ten (83 per cent) of the 12 patients who survived surgery and received the drugs are living after eight to 14 ½ months; another lived for a year, before dying of a recurrence of cholangiocarcinoma.

Although longer follow-up periods and more case studies will be required to establish the safety and effectiveness of this form of therapy, the exceptionally encouraging early results seem attributable to the use of cyclosporin A in combination with low doses of steroids for immunosuppression. The first use of cyclosporin A in liver transplantation was reported by Calne et al.[3]

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METHODS

Fourteen patients (age range, eight to 41 years) were accepted for the pilot trial. Liver replacement was attempted between March 10 and September 28, 1980. Two patients who were scheduled to be treated with cyclosporin A plus prednisone died during operation. One bled to death from a laceration of the portal vein, and the other received a homograft too large to permit the abdomen to be closed. Thus only 12 patients were treated with immunosuppression.

Transplantation

The general techniques used in these operations have been previously described.[1,4] Seven of the 14 livers were removed during operations in cities other than Denver (75 to 2000 miles [120 to 3200 km] away). All 14 livers were preserved with Collins' solution, as described by Benichou et al.[5] Ischemia lasted from 1½ to 10½ hours. Biliary-tract reconstruction was performed through duct-to-duct, gallbladder-to-jejunal-Roux-limb, and common-duct-to-Roux-limb anastomosis, in that order of frequency.

Selection of Recipients and Donors

Of the 12 patients who survived the operation, three had chronic aggressive hepatitis and three had the Budd–Chiari syndrome. The following diseases were present in one patient each: primary biliary cirrhosis, secondary biliary cirrhosis, sclerosing cholangitis, hepatoma, Byler's disease, and intrahepatic atresia. Of the two patients who died during operation, one had sclerosing cholangitis and the other had secondary biliary cirrhosis (caused by a gunshot wound to the hepatic hilum).

Each donor was blood-group compatible with each respective recipient. There were no positive T-cell or B-cell cytotoxic cross matches at warm temperatures. In the 12 surviving patients, mismatches at the A and B loci averaged 3.3±0.7 (S.D.) and matches averaged 0.6±0.5. The number of matching DR loci ranged from 0 to 1 (mean, 0.4).

Immunosuppression

Cyclosporin A treatment was started on the day of operation (17.5 mg per kilogram of body weight per day, given intramuscularly or by mouth). After six to eight weeks the doses were reduced to 10 mg per kilogram per day or less. In the first few patients (Table 1), prednisone was not given until rejection supervened. In the other patients, either prednisone was administered in low doses on the day of operation or, in adults, 200 mg was given on the day of operation. When the 200-mg dose was given, prednisone was reduced by decrements of 40 mg daily for four days. On the fifth day a further decrease of 20 mg was made. Later reductions in maintenance doses of prednisone were made according to the patient's course and body weight.

Table 1. Prednisone Dosage in Liver-Transplant Recipients Given Cyclosporin A Immunosuppression.

PREDNISONE DOSAGE	PATIENT NOS.	TOTAL
No initial dose *	1,2,3,4,5,10	6
Low initial dose (<1 mg/kg body wt)	8,12	2
Short cycle of doses †	6,7,9,11	4

*Prednisone therapy was started in all patients within six to 60 days because of faulty liver function.

†See Methods — Immunosuppression.

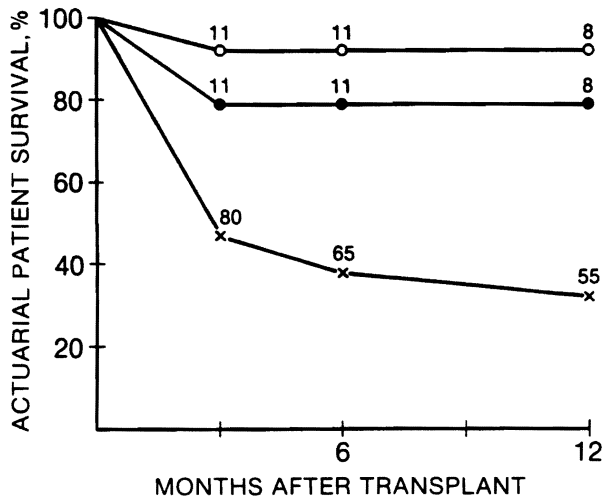

Figure 1. One-Year Actuarial Survival in Patients Given Liver Transplants.

The follow-up period ranged from eight to 14½ months. The figures above the symbols denote the numbers of patients alive at different intervals.

The open circles represent survival in the 12 patients who lived through the operation and were treated with cyclosporin A and prednisone, the solid circles represent survival in all 14 patients who underwent transplantation (including the two who died during the operation), and the crosses represent survival in 170 patients from a previous series who were treated with conventional immunosuppressants.

At the slightest indication of liver-graft dysfunction, aggressive diagnostic steps were taken, including biopsy and transhepatic cholangiography.

Pathological Studies in Survivors of Operation

Tissue specimens were obtained at autopsy in one patient and by hepatic biopsy in eight others. The number of biopsies of individual liver homografts ranged from one to five, with an overall total of 17. The tissue was examined with light and electron microscopy and with the immunoperoxidase technique.

Results

Survival

Survival of a graft was concomitant with survival of its recipient. Of 12 patients who survived operation and who could be treated with immunosuppression, 10 (83 per cent) are still living after 12.1±2.4 months (±S.D.). When the two recipients who died during operation are also considered, the survival rate is 71 per cent. The only early postoperative death was that of a child 19 days after transplantation; the hepatic artery of the homograft had thrombosed.

The patient whose original diagnosis was thought to be sclerosing cholangitis had a metastatic cholangiocarcinoma in the subhepatic space; this tumor was diagnosed 10 months after operation. Her native liver was reexamined and found to contain part of the same tumor. She died one year after transplantation.

Of the eight recipients who have lived for a year since transplantation, seven are still alive, although recurrent Budd–Chiari syndrome developed in one 14 months after operation. The actuarial life-survival curves for the first year of survival are shown in Figure 1, with and without the two patients who died during operation and who never received immunosuppressants. The improvement over our previous results in liver replacement is striking (Fig. 1).

One of the patients who passed the one-year mark had an advanced hepatoma with tumor invasion of the retrohepatic inferior vena cava. The absence of a recurrence is surprising in view of our discouraging earlier experience under such circumstances.[1]

Morbidity

Two of the recipients required secondary conversion of cholecystojejunostomy to choledochojejunostomy. These revisions of biliary-tract drainage were made in one recipient at four weeks and in the other at five weeks after transplantation.

One patient had a cardiac arrest a few hours after transplantation. She has recovered mentally but still has residual locomotor abnormalities that are slowly lessening a year later.

A recipient whose original hepatic disease was the Budd–Chiari syndrome had mesenteric-vein infarction that required partial intestinal resection. She required more than three months of ventilatory support because of an acute and chronic respiratory-distress syndrome, from which there developed a pleural complication necessitating decortication. The Budd–Chiari syndrome recurred more than a year after transplantation, and thus her prognosis is guarded.

One woman had an accident after returning home and fractured two ribs, the right humerus, the pelvis, the left hip, the right femur, and three vertebras. Replacement of the left hip and internal fixation of a right-femoral-shaft fracture were required. Bone fragility secondary to longstanding secondary cirrhosis contributed to the severity of her injuries.

Another woman had subphrenic and subhepatic abscesses that were treated with drainage, a duodenal ulcer that was treated with vagotomy and pyloroplasty, and an intrasplenic abscess that was treated with splenectomy.

All the surviving patients except the one with recurrent Budd–Chiari syndrome now live outside of the hospital. The postoperative hospitalization periods averaged 75.5±57.6 days (range, 23 to 210 days; median, 61 days).

Liver Function and Immunosuppression

Current liver functioning and the maintenance doses of cyclosporin A and prednisone are given in Table 2. Most of the recipients have never been given more than 20 mg of prednisone per day for longer than five or six days. The ultimate maintenance doses of cyclosporin A were influenced by the presence or absence of abnormalities in renal function. When rises

Table 2. Current Liver Function and Maintenance Therapy in 10 Patients.

Patient No.	Age/Sex	Time after Surgery	Current Liver Function			Serum Creatinine	Maintenance Therapy	
			Serum Bilirubin	Alkaline Phophatase	SGOT *		Cyclosporin	Prednisone
		mo	mg/dl (μmol/liter)	units/liter		mg/dl (mmol/liter)	mg/kg/day	mg/day
1	28/F	14½	1.2 (20.5)	155	21	1.6 (141)	7.9	20
2	25/M	14½	1.3 (22.2)	477	48	1.8 (159)	5.1	15
3	37/F	14	0.5 (8.6)	136	35	1.0 (88)	9.5	10
4 †	20/F	14	2.2 (37.6)	55	10	4.6 (407)	5.1	5
5	41/F	13½	0.3 (5.1)	332	93	1.3 (115)	9.1	10
7	26/M	12½	1.2 (20.5)	141	38	2.0 (177)	9.8	10
8	21/F	12	1.1 (18.8)	52	26	1.0 (88)	6.8	15
9	16/F	9	1.7 (29.1)	151	49	1.3 (115)	9.8	10
10	28/F	9	2.4 (41.0)	220	67	1.6 (141)	7.7	12.5
12	10/F	8	0.8 (13.7)	863	39	0.5 (44)	7.1	10

*Serum aspartate aminotransferase.

†This patient has recurrent Budd–Chiari syndrome with secondary renal dysfunction.

in creatinine and blood urea nitrogen seemed related to nephrotoxicity from cyclosporin A, the doses of cyclosporin were reduced gradually to a nontoxic level.

Pathological Findings

The biopsies, usually performed because of postoperative liver-function abnormalities, revealed a variety of findings, of which the most common was acute cellular rejection (Table 3). Cellular rejection of a transplant was always responsive to increased steroid therapy.

Table 3. Histopathologic Findings in Nine Patients.

Patient No.	Date of Operation	Date of Biopsy	Findings
1	9 March 1980	9 May 1980	Mild cellular rejection
		6 Aug 1980	Few tiny foci of necrosis; otherwise normal
2	10 March 1980	1 April 1980	Acute cellular rejection
		16 April 1980	Cytomegalovirus hepatitis
		30 April 1980	Recovering from cytomegalovirus hepatitis
		11 June 1980	Very early fibrosis
		18 Sept 1980	As in fourth biopsy, but with superimposed acute cellular rejection
3	21 March 1980	22 April 1980	Acute cellular rejection
		11 June 1980	Low-grade cellular rejection
4	25 March 1981	10 May 1981	Recurrent Budd–Chiari syndrome
5	13 April 1980	30 April 1980	Acute cellular rejection
		6 May 1980	Acute cellular rejection
6	14 May 1980	11 June 1980	Acute cellular rejection
		6 March 1981	Normal
9	5 June 1980	2 March 1980	Acute cellular rejection
11	17 Sept 1980	5 Oct 1980 *	Widespread liver necrosis †
12	28 Sept 1980	14 Oct 1980	Small focal infarcts & cholangitis
		4 Nov 1980	Early fibrosis & changes suggestive of some bile-duct obstruction

*Date of autopsy.

†Hepatic-artery thrombosis.

Discussion

The follow-up period in this small number of patients is still short. However, it is unlikely that the striking improvement in the early results after liver replacement could be a statistical accident. The transplant rejections that were seen in these patients were common, but they were easy to control with small increases in prednisone. The same phenomenon has been noted in recipients of kidney homografts, whose prognosis has also been markedly improved by therapy with cyclosporin A and prednisone, as compared with conventional immunosuppression.[6] Like previous patients, the liver recipients described in this paper had major complications; a new feature was the ability to treat complications successfully in patients whose livers were functioning well and who were given low doses of prednisone.

The histopathologic features of the relatively self-limited and easily treated rejection during therapy with cyclosporin A and prednisone were compared with the features of rejection during conventional immunosuppression. There was only one striking difference — the presence of a high proportion (5 to 20 per cent) of eosinophils in the cellular infiltrate. There was no evidence of long-term rejection, and no hepatic arteriolar or arterial lesions.

Successful use of cyclosporin A in liver transplantation depended on a thorough understanding of the drug's toxicity. Injury to the kidney and liver was monitored with the idea of reducing the dose when indicated. The toxic properties of cyclosporin A were not serious enough to prevent its long-term use in all the surviving patients. There was no occurrence of de novo neoplasms (including lymphomas). One patient, who received a transplant because of an advanced hepatoma, has so far escaped the kind of recurrence that followed all our previous attempts at transplantation for this indication and that was confirmed in the recipient in this series whose native liver contained a cholangiocarcinoma.

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