LIVER AND PANCREAS TRANSPLANTATION

Report of Colorado-Pittsburgh Liver Transplantation Studies

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THE PURGATORY in which liver transplantation was mired has ended in the cyclosporine era. Long-term survival after liver replacement was achieved in 1964 with dogs[1] and in humans[2] beginning in 1967. The longest surviving patient is now in her 14th postoperative year.

In spite of such tantalizing successes, the operation was unpredictable and unreliable, with 1-year survival rates that did not improve with increased experience over a 16-year period.[3] Of the first 111 patients, less than 1/3 lived for 1 year. The 1-year survival rose to 50% in a second but small series of 30 patients, but in a third series, the survival sank again, almost to the original level. The overall 1-year survival rate for 170 patients was 33%.

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MATERIALS AND METHODS

We have used cyclosporine (CsA) with prednisone in all liver transplantations since early 1980.[3] The standard therapy begins with a 5-day burst of steroids, leveling off at about 20 mg/day in adults after a few days. The dose of CsA is 6 mg/kg i.v. or 17 mg/kg orally. When nephrotoxicity of CsA is suspected, the CsA dose is reduced; in a few instances it has been replaced temporarily with azathioprine.

RESULTS

The survival in the first 67 consecutive recipients in the cyclosporine era is summarized in Fig. 1 and contrasted with the pooled previous experience. All of the CsA patients in Fig. 1 had their operations before May 1, 1982, and thus have minimum 1-year follow-ups. The 1-year and subsequent survival was doubled overnight compared to past expectations.

Of the first 67 recipients in the CsA series treated over a period of <2 years, 42 passed the 1-year mark. This was almost as many survivors as had been acquired in the nearly 17 preceding years. Six of the 42 one-year survivors subsequently died. In four, the cause of the late failure was recurrence of the original disease (two hepatic malignancies, one example each of Budd-Chiari syndrome and B-virus chronic hepatitis) (Table 1). The other late deaths were caused by an airway obstruction secondary to an upper respiratory infection in one patient and by complications

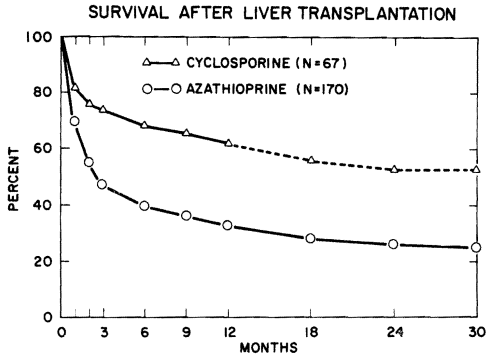

Fig. 1. Life survival curves of patients under conventional immunosuppression vs. CsA-steroid therapy. In the latter group, note that survival after 1 year is actuarial.

after retransplantation in a patient whose first graft was chronically rejected (Table 1). In spite of these six deaths after 1 year, the late decline of the life-survival curve has been slower than in past patients who entered the second postoperative year under azathioprine and prednisone (Fig. 1).

A natural question would be whether these results could be explained by a sudden change in candidacy criteria or by a difference in the diseases for which transplantation was performed. Analysis according to the recipient diseases showed that this was not the case. Instead, the results with almost all of the diseases were improved (Table 2). This was obvious with all the diagnoses that contributed heavily to the case material before and after the introduction of cyclosporine, such as biliary atresia, nonalcoholic cirrhosis, primary hepatic malignancy, primary biliary cirrhosis, and the heterogenous group of inborn errors of metabolism.

With these improved results, the pace of liver transplantation has quickened. Between 1963 and the end of 1979, the average yearly caseload was not much over a dozen. The number of transplantations rose to 30 in 1981 and to 80 in 1982 (Table 3). In the first 4 months of 1983, 34 liver replacements were

Table 1. Late Deaths Under Cyclosporine-Steroid Therapy

Original Diagnosis	Cause of Death	Time (Months)
Chronic active hepatitis	Airway obstruction, tonsillitis	12
Cholangiocarcinoma	Recurrent cancer	13
Budd-Chiari syndrome	Recurrent Budd-Chiari syndrome	15
Chronic active hepatitis	Recurrent chronic active hepatitis (B virus)	15
Budd-Chiari syndrome	After retransplantation (for chronic rejection)	20
Hepatoma (fibrolamellar)	Recurrent cancer	33

Table 2. Influence of Disease on 1-Year Survival in 237 Patients*

	Conventional Therapy		Cyclosporine + Steroids	
	No.	After 1 Year†	No.	After 1 Year‡
Biliary atresia	51	14 (27.0%)	11	6 (54.5%)
Nonalcoholic cirrhosis	46	16 (34.8%)	16	9 (56.3%)
Primary liver malignancy	18	5 (27.8%)	9	6 (66.7%)
Inborn errors§	15	8 (53.3%)	10	7 (70.0%)
Alcoholic cirrhosis	15	4 (26.7%)	0	—
Primary biliary cirrhosis	6	1 (16.7%)	6	5 (83.3%)
Sclerosing cholangitis	7	2 (28.6%)	3	2 (66.7%)
Secondary biliary cirrhosis	4	3 (75.0%)	5	1 (20.0%)
Budd-Chiari syndrome	1	1 (100.0%)	3	3 (100.0%)
Miscellaneous‖	7	2 (28.6%)	4	3 (75.0%)

*The same case material was analyzed in detail elsewhere,[3] but with shorter follow-ups.

†32 of these 52 patients are still alive with follow-ups of 3½–13½ years.

‡36 of these 42 patients are still alive with follow-ups of 1–3¼ years.

§Alpha-1-antitrypsin deficiency (17 examples), Wilson's disease (3), tyrosinemia (2), glycogen storage disease (2), sea blue histiocyte syndrome (1).

‖Neonatal hepatitis (3 examples), congenital hepatic fibrosis (2), Byler's disease (2), adenomatosis (1), hemachromatosis (1), protoporphyria (1), acute hepatitis B (1).

Table 3. Yearly Total of Orthotopic Liver Transplantations

Year	No. of New Patients	Retransplantation	Total
1963	5	0	5
1966	1	0	1
1967	6	0	6
1968	12	2	14
1969	6	1	7
1970	10	1	11
1971	11	0	11
1972	11	1	12
1973	13	4	17
1974	20	1	21
1975	9	4	13
1976	14	3	17
1977	21	2	23
1978	19	2	21
1979	11	0	11
1980	15	0	15
1981	26	4	30
1982	62	18	80
1983*	24	10	34
Total	296	53	349

*January–April, 1983.

done, a rate that extrapolates to 100 for this year.

To be a service, a new surgical procedure must be within the capability of more than the occasional surgeon. Until 1982, virtually all our liver transplantation procedures over a span of 19 years were performed by a single surgeon. During 1982, 40% of the procedures were performed by another young faculty member or by the fellows, and this year this figure has been 70% (Table 3).

In 1983, most of the adult patients have had pump-driven nonheparin venovenous bypasses during the anhepatic phase, when the portal vein and vena caval systems must be obstructed. This simple technique has removed the urgency of the implantation and should place the operation of liver replacement within the grasp of a much greater number of surgeons.

We have had one example of multiple intestinal "lymphomatosis" in a liver recipient 6 months postoperatively. His cyclosporine dose was dropped from 20 mg/kg/day to 1.4 mg/kg/day, and the steroid dose was reduced from 25 mg/day to 10 mg/day. After several months on these almost homeopathic drug doses, he began to reject his liver, necessitating resumption of more standard immunosuppressive therapy (Fig. 2). The rejection was easily controlled, and this boy has returned to his university studies; he has no evidence of lymphoma. At autopsy, one other liver recipient had similar lymphoproliferative lesions as an incidental finding.

DISCUSSION

Most of the mortality that remains with liver transplantation is perioperative and is

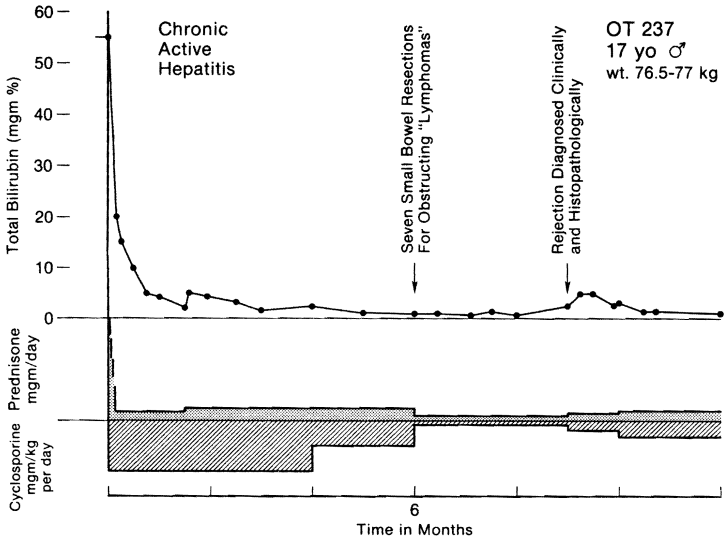

Fig. 2. Course of a 17-year-old boy with chronic active hepatitis, who developed "pseudo lymphomas" of the small intestine. Note that immunosuppression was drastically reduced, followed by evidence of rejection, which was easily reversed. The patient is now well and without evidence of malignant disease.

Table 4. Change in Pattern of Surgeons Performing Liver Transplantation Since Introduction of Cyclosporine

	1963–1979	1980–1981	1982	1983 (4 months)
New patients	170	40	62	24
Total transplantations	191	45	80	34
Transplantations by single surgeon (T. E. Starzl)	187 (97.9%)	45 (100%)	48 (60%)	10 (29.4%)

related to technical surgical errors, to inadvertent use of damaged homografts, and to continuing acceptance into candidacy of patients who are moribund and with irreversible pathophysiology of other organ systems.

One of the recent developments that may further reduce perioperative mortality is the nonheparin venovenous bypass system now being used for almost all adult recipients. Aside from reducing the stresses to the operating surgeon, an extra incentive to use the bypass is the protection to the recipient kidneys offered by avoidance of inferior vena caval occlusion. This will be important because it may be that a physiologic or mechanical renal injury could amplify the potential nephrotoxicity of cyclosporine. In liver recipients, the necessity to juggle the CsA doses in the face of renal failure may force a decision to switch temporarily to azathioprine.[3] Starting the postoperative period with good renal function is one of the premonitors of success.

When CsA was first used clinically, the appearance of lymphomas in an alarming number of patients cast a shadow over the fate of this new drug. As it has turned out, the mere chronicling of these so-called lymphomas is a relatively meaningless exercise. The lesions are almost always a manifestation of Epstein-Barr virus infection,[4] and thus they imply overimmunosuppression. More important, virtually all the lymphoproliferative lesions (Iwatsuki has appropriately called them pseudolymphomas[5]) can be expected to involute spontaneously providing immunosuppression is stopped or reduced and if the temptation is resisted to use the toxic (and immunosuppressive) chemotherapeutic regimens that are customarily recommended by hemotologic oncologists. Lightening of immunosuppression apparently led to disappearance of the intestinal lesions in one of our liver recipients. The story of the appropriate treatment of these pseudolymphomas has been most completely worked out in renal recipients and is discussed by Dr. Tom Rosenthal elsewhere in this volume.

SUMMARY

Immunosuppression with cyclosporine and prednisone has transformed liver transplantation from an agonizingly difficult and highly unpredictable experimental undertaking to one that can be defended as a bona fide service.

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