Transplantation and clinical immunology XIX. J.L. Touraine et al. eds.

LONG TERM RESULTS OF HEPATIC TRANSPLANTATION DURING THE CYCLOSPORINE ERA: THE PITTSBURGH EXPERIENCE

CARLOS O. ESQUIVEL, M.D., PH.D., IGNAZIO R. MARINO, M.D., SHUNZABURO IWATSUKI, M.D., ROBERT D. GORDON, M.D., DAVID VAN THIEL, M.D., THOMAS E. STARZL, M.D., Ph.D.

Departments of Surgery and Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15213.

ABSTRACT

We have reviewed the long term results of the first 500 liver transplant recipients performed by our group during the cyclosporine era. Three hundred and forty-nine recipients lived (69.8%) more than 1 year and the projected 5 year actuarial survival for this sub-group of patients is 88%. The two most common causes of graft dysfunction after the first year were recurrence of the original disease, usually malignancy, and chronic rejection. Most episodes of rejection can be controlled with medical treatment; however, 16 patients of 34 patients who experienced rejection episodes after the first year required retransplantation. Eleven of these 16 are currently alive and free of jaundice. Another common cause of late graft dysfunction is biliary strictures. The recognized side effects of cyclosporine such as nephrotoxicity and lymphoproliferative disease have been lesser problems as a result of the judicious use of the drug. The quality of life of long term survivors is excellent.

INTRODUCTION

It is almost a quarter of a century since the first human liver transplant (OLT) was attempted. For the fist 20 of these 25 years, the operation was considered experimental and was performed in only a handful of centers throughout the world [1-3]. The development of and use of cyclosporin A (CyA) was the turning point in OLT because of the marked improvement in patient survival that occurred as a consequence of its use. As a result of its availability, the number of transplants and centers performing the operation proliferated world wide [2, 4]. The impact of cyclosporine on short term patients survival after OLT has been the topic of many reports; however, information about long term survival and the quality of life after OLT during the CyA era is almost nonexistent. Herein we report our experience with the first 500 liver transplant recipients during the CyA era with the emphasis on those who have survived for more than 1 year.

PATIENTS AND METHODS

Between March 1980 and December 1986, 500 patients received liver transplants for varying reasons at the University of Pittsburgh Health Hospitals. Three hundred and three were adults and the remainder were children. (<18 years of age). The immunosuppression used in each case consisted of CyA and prednisone [2]. The techniques utilized for the donor and recipient operations have been reported in detail elsewhere [5].

Only patients who survived a full year were considered for this study. The following parameters were obtained: the indication for the transplantation, duration of survival, causes of death if dead, incidence of rejection, the frequency of the causes of jaundice in the patients and the prevalence of biliary tract complications, presence of or history of CyA induced lymphoproliferative disease and the quality of their life.

Liver function was assessed by determination of the total bilirubin and clinical jaundice was defined as a total bilirubin greater than 2mg/dl. renal function was considered abnormal if the serum creatinine was greater than 2mg/dl for adults and greater than 1mg/dl for children.

Statistical Analysis

Patient survival was calculated by the life table method (BMDP Statistical Software, Los Angeles, CA).

RESULTS

Disease Indication

The original indication for transplantation in the subjects studied is listed in Table I. The two most common indication in adults were post necrotic cirrhosis followed by primary biliary cirrhosis. In children the two most common indications were biliary atresia followed by any of a variety of inborn errors of metabolism. In the last group cirrhosis associated with alpha-1-antitrypsin deficiency was the most common.

Other less common metabolic liver disease indications for OLT included hemophilia type A although the underlying problem in these cases was post hepatic cirrhosis, glycogen storage disease, cystinosis and cystic fibrosis.

TABLE I

DISEASE INDICATION FOR LIVER TRANSPLANTATION DURING THE CYCLOSPORINE ERA

	Adults		Children	
	Alive	Dead	Alive	Dead
Post Hepatic Cirrhosis	59	35	18	6
Biliary Atresia	1	2	66	32
Primary Biliary Cirrhosis	56	28	--	--
Inborn Errors	18	7	32	11
Sclerosing Cholangitis	28	12	--	2
Primary Tumor	6	18	--	1
Familiar Cholestasis	--	--	11	3
Acute Hepatic Failure	3	3	1	3
Secondary Biliary Cirrhosis	6	4	--	3
Budd-Chiari	3	4	--	1
Congenital Fibrosis	1	--	2	--
Neonatal Hepatitis	--	--	3	--
Trauma	1	1	--	--
Adenoma	2	--	--	--
Polycystic Disease	2	--	--	--
Toxic	1	--	1	--
Infection	--	1	--	--
Idiopathic Purpura	--	--	--	1
Other	--	1	--	--
Total	**187**	**116**	**134**	**63**
	303		**197**	

SURVIVAL

Three hundred and forty-nine patients (69.8%) survived more than 1 year. Most of the deaths occurring during the first year took place within 6 months of surgery. The 1 and 5 year actuarial survival for the entire group is 69% and 60%, respectively. (Figure 1). If one omits from the calculations the patients who died within the first year, the projected 6 year actuarial survival for patients surviving the first year is 88% (Figure 2).

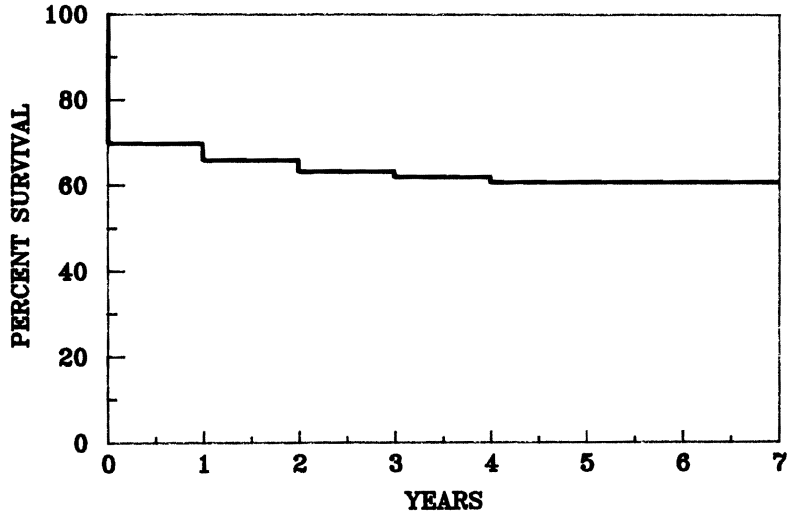

Figure 1: Actuarial survival of the first 500 liver transplant recipients during the cyclosporine era at the University of Pittsburgh.

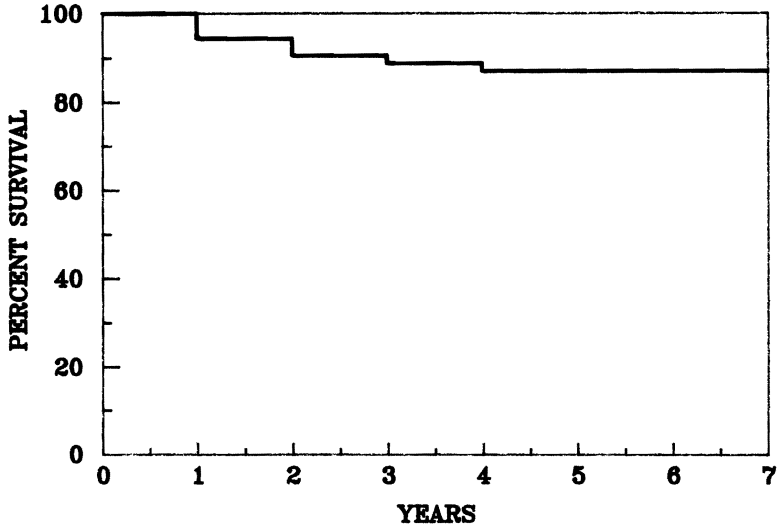

Figure 2: Actuarial survival of the 349 liver transplant recipients who survived more than one year.

Only 28 (8%) patients who survived the first year died after the first year. The causes of their death are listed in Table II. Eleven of these 28 patients died of recurrence of their original disease. The recurrent diseases seen included: carcinoma (8 cases), Budd-Chiari (2 cases) and hepatitis (1 case). Nine other patients died as a result of chronic rejection or its treatment and the remaining patients died of miscellaneous causes (Table II). Seventeen additional patients died between the first and second year, 8 between the second and third year, 2 between the third and fourth year and only 1 between the fourth and fifth year following OLT. There were no deaths after the fifth year of survival following OLT with 33 patients at risk.

TABLE II

CAUSES OF DEATH OF 28 PATIENTS WHO SURVIVED AT LEAST 1 YEAR POST LIVER TRANSPLANT

Time	No. of Patients	Recurrence of Disease	Comments	Rejection	Other*	Comments
1-2yrs	17	8*	*Recurrence of carcinoma (6 cases) hepatitis (1 case) Budd-Chiari (1 case)	3	6**	**Pancreatitis and sepsis (2 cases); oat cell carcinoma (1 case) and variceal hemorrhage (1 case)
2-3yrs	8	3+	+Recurrence of Cancer (2 cases) Budd-Chiari (1 case)	5	—	
3-4yrs	2	0		1	1++	++Lymphoproliferative disease and aspergillosis.
4-5yrs	1	0		--	1	Pancreatitis and sepsis
Total	**28**	**11**		**9**	**8**	

Death due to recurrent disease occurred most often between the first and second OLT year, and rejection lead to death most often between the second and third years. The numbers in each category are too small for any meaningful statistical analysis to be performed.

Two patients died as a result of seizures caused by acute arterial hypertension probably secondary to CyA toxicity. These two patients suffered severe hypoxia which resulted in cerebral injury and allograft failure. Two other patients died of pancreatitis, sepsis and graft failure. Another patient died of gastrointestinal bleeding and allograft failure due to rethrombosis of the portal vein and the last patient died of an oat cell carcinoma of the lung. Finally, two more patients died after 3 years post-transplantation of diseminated lymphoproliferative disease and complications of pancreatitis, respectively.

CLINICAL JAUNDICE

Rejection

Two hundred and ninety-five out of 349 (85%) patients who survived more than 1 year are free of jaundice (up to June 30, 1987); however, 54 (15%) patients have experienced at least one episode of clinical jaundice (bilirubin >2mg/dl postoperatively. The most common cause of postoperative jaundice was rejection (Table III). A total of 34 out of 54 (63%) patients had at least 1 episode of rejection severe enough to require re-hospitalization. In 16 of these 34 cases the rejection episode was brought under control with medical treatment with the exception of 1 patient, who died of unrelated causes in this group of 16 cases. The other 15 currently have a total bilirubin of less than 2mg/dl at the time of the last follow-up.

TABLE III
CAUSES OF JAUNDICE AFTER ORTHOTOPIC LIVER TRANSPLANTATION IN PATIENTS WHO SURVIVE MORE THAN ONE YEAR

	No. of Patients	Successful	Not Successful
Rejection requiring retransplantation	16	11	5
Rejection treated medically	18	16	2
Biliary tract strictures	16	9	7
Miscellaneous	4	1	3
TOTAL	**54**	**37**	**17**

Successful = bilirubin < 2mg/dl at last follow-up
Unsuccessful = bilirubin > 2mg/dl at last follow-up

One of the remaining 18 patients died of rejection while waiting for retransplantation and another is currently awaiting retransplantation.

The remaining 16 patients with at least one episode of rejection underwent liver retransplantation because of failure of medical treatment to control their rejection. Eleven of these patients (69%) are alive with no evidence of clinical jaundice (<2mg/dl) at the time of the last follow-up. The other 5 died of complications of the retransplantation experience.

Six patients not induced among the 34 patients discussed above had rejection in addition to one or more intrahepatic biliary strictures. Five of these 6 patients were retransplanted and 2 of them are doing well and are free of jaundice. Three of the 6 died of retransplantation complications and the sixth patient is currently on the waiting list for a second transplant.

BILIARY COMPLICATIONS

Sixteen of 54 (30%) patients with postoperative jaundice experienced jaundice because of one or more biliary strictures. These strictures occur both at the level of the bile duct anastomosis and within the liver. Eight of these patients (50%) had a successful surgical correction of the biliary stricture. In general, the surgical intervention consisted of converting a previous end-to-end choledocholedochostomy to an end-to-side choledochojejunostomy using a Roux-en-Y limb. Another patient, a 4 year old female with multiple intrahepatic strictures due to thrombosis of the hepatic artery received a secondary transplant.

Five of these 16 patients have persistent jaundice as a result of their biliary stricture. Two of these 5 have had surgical reconstructions, but the procedures were unsuccessful since these patients may have ongoing chronic rejection. Another patient is a 3 year old who received a liver transplant for biliary atresia. This child has complete obstruction of the junction of the main bile ducts and his biliary system is drained externally through a percutaneous catheter. Although this child is free of jaundice, he is a candidate for retransplantation because of the problems associated with the chronic indwelling catheter. Another patient with intrahepatic biliary strictures in the allograft may have recurrence of his original sclerosing cholangitis although it is difficult if not impossible to prove this conclusion. Although this patient had his OLT 2 years ago, he is currently free of jaundice but his serum transaminases are twice normal and the alkaline phosphatase is 910 IU/ml [6]. The fifth patients is a 32 year old man who was transplanted because of a fibrolamellar tumors involving the liver. Currently he has intrahepatic strictures and recurrence of the neoplasm. His hepatic chemistries are close to normal.

MISCELLANEOUS CAUSES

After the first year clinical jaundice occurred in 2 patients because of recurrence of viral hepatitis; one of these 2 has died and the other is doing well after retransplantation. Two other patients have had a recurrence of their original tumor and both have died. A fifth patient died with allograft failure due to pancreatitis and septicemia. Another patient died of recurrent alcoholism and allograft rejection. Lastly, a sixth patient who received a liver transplant because of a Budd-Chiari syndrome died of recurrence of her disease when the anticoagulation she was on was discontinued for a liver biopsy.

RENAL FAILURE

Twenty adult patients have a serum creatinine greater than 2mg/dl at the time of the last follow-up. In 3 of these patients, the CyA has been discontinued because of deterioration of their renal function. In each case these patients are being maintained on an immunosuppressive regimen consisting of a combination of azathioprine and prednisone.

Thirteen surviving children (<18 years of age) have a serum creatinine greater than 1mg/dl at the time of the last follow-up. None of the adult or children who have survived for more than 1 year have required dialysis for renal dysfunction.

LYMPHOPROLIFERATIVE DISEASE

Fifteen of the 500 patients transplanted during this period have developed a post-transplant lymphoproliferative disease (3.0%). The onset of the disease in 9 of these 15 patients took place during the first year after transplantation. In the remaining 6 the disease developed after the first year but between the first and second year in 3, between the second and third year in 1, and after the third year in 2 others. Lymphoproliferative disease has been treated successfully in 3 of these 6 patients by either decreasing or temporarily discontinuing immunosuppression. One patient currently has a lymphoproliferative disease involving the retroperitoneum and mesenteric nodes despite discontinuation of his immunosuppression for 11 months and 2 debulking laparotomies. Another child has had repetitive recurrences of lymphoproliferative tumors in the trachea. Reductions in CyA usage in this case has not resulted in resolving the lymphoproliferative problem. The sixth patient died of disseminated lymphoproliferative disease involving the retroperitoneum, kidneys, adrenals, heart, brain, bone marrow and gastrointestinal tract. A summary of these 6 patients is given in Table IV and a recent review of this subject has been published [7].

TABLE IV

LYMPHOPROLIFERATIVE DISEASE IN LIVER TRANSPLANT RECIPIENTS WHO HAVE SURVIVED MORE THAN 1 YEAR

Case	Age at TX	time of onset of PTLD after OLT (months)	Organs Involved	Treatment	Outcome
1	8	39	lymph nodes kidneys, adrenals heart, bone marrows, CNS, GI tract	none	died
2	15	16	lymph nodes CNS, nasopharynx	transient discontinuation of immuno-suppression	no residual tumor
3	4	24	retroperitoneal and mesenteric lymph nodes, GI tract	discontinuation of immunosuppression	residual tumor
4	5	48	trachea	reduction of immunosuppression	recent recurrence
5	3	12	nasopharynx cervical nodes	reduction of immunosuppression	no residual tumor
6	7	13	nasopharynx cervical nodes	reduction of immunosuppression	no residual tumor

QUALITY OF LIFE

The quality of life following OLT was assessed in 37 patients who have survived more than 5 years after hepatic transplantation. Twenty-one of these 37 are children (<18 years old) and 16 are adults. One of these long term surviving children has a neurologic deficit as a result of recurrence of the original lipid storage disease. This case has been reported elsewhere [8]. A second child has decreased visual acuity due to a pseudotumor, but his liver function is normal. A third child has abnormal transaminase levels although he is not jaundiced. A liver biopsy in this case showed a reduction in the number of the bile ducts within the liver. Finally, a fourth child who experienced portal vein thrombosis postoperatively has required sclerotherapy for variceal hemorrhage; however, this child has been doing very well with no subsequent episodes of bleeding (for the last year). The remainder of the children are growing well, attend school and are free of jaundice.

Among the 16 adults who are long term survivors, one patient has recurrence

of a hepatocellular carcinoma involving the lungs. Another has developed chronic renal failure due to CyA and at the present time is being treated with azathioprine instead of CyA. Dialysis is not necessary. A third patient is disabled because of a severe neurologic deficit sustained during the liver transplantation procedure. A fourth patient is on triple drug therapy (azathioprine, cyclosporine and prednisone) after experiencing a recent episode of rejection. Nonetheless, she is working full time. Four patients are housewives and require no outside help and the remaining 8 are currently working full time.

Among the 37 patients who have survived 5 years or more, only 5 patient required a second transplant and none have required a third transplant.

DISCUSSION

Liver transplantation is the treatment of choice for patients with hopelessly advanced chronic liver disease. The operation has become a routine procedure in many centers throughout the world. Despite the overall good results with OLT, it should be remembered that serious complications can occur following hepatic transplantation. Several factors have been implicated in their pathogenic and include the difficulty with the operation and the previous condition of the recipient.

Most of the complications and deaths following liver transplantation occur during the first year and almost 90% of the patients who survived the first year can be expected to be alive at 5 years. The most common causes of death after the first year are recurrence of the original disease and rejection [9]. Most patients who died of recurrent disease did so between the first and second year after transplantation. Recurrence of hepatic malignancy accounts for the majority of these cases [10]. Rejection, on the other hand, occurs more often between the second and third post OLT year. An explanation for this late onset of rejection which leads to patient death may be that most patients at this time are taking very small doses of immunosuppression which may not be optimal for allograft immunotolerance.

Biliary strictures are a frequent cause of jaundice in patients who survive more than 1 year [11]. In several of these patients, the clinical presentation has been similar to that associated with rejection and the biliary strictures were suspected only after no improvement occurred after a full course of anti-rejection therapy. Ultrasound has not been useful in these cases and if a biliary stricture is suspected a percutaneous cholangiography is absolutely indicated.

The introduction of CyA into the clinical practice of transplantation was followed by significant concerns about its side effects, namely nephrotoxicity and malignancy. However, the nephrotoxicity associated with long term use of CyA has been minimized by adjusting the doses according to renal function and the

addition of azathioprine when necessary. In fact, CyA has had to be discontinued in only 3 patients because of nephrotoxicity. Fortunately, effective immunosuppression in these 3 patients has been achieved with a combination of azathioprine and prednisone. A second major concern with the chronic use of CyA is immunosuppression-induced lymphoproliferative disease. Most patients with this problem respond to drastic reductions or discontinuation of their CyA. It appears as if the sooner such a complication is detected, the better is the prognosis. Thus, lesions that are detected early seem to respond quickly to a reduction in the immunosuppression being used.

The quality of life of most long term liver transplant survivors is excellent. Following OLT children have been shown to have normal growth patterns [12]. The reintegration of both children and adult survivors back into society is very high, the majority either attend school or work full time.

ACKNOWLEDGEMENTS

Supported by Research Grants from the Veterans Administration and Project Grant No. AM-29961 from the National Institutes of Health, Bethesda, Maryland.

REFERENCES

1. Starzl, T.E., Marchioro, T.L., Von Kaulla, K.N., Hermann, G., Brittain, R.S., Waddell, W.R. (1963) Surg Gynecol Obstet 117:659-676.

2. Starzl, T.E., Iwatsuki, S, Van Thiel, D.H., Gartner, J.C., Zitelli, B.J., Malatack, J.J., Schade, R.R., Shaw, B.W., Jr., Hakala, T.R., Rosenthal, J.T., Porter, K.A. (1982) Hepatology 2:614-636.

3. NIH Consensus Development conference Statement (1984) Liver Transplantation. June 20-23, 1983. Hepatology 4:107S-109S.

4. Starzl, T.E., Iwatsuki, S., Bahnson, H.B., Van Thiel, D.H., Hardesty, R., Griffith, B., Shaw, B.W., Jr., Klintmalm, G.B.G., Porter, K.A. (1982) Amsterdam, Biomedical Press, pp. 431-436.

5. Starzl, T.E., Iwatsuki, S., Esquivel, C.O., Todo, S., Kam, I., Lynch, S., Gordon, R.D., Shaw, B., Jr. (1985) Seminars in Liver Disease 5:349-356, 1985.

6. Marsh, J.W., Iwatsuki, S., Makowka, L., Esquivel, C.O., Gordon, R.D., Todo, S., Tzakis, A., Miller, C., Van Thiel, D., Starzl, T.E. Ann Surg, in press.

7. Makowka, L., Nalesnik, M., Stieber, A., Tzakis, A., Jaffe, R., Ho, M., Iwatsuki, S., Demetris, A.J., Griffith, B.P., Breing M.K., Starzl, T.E. (1987) Control of Post-transplant Lymphoproliferative Disorders and Kaposi's Sarcoma by Modulation of Immunosuppression. New York, F.K., Schattauer Verlag, Stuttgart.

8. Gartner, J.C., Jr., Bergman, I., Malatack, J.J., Zitelli, B.J., Jaffe, R., Watkins, J.B., Shaw, B.W., Iwatsuki, S., Starzl, T.E. (1985) Pediatrics 77:104-476.

9 Iwatsuki, S., Starzl, T.E., Gordon, R.D., Esquivel, C.O., Todo, S., Tzakis, A.G., Makowka, L., Marsh, J.W., Jr., Miller, C.M. (1987) Transplant Proc 19:2373-2377.

10. Esquivel, C.O., Iwatsuki, S., Marino, I.R., Markus, B., Van Thiel, D., Starzl, T.E. (1987) Sugahara K (ed) Liver Transplantation for Hepatocellular Carcinoma and Other Primary Hepatic Malignancies. Trends in Gastroenterology, in press.

11. Lerut, J., Gordon, R.D., Iwatsuki, S., Esquivel, C.O., Todo, S., Tzakis, A., Starzl, T.E. (1987) Transplantation 43:47-50.

12. Urbach, A.H., Gartner, J.C., Jr., Malatack, J.J., Zitelli, B.J., Iwatsuki, S., Shaw, B.W., Starzl, T.E. (1987) Am J Dis Child, 141:547-549.