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Long-term results of cyclosporine-steroid therapy in 131 non-matched cadaveric renal transplants

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Abstract: One-hundred-and-twenty-eight recipients of 131 consecutive, non-matched cadaver renal allografts were treated with cyclosporine and steroids. They have been followed for 4 to 6 yr. Cumulative patient survival at 1-yr was 92.2% and at 6yr it is 77.8%. Cumulative graft survival at 1-yr was 79.4% and at 6 yr it is 50.0%. After the high-risk 1st yr, the rate of graft loss was even and similar to that reported after the 1st yr for grafts treated with azathioprine and steroids. This indicates that cyclosporine nephrotoxicity has not had an obvious adverse effect on the survival of chronically functioning grafts. The results were better with primary grafting versus retransplantation, but were not significantly influenced by age, diabetes mellitus, or a delayed switch in patients from cyclosporine to azathioprine. We have concluded that cyclosporine-steroid therapy is safe and effective for long-term use after cadaveric renal transplantation.

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Cyclosporine is now in widespread use for the prevention of rejection after cadaveric renal transplantation. The drug was first used clinically by Calne and associates (1, 2) who were able to achieve chronic graft function in many of their patients without any other agent. However, patient mortality was high, significant nephrotoxicity was common, and 3 of their first 34 recipients developed lymphomas (1).

We have recommended combined immunosuppressive therapy with cyclosporine and steroids (3, 4). Although the drug combination has been safe and effective (5, 6), nagging doubts have remained about the long-term efficacy and safety of cyclosporine. We present here results from our first 131 consecutive cadaveric renal transplantations performed from late 1979 through 1981. Follow-ups are available for 4 to 6 yr.

Material and methods

Case Material

There were 128 patients in the trial of whom 93 were given primary grafts. Second, third or fourth

transplantations were carried out in 35 patients who had rejected grafts at earlier times under conventional immunosuppression. Three of the 128 patients in the trial, 2 from the primary group and 1 from the retransplantation group, lost their grafts despite cyclosporine-steroid therapy and were retransplanted during the 1979-1981 period of case accrual. Thus, there was a total of 131 transplantations done under cyclosporine-steroid therapy.

The first 57 primary transplantations and 10 retransplantations were done at the University of Colorado Health Sciences Center in Denver (5). The remainder were done at the University Health Center of Pittsburgh (4, 6). Deliberate blood transfusion for recipient conditioning was not practiced in Colorado during these trials and was inconsistently used in Pittsburgh. Consequently, only a minority of recipients had a history of transfusion (3-6). There were 86 males and 42 females, from 9 to 63 yr old (mean 37.5 ± 11.9 , S.D.). Eleven patients (8.5%) were juvenile onset diabetics. In nearly half the patients, the cause of end stage renal disease was not definitively known.

Tissue matching

Cytotoxic antidonor antibodies were avoided with conventional crossmatch techniques using current

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recipient sera. Otherwise, matching was random in most cases. In the Colorado series, HLA antigen mismatches at the A and B loci averaged 3.3 ± 1.3 , S.D. and only 10 of the 66 patients had as few as 2 mismatches (5). In the Pittsburgh series, HLA A or B matches averaged 0.79 ± 0.9 , S.D. from primary graft recipients and 1.46 ± 1.3 , S.D. for patients undergoing retransplantation (6). Since D_R typing data were not available at the time of transplantation, D_R matching was random and uniformly poor.

Immunosuppression

The first 22 patients in the Colorado series had pretreatment, from a few days up to 3 months with cyclosporine, thoracic duct drainage, or lymphapheresis (3, 5). Pretreatment was not used thereafter. In the first recipients, prednisone was withheld postoperatively until there were clinical signs of rejection. It became obvious that rejection occurred in most of the patients unless steroids were used from the beginning and therefore steroids were used prophylactically in all subsequent patients (4).

Several hours before operation, 17.5 mg/kg of cyclosporine were given orally. If tolerated, this daily dose was continued for 2 months postoperatively before being reduced. Earlier reductions were made in the event of toxic side-effects (4). Later in the course, the cyclosporine doses were almost always weaned so that the average daily dose by the end of 1-yr was 5 to 6 mg/kg (5, 6). Blood plasma levels of cyclosporine were not regularly monitored in 1979–1981.

In adults, a 5-d burst of steroids was given, beginning with 200 mg of methylprednisolone or prednisone on the day of operation. The dose was reduced by 40 mg/d until a daily maintenance dose of 20 mg was reached (4). Further reductions in the dose of prednisone were dictated by the clinical course. Rejections were treated with a 1 g bolus of methylprednisolone followed by a repeat of the 5-d cycle of high-dose prednisone. In children the steroid doses were adjusted downward in accordance with size and weight.

Statistics

Follow-up was available for all 131 grafts and 128 patients 48 to 72 months after transplantation. There were no exclusions. Actuarial patient and graft survivals were calculated by the life table method (7, 8). In transplantation, most patient deaths bear some potential relationship to therapy. Therefore, all graft losses, including those which

Table 1. Principal cause of 27 deaths

	Before 1 year	After 1 year	Total
Infection	7 (5)	6 (3)	13 (8)
Myocardial infarction	1 (1)	4 (2)	5 (3)
Aortic aneurysm	0	3 (3)	3 (3)
Sudden death during coronary angiography	1 (1)	0	1 (1)
Hemorrhage after coronary revascularization	1 (1)	0	1 (1)
Pulmonary embolus after hip surgery	1 (1)	0	1 (1)
Suicide	0	1 (1)	1 (1)
Auto accident	0	1 (1)	1 (1)
Unknown	0	1 (0)	1 (0)
Total	10 (8)	17 (11)	27 (19)

() indicates grafts functioning at time of death.

were functioning at the time of death, were counted as failures.

Results

Patient survival

Patient survival for the entire series is summarized in Fig. 1. Twenty-seven (21.1%) of the patients have died, including 10 (7.8%) deaths within 1 yr of operation. Three (2.3%) of these fatalities were from myocardial infarction, sudden death during coronary angiography, or hemorrhage during coronary artery reconstruction within 30 d after transplantation and these were counted as operative deaths (Table 1). Four other patients died of myocardial infarctions 16, 23, 52 and 54 months after transplantation. Ruptured or dissecting abdominal aneurysms accounted for 3 late deaths.

Infections were responsible for 13 deaths (Table 1) including 2 from pulmonary nocardiosis after 8 and 10 months, 1 from a perforated colonic diver-

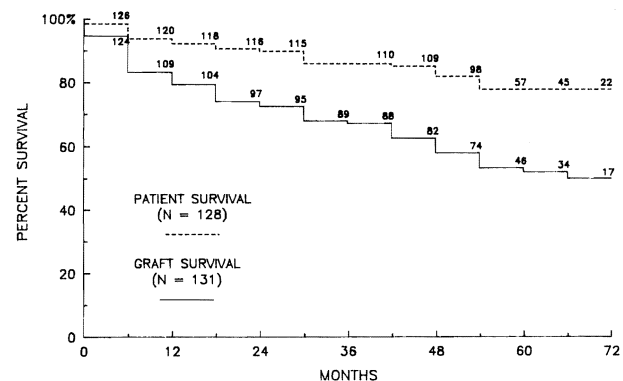


Fig. 1. Actuarial (life table) survival for 128 patients and 131 non-matched cadaveric renal transplants performed between December, 1979 and December, 1981 with cyclosporine-prednisone therapy.

ticulum after 25 months, 1 from disseminated histoplasmosis after 27 months, and 2 from hepatitis after 26 and 45 months. Nineteen (70.4%) of the 27 deaths occurred while there was still adequate graft function (Table 1).

There was no statistically significant difference in survival between recipients of primary grafts and retransplants (Fig. 2A). Seventeen patients were taken off cyclosporine therapy 6 to 53 months after transplantation, usually because of suspected nephrotoxicity. These 17 recipients survived at the same rate as recipients kept on cyclosporine. Fourteen are still alive. Of the 3 who died, 2 had functioning grafts after 25 and 26 months. Colonic diverticulitis and perforation and a pulmonary embolus after hip surgery accounted for 2 deaths. The 3rd patient, who lost his primary graft, died of a ruptured abdominal aneurysm 16 months after he was retransplanted.

There were 11 diabetic patients in the series (8.6%). Their percentage survival was the same as nondiabetics. Three diabetic patients were lost with functioning grafts including 1 at 37 months in an automobile accident, the 2nd at 45 months from peripheral vascular disease, septicemia and myo-

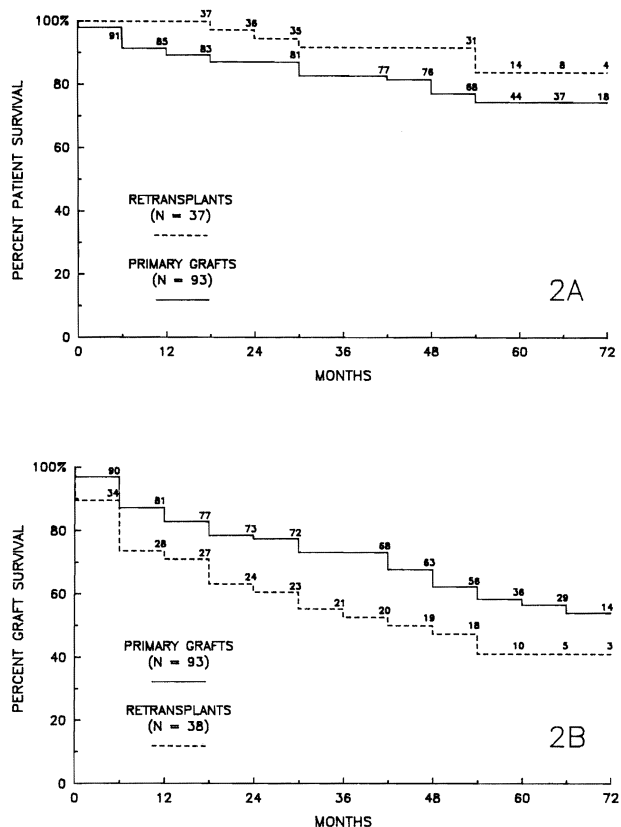


Fig. 2. Actuarial patient survival (A) and graft survival (B) for 93 recipients of 93 primary and 37 recipients of 38 second or third non-matched cadaveric renal transplants.

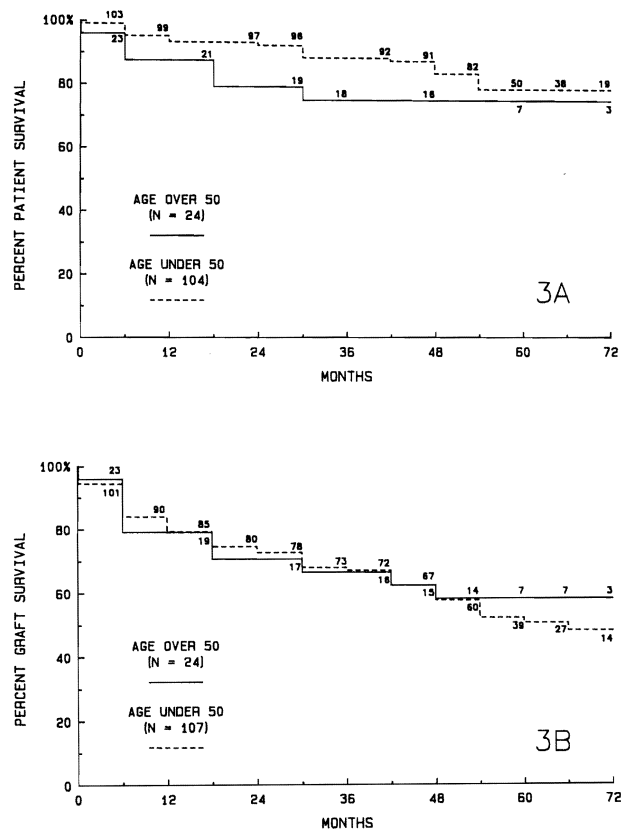


Fig. 3. Actuarial patient survival (A) and graft survival (B) for 24 recipients over 50 yr of age and 104 recipients under 50 yr at transplantation.

cardial infarction, and the 3rd at 52 months from myocardial infarction. Eight diabetic patients (72.7%) remain alive.

The 24 patients in this series over the age of 50 yr at the time of transplantation survived at the same rate as younger patients during the 4 to 6 yr of follow-up (Fig. 3A).

Graft survival

Overall, 79.4% of the 131 grafts functioned for at least 1 yr (Fig. 1). At 4 yr, 76 (58.0%) were still functioning (Fig. 1). After 49 to 72 months, 69 (52.7%) are functioning with a mean serum creatinine of 158.9 ± 0.9 , S.D. $\mu\text{mol/ml}$ (range 70.6 to 441.5). Three patients with functioning grafts have a serum creatinine of greater than $350 \mu\text{mol/ml}$ and evidence of chronic rejection. At present, these are the only grafts at probable high risk of imminent loss.

Graft survival for primary grafts was significantly better than after retransplantation. The difference was evident at 6 months ($p < 0.01$) and has remained significant out to 60 months (Fig. 2B). After the 1st yr, the annual rate of loss has been approximately the same for primary grafts as for

Table 2. Causes of 62 graft losses

	Primary	Re-graft	All
Rejection	22	16	38
Patient death	16	3	19
Oxalosis	1	1	2
Hemolytic uremic syndrome	0	1	1
Technical accident	1	1	2
Total	40	22	62

retransplants. After 4 to 6 yr, 53 (57.0%) of the 93 primary grafts and 16 (42.1%) of the 38 retransplants are functioning.

The most frequent causes of graft loss were rejection and recipient death (Table 2). One primary graft was lost to recurrent oxalosis at 11 months. The patient was retransplanted but lost the 2nd graft to oxalosis within 2 months. The patient is still alive on dialysis. Hemolytic uremic syndrome destroyed 1 graft following a pregnancy 33 months after transplantation. The 2 technical losses were from ureteral necrosis and renal vein thrombosis.

Graft survival in the 17 patients who were withdrawn from cyclosporine was not significantly different from that in patients who were kept on the drug. Sixteen of these patients were converted to azathioprine 20.8 ± 11.0 , S.D. months (range 6 to 45 months) after transplantation. The 17th recipient withdrew himself from cyclosporine at 53 months and has a perfectly functioning graft at 65 months on 15 mg/d of prednisone. He has declined therapy with azathioprine. In addition to 2 functioning grafts lost by patient death, 3 grafts were lost to rejection in patients switched to azathioprine after 6, 19 and 21 months. The 3 grafts failed 4, 46 and 4 months later, respectively. Twelve (70.6%) of the 17 grafts are still functioning after 50 to 72 months.

Graft survival has been the same for diabetics and non-diabetics. In addition to 3 grafts in diabetics lost by patient death, 1 graft was lost to an early renal vein thrombosis in a patient of O-positive ABO blood type who was accidentally given a kidney from an A donor. Only 1 graft has been lost to rejection in a diabetic patient and that occurred after 45 months. Seven (63.6%) of the grafts in diabetic patients are still functioning.

Graft survival in patients over 50 yr of age at the time of transplantation has been the same as graft survival in younger patients (Fig. 3B).

Current cyclosporine dose

For the 57 patients still being treated with cyclosporine, the mean daily dose is 4.3 ± 1.8 , S.D. mg/kg.

Daily dosage has remained fairly constant beyond 2 yr after transplantation.

Malignancy

Two lymphomas diagnosed during life and treated with local resection and reduction of immunosuppression (9) have not recurred after 51 and 66 months. A third similar lesion was an incidental autopsy finding in a patient who died of pneumonitis. Another patient has been living for more than 4 yr in symbiosis with a disseminated Kaposi's sarcoma which waxes and wanes with adjustments in cyclosporine dose, which is presently 1 mg/kg/d. Two carcinomas have been diagnosed in males with excellent graft function. One patient has widespread metastases from an unknown primary 71 months after transplantation. The other patient developed a lacrimal duct cancer 3 yr after transplantation which was controlled with radiotherapy, and then committed suicide when a separate oropharyngeal carcinoma developed after 4 yr.

Discussion

Nephrotoxicity as the principal dose-limiting factor with cyclosporine administration has been recognized since the first clinical trials with this drug (1). The strategy of adding steroids, azathioprine, or antilymphocyte globulin (ALG) to reduced doses of cyclosporine has permitted good immunosuppression without excessive nephrotoxicity. However, chronic interstitial fibrosis has been described in renal allografts (10) and in the kidneys of heart transplant recipients (11) long after transplantation.

Determination of the possible adverse influence of chronic cyclosporine upon patient or renal graft

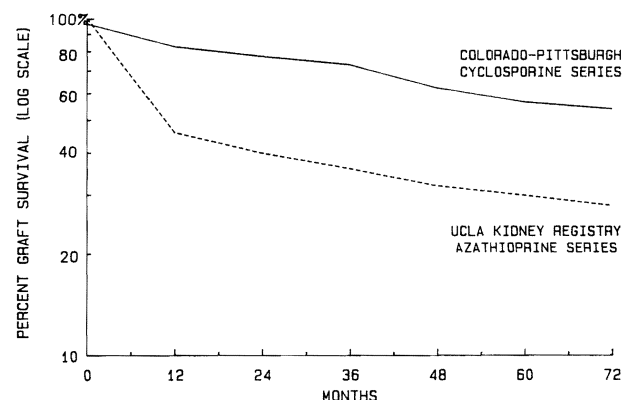


Fig. 4. Actuarial survival (log scale) for 93 primary non-matched cadaveric renal transplants with cyclosporine-steroid therapy compared with 11 861 cadaveric transplants with conventional immunosuppression from the UCLA kidney transplant registry (13).

survival was the principal focus of this review of our earliest series of patients. The results were similar to those in a 3-yr follow-up study by Calne & Wood (12) of European renal recipients. The patient mortality, which was 7.8% in the 1st yr, is projected to be about 22% at the end of 5 yr, a half decade mortality which is far lower than in pooled series from North America (13) or the southern region of the United States (14) for patients under azathioprine-steroid maintenance. The principal causes of death from infection and cardiovascular complications have been the same as in the past but at a reduced rate. The hypertension which has been associated with cyclosporine (15) may have been an added risk factor in the 9 patients who died from cardiovascular complications, but there is no clear evidence for this. Six patients developed malignant tumors, but 3 were of the lymphoma variety associated with Epstein-Barr virus infections which have been shown to regress with discontinuance or reduction of immunosuppression (9). There were only 2 malignant epithelial tumors, an incidence greater than in a normal population averaging nearly 40 yr of age, but less than that recorded by Penn in renal transplant recipients under chronic immunosuppression (16).

The chronic survival and stability of function of these largely unmatched cadaveric kidneys was encouraging. During the first years of treatment, little was known about how to best use cyclosporine and routine pharmacologic monitoring of drug levels was not available. It is likely that many of these patients were treated at toxic levels for significant periods of time. Despite evidence of cyclosporine nephrotoxicity in many patients during the 1st yr, graft function has not significantly deteriorated during the subsequent 3 to 5 yr. Some patients with extreme elevations of BUN and creatinine at 1 yr have had stable and even improving function during ensuing years.

The fact that 1-yr cadaver graft survival could be improved with cyclosporine has been evident for some time. Now it can be stated that the rate of graft loss after 1 yr is no greater than that reported by Terasaki et al. (13) in nearly 12 000 North American recipients of primary cadaveric allografts under conventional immunosuppression (Fig. 4) and by McDonald et al. (14) in the region of the United States served by the Southeast Organ Procurement Foundation. The comparable rate of late graft loss under cyclosporine-steroid therapy is especially significant because conditions which can favorably influence survival curves, such as selection of patients on the basis of tissue matching, immunologic or medical low risk factors, or sys-

tematic conditioning of patients by deliberate blood transfusion were not features of this trial.

It was interesting that the rate of late graft loss in the 15 patients switched from cyclosporine to azathioprine was less than in the larger group maintained on cyclosporine. However, the number of cases was small and the differences were not significant. We do not suggest on the basis of this trial that late switchover from cyclosporine to azathioprine should be considered more commonly.

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