Transpl Int (1994) 7: 33–38

ORIGINAL ARTICLE

Diego Cantarovich
Remy Baatard
Thierry Baranger
Ashok Tirouvanziam
Jean-Noel Le Sant
Maryvonne Hourmant
Jacques Dantal
Jean-Paul Soulillou

Cadaveric renal transplantation after 60 years of age

A single center experience

Received: 30 November 1992
Received after revision: 12 March 1993
Accepted: 16 April 1993

D. Cantarovich (✉) · R. Baatard
T. Baranger · A. Tirouvanziam
J.-N. Le Sant · M. Hourmant · J. Dantal
J.-P. Soulillou
Service de Néphrologie
et Immunologie Clinique,
Centre Hospitalier
et Universitaire de Nantes,
1 Place Alexis Ricordeau,
F-44035 Nantes, France

Abstract We report the outcome of 121 cadaveric renal transplants performed in our institution between September 1985 and April 1992 in 117 patients, aged 60–71 years (mean 63 years) at the time of transplantation. Compared to 640 patients 20–59 years of age transplanted during the same study period, a nonstatistically significant difference was observed in the 5-year actuarial patient (80% and 90%, respectively, in recipients over and under 60 years of age) and transplant (80% and 72%, respectively, in recipients over and under 60 years oaf age) survival rates. However, elderly patients had significantly lower survival than recipients 20–29 years of age ($P < 0.009$). Fourteen patients died (all but one with a functioning graft) due to cardiovascular diseases (5%; 42.8% of total deaths), infections (3%; 28.6% of total deaths), and gastrointestinal complications (3%; 28.6% of total deaths). Younger patients showed a similar and nonsignificantly different incidence of cardiovascular- (35%) and infectious- (30%) related deaths. The incidence of acute rejection episodes and cytomegalovirus (CMV) infectious episodes was 27% and 24%, respectively, during the 1st post-transplant year. Ongoing acute rejection and CMV infectious episodes were significantly higher in patients who died than in those still alive ($P < 0.002$ and $P < 0.02$, respectively). Cyclosporin maintenance therapy was well tolerated in all patients but one, and 64% of the patients could be maintained without steroids. These data indicate that cadaveric renal transplantation is a safe and effective procedure in the management of chronic renal failure of selected patients 60 years of age or older.

Key words Renal transplantation, advanced age recipients · Sixty years and older, renal transplantation

Introduction

There is still some controversy surrounding the value of renal replacement therapy in sustaining an adequate quality of life with low morbidity and mortality in elderly patients. Until recently, patients 60 years of age were considered "poor" candidates for renal transplantation because of the increased morbidity and mortality encountered with aging [9]. After the introduction of cyclosporin (CyA), a significant improvement in the survival of elderly recipients of cadaveric renal transplants was reported by some authors [11] but not confirmed by others [8]. We previously reported a significantly lower ($P < 0.05$) 2-year actuarial patient survival rate in a small number ($n = 36$) of cadaveric renal transplant recipients aged 60 years and over than in younger patients [1]. In the present study, we analyzed a much larger number of transplanted patients 60 years of age or older who were followed up for as long as 6.5 years.

Our aim was to determine whether being over 60 years of age at the time of transplantation had a negative impact on patient and transplant survival. In addition, patients' pretransplant clinical state, demographic data, and post-transplant medical complications were investigated to determine predictive factors for patient outcome

Patients, materials, and methods

Patients

Between September 1985 and April 1992, a total of 117 patients 60 years of age or older underwent 121 of the 761 single cadaveric kidney transplants (16%) performed in our institution in recipients 20 years of age or older. All but 12 of the elderly patients (11 second and 1 third retransplants) were recipients of primary cadaveric renal transplants. Sixty-three patients (54%) were men and 54 (46%) women. Their mean age was 63 ± 2.6 years (range 60–71 years; 22% older than 65). All but two recipients had been maintained on dialysis for 1–236 months prior to transplantation (mean 39 ± 40 months; 55% were on dialysis for more than 2 years). Mean recipient pretransplant proteinemia was 70.2 g/l (range 49–95 g/l). Causes of end-stage renal disease were chronic glomerulonephritis (n = 35), type 2 diabetes (n = 2), polycystic kidney disease (n = 29), chronic pyelonephritis (n = 20), hypertension (n = 18), urological causes (n = 8) and others (n = 5). Mean donor age was 33.5 ± 14 years (range 0.5–65 years). The mean preservation time was 36 ± 9.6 h (range 16–54 h).

Follow-up ranged from 2 to 79 months: 6% were followed up for less than 3 months, 23% for 4–12 months, 13% for 13–24 months, 17% for 25–36 months, 16% for 37–48 months, 16% for 49–60 months, and 9% for more than 61 months).

Results of the 640 renal transplantations performed during the same period in recipients 20–59 years of age were used as controls.

Pretransplant cardiac evaluation

Echocardiography and/or thallium (exercise and/or pharmacological stress test) scan [13] and/or gamma angiography were routinely performed. Cardiac catheterization was done in three cases. None of the 117 patients required coronary revascularization or a heart transplant before transplantation. Ischemic heart disease was not considered an exclusion for undergoing transplantation. More appropriate anesthetic and post-transplant medical care and monitoring were given to these patients.

Immunosuppression

The imunosuppressive regimen consisted of a transient triple induction immunosuppressive protocol (that started following surgery) consisting of azathioprine (Aza; 2 mg/kg per day), prednisolone (Pred; 1 mg/kg per day), and a monoclonal anti-interleukin-2 receptor antibody (n = 15; given at 10 mg/day for the first 2 weeks) [12] or a polyclonal rabbit or horse antilymphocyte globulin (n = 106; usually given until a serum creatinine level of 300 μmol/l was obtained, at an initial dosage of 2 mg/kg per day and thereafter adjusted according to the rosette test) [12].

CyA was administered following discontinuance of bioreagents (mean 11 ± 4.5 days; range 2–27 days), at an initial oral dosage of 6–8 mg/kg per day. Thereafter, the dosage was permanently adjusted according to CyA trough blood level (therapeutic level between 150 and 250 ng/ml).

Pred dosage was regularly decreased (every 5 days) until definitive discontinuance (together with Aza) between days 45 and 60. Maintenance immunosuppression consisted of CyA monotherapy. After 1989, Aza (or Pred in case of Aza intolerance) was reintroduced in patients who underwent a rejection episode [5]. In addition, for patients in a prospective study conducted since 1990 to compare two different dosages of CyA at 1 year post-transplant, Aza (or Pred in case of Aza intolerance) was added to patients under CyA monotherapy.

Ongoing acute rejection episodes were treated with intravenous methylprednisolone boluses at a dosage of 5, 5, 4, 3, and 2 mg/kg, respectively, for 5 consecutive days. In cases of steroid resistance, ATG was added for 7–10 days. Younger patients received the same induction, maintenance, and antirejection treatment as older patients.

Mean HLA-A, -B and -DR mismatches were 1.1, 1.4, and 1.1, respectively. All patients received an ABO-compatible graft and had a negative T-lymphocytotoxic crossmatch on current sera.

Anti-infectious prophylaxis

Oral penicillin was given prophylactically during the first 10 post-operative days. Since 1987, oral B amphotericin and sulfadoxine-pyrimethamine (Fansidar, Roche) have been added for a 2-month period. In 1989, oral penicillin and Fansidar were replaced by sulfamethoxazole-trimethoprim (Bactrim, Roche) given during the first 3 months. Carbonate aluminium was given to prevent gastroduodenal complications. No antiviral prophylactic treatment was given, and no selection was done regarding donor/recipient cytomegalovirus (CMV) serologic status.

Statistical tests

Patient and transplant survival rates were calculated using the actuarial method technique and compared using the log-rank test. Further comparisons were performed using the chi-square test. All P values were two-tailed and considered significant when less than or equal to 0.05.

Results

Patient survival

The 1- and 5-year actuarial patient survival rates were 92% and 80%, respectively (Table 1). Although differences were not statistically significant when compared to the 640 recipients 20–59 years of age transplanted during the same period, elderly patients had significantly lower survival than patients 20–29 years of age ($P < 0.009$; Table 1).

During the 79-month study period, 14 out of 117 patients (12%) 60 years of age or older and 43 out of 640 (6.7%) 20–59 years of age died ($P < 0.04$). Deaths in elderly patients were due to cardiovascular diseases (n = 6; 42.8%), infections (n = 4; 28.6%), and gastrointestinal complications (n = 4; 28.6%). Deaths in younger patients

Table 1 Five-year actuarial patient survival rates in cadaveric renal transplant recipients 60 years of age or older compared to 640 younger patients transplanted during the same period and also under CyA maintenance immunosuppression. Recipient age indicated is that at the time of transplantation. Only patients 20–29 years of age had significantly better survival ($P < 0.009$) than those 60 years of age or older

	Months after transplantation				
Age (years)	12	24	36	48	60
≥ 60	92%	90%	90%	87%	80%
50–59	91%	85%	85%	80%	80%
40–49	95%	95%	91%	91%	91%
30–39	96%	94%	93%	93%	91%
20–29	99%	96%	96%	94%	94%

Table 2 Five-year actuarial transplant survival rates in cadaveric renal transplant recipients 60 years of age or older compared to 640 younger patients transplanted during the same period and also under CyA maintenance immunosuppression. Recipient age indicated is that at the time of transplantation. Results are not significantly different

	Months after transplantation				
Age (years)	12	24	36	48	60
≥ 60	86%	85%	82%	82%	80%
50–59	88%	84%	81%	73%	70%
40–49	93%	92%	89%	86%	84%
30–39	89%	86%	82%	80%	75%
20–29	83%	75%	71%	70%	64%

were due to cardiovascular diseases ($n = 15$; 35%; P = NS compared to elderly patients), infections ($n = 13$; 30%; P = NS compared to elderly patients), malignancies ($n = 8$; 19%), gastrointestinal complications ($n = 4$; 9%), and unknown causes ($n = 3$; 7%). As shown in Table 3, only one patient experienced a fatal cardiovascular complication within the first 3 postoperative months. This 61-year-old patient had a history of severe non-obstructive cardiomyopathy and arrhythmia. For these reasons, intravenous heparin at a hypocoagulant dosage was given following surgery. Massive bleeding from the transplant site occurred on day 7, requiring urgent surgery. Postoperative follow-up was marked by multivisceral dysfunction (including hepatic failure and intravascular disseminated coagulation), and death occurred on day 11.

As a sole parameter, age did not correlate with the risk of death in elderly patients (equal mean age in patients who died and those still alive). Nor was there a correlation between the risk of death and the end-stage chronic renal failure etiology, length of time of end-stage chronic renal failure therapy [8/53 patients (15%) on dialysis for less than 2 years and 6/64 (9.4%) for more than 2 years died], recipient sex, recipient pretransplant clinical state (particularly the presence or absence of cardiovascular diseases), necessity of post-transplant dialysis, duration of prophylactic polyclonal ALG or ATG treatment, or use of a monoclonal antibody against the interleukin-2 receptor. Two factors were found to have a negative influence on the outcome of elderly patients who subsequently died: ongoing acute rejection episodes and their therapy, and CMV infectious episodes.

Transplant survival and function

The 5-year actuarial graft survival rate was 80% (Table 2). A nonstatistically significant difference was observed in 1-, 2-, 3-, 4-, and 5-year graft survival rates between patients over and under 60 years of age (Table 2). Hospitalization time ranged from 7 to 61 days (mean 19 ± 9 days), and 44% of the patients required postoperative dialysis. A total of 28 transplants (23%) were lost. Causes of transplant loss were 13 deaths (11%; 1 patient died following transplant removal because of sepsis), 1 hyperacute, 1 acute, and 4 chronic rejection episodes (5%), 2 immediate renal vascular thromboses (1.6%), 2 renal mycotic aneurysms (1.6%) 2 recurrences of native renal diseases (1.6%), 2 nonfunctional transplants (1.6%), and 1 transplant lymphoma (0.8%).

Among the 37 acute rejection episodes recorded during the observation period in 32 patients, 5 (13%) were considered steroid-resistant, 4 responded to ATG, and 1 became irreversible. The incidence of patients experiencing rejection episodes during the first 3 and 12 post-transplant months was 22% and 27%, respectively. Eight out of the 32 patients (25%) who experienced an acute rejection episode subsequently died. Among the 12 patients who died after the 2nd post-transplant week, 8 (67%) had at least one rejection episode. The incidence of rejection episodes in patients still alive was 21%, significantly lower than that of patients who died (Table 3; $P < 0.002$).

When analyzed at 1 year, the mean serum creatinine level was 138 ± 51 μmol/l and creatinine clearance 54 ± 21 ml/min.

Surgical complications

Seventeen patients (14%) required surgery or endoscopic treatment during the first 6 months because of six ureteral fistulas, five ureteral obstructions, two prostate resections, two transplant bleedings (resulting in two graft losses) and two gastrointestinal complications. No surgical complication resulted in patient death.

Infectious episodes and malignancies

The incidence of CMV infectious episodes was 24%. Seventeen out of the 29 CMV infectious episodes (58.6%) were considered severe and treated with 1,3-dihydroxy-2-propoxymethyl guanine (DHPG, Gangci-

Table 3 Causes of death of cadaveric renal transplant recipients 60 years of age or older. CMV, Cytomegalovirus; RE, rejection episode; d, days post-transplantation; m, months post-transplantation. Rejection and CMV infectious episodes were significantly more numerous in patients who died than in those still alive ($P < 0.002$ and $P < 0.02$, respectively)

No.	Diagnosis[a]	Age[b] (years)	Time of death	CMV	RE
	Cardiovascular				
1.	Hematogenic shock	61	d 11	No	No
2.	Pulmonary embolus	61	d 95	Yes	Yes
3.	Myocardial infarction	65	m 13	Yes	No
4.	Valvuloplasty surgery	69	m 15	No	Yes
5.	Cerebral hemorrhage	60	m 42	No	Yes
6.	Cerebral infarction	63	m 54	No	Yes
	Infections				
7.	*Pneumocystis carinii* pneumonia	61	d 50	No	Yes
8.	*Pseudomonas aeruginosa* septicemia	66	d 60	No	No
9.	Encephalopathy	62	d 60	Yes	Yes
10.	*Cryptococcus meningitidis*	64	d 120	Yes	No
	Gastrointestinal				
11.	Gastric hemorrhage + sepsis	63	d 6	No	No
12.	Duodenal perforated ulcer + sepsis	60	d 120	No	No
13.	Perforated sigmoiditis + sepsis	62	d 120	Yes	Yes
14.	Perforated sigmoiditis + sepsis	60	d 150	Yes	Yes

[a] Principal cause of death
[b] At the time of transplantation

clovir, Syntex). Six out of the 29 patients (20%) who experienced CMV infectious episodes subsequently died. Although no CMV infectious episode was per se fatal, a history of CMV disease was found among six (50%) patients who subsequently died versus 21% in patients still alive ($P < 0.02$; Table 3).

Six patients (5%) developed five skin cancers and one lymphoma. No case was fatal.

Immunosuppression

CyA was well tolerated in all cases and no patient required a switch to conventional therapy because of drug-related renal toxicity. CyA was definitively discontinued in only one patient, as soon as day 25, because of poor renal function related to preservation injury. This patient remained under Aza and Pred. A reversible acute rejection episode occurred 9 months after transplantation, and this patient died 54 months after transplantation as a result of cerebral infarction. The serum creatinine level was 450 μmol/l at the time of death.

At 1 year, the mean CyA dosage was 4 ± 1.6 mg/kg per day and 64% of the patients were off steroids.

Discussion

Better medical management of end-stage renal failure and more effective dialysis techniques are increasing the survival of uremic patients and improving their quality of life. As a result, the number of elderly patients on dialysis is increasing [10], and re-evaluation of transplantation in the elderly has become necessary.

However, it is difficult to compare survival between hemodialyzed and renal transplanted patients since most elderly patients remaining on hemodialysis are not accepted for renal transplantation due to their poor clinical state. As a result, patient survival in elderly hemodialyzed patients is lower than that observed following renal transplantation [4, 10].

Patients are considered for transplantation at the University of Nantes after they have been referred by their attending nephrologist. Since a strict clinical evaluation of each patient (mainly cardiovascular) is performed before the transplant medical visit, only patients considered "good candidates" by their nephrologists are evaluated by the transplant medical team. Although all dialysis centres evaluate elderly patients for transplantation in a similar way, the criteria used by different nephrologists to indicate or contraindicate transplantation is difficult to list. More than 50% of the patients on dialysis are over 60 years of age. However, only 10%–15% of the patients on our waiting list are 60 years of age or older. This difference tells something about patient selection and should be considered when analyzing our results.

Fauchald et al. [2], however, in a study including 368 patients with chronic renal failure aged 60 years or older when starting dialysis or at the time of transplantation, found that the survival of patients accepted for renal transplantation but still on the waiting list did not differ from that of patients on dialysis who were excluded for transplantation due to poor clinical condition (48% and 44%, respectively, at 1 year and 29% and 30%, respectively, at 2 years); these two survival rates were significantly lower than those for transplanted patients (76% and 68%, respectively, at 1 and 2 years). This study strongly suggests that factors other than patient selection may be responsible for the different results between centres [1, 3, 6, 8, 11, 14].

The incidence of death due to cardiovascular diseases did not statistically differ between our older and younger transplant populations. In addition, the incidence of fatal cardiovascular diseases observed in elderly patients (42.8%) was roughly similar when compared to the 30% incidence of the French population 55–74 years of age [7]. Moreover, only 50% of the patients who died because of cardiocascular diseases had cardiac symptoms of coronary artery disease before transplantation. These factors suggest that elderly renal transplant patients, when correctly selected, may not have an increased risk of death due to cardiovascular disease when compared to an age-matched and nontransplanted population.

It is well known that the immune system becomes less effective with aging. Indeed, 27% of the elderly patients we studied experienced rejection episodes during the 1st posttransplant year. This rejection episode incidence is, however, lower than the 38% and 40% incidence reported by Pirsch et al. [11] and Vivas et al. [14], respectively. Most rejection episodes (87%) were easily reverted under steroid boluses and did not impair late renal function. Such high doses of steroids and/or additional ATG therapy should, however, be carefully monitored to prevent overimmunosuppression; the number of rejection episodes was significantly higher in patients who died than in patients still alive (Table 3).

Despite the relatively low dose of steroids given, gastroduodenal and intestinal complications were unpredictable, severe, and almost fatal. Despite early and successful surgery, uncontrolled sepsis occurred in all cases (Table 3).

The incidence of fatal infections was similar in elderly and younger patients. No CMV infectious episode was fatal; however, a significantly higher number of CMV infectious episodes was observed in elderly patients who died than in patients still alive (Table 3).

A history of long-term dialysis therapy (> 2 years) appears to have a detrimental effect on the survival of transplanted patients [15]. Although 55% of our elderly patients were on dialysis for more than 2 years before transplantation, their post-transplant mortality risk was no higher than for patients on dialysis for less than 2 years. We, however, agree with West et al. [15] that renal transplantation should be considered as early as possible in elderly patients with end-stage renal failure in order to avoid the high mortality rate observed within the 1st months following the initiation of dialysis.

In the absence of a satisfactory control group allowing reliable and coherent comparisons on the strict basis of patient morbidity and mortality, our results should be interpretated with caution and no definitive conclusions drawn. However, our results indicate that:

1. Cadaveric renal transplantation can be performed safely and effectively in selected patients 60 years of age or older.
2. Patients with ischemic heart disease should not be systematically excluded from renal transplantation.
3. Adequate therapy for all CMV infectious episodes should be given in practically all cases (even "minor" episodes) and may also be used prophylactically in CMV seronegative recipients receiving seropositive CMV transplants.
4. Exploration and treatment of intestinal diverticulosis and gastroduodenal ulcer (especially in symptomatic patients and those with a clinical history of disease) seem necessary in all elderly renal transplant candidates, followed by appropriate medical prophylactic therapy after transplantation.
5. Maintenance immunosuppression with CyA therapy is well tolerated and allows early discontinuance of steroids.

Currently, we have no absolute age limit for transplantation. As long as the patient is an operative candidate, renal transplantation is also considered in the management of end-stage renal failure, regardless of age.

References

1. Babinet F, Hourmant M, Cantarovich D, Karam G, Bouchot O, Soulilou JP (1990) Transplantation rénale après 60 ans. Presse Med 5: 201–204
2. Fauchald P, Albrechtsen D, Leivestad T, Feffer P, Talseth T, Flatmark A (1988) Renal replacement therapy in patients over 60 years of age. Transplant Proc 20: 432–433
3. Fehrman I, Brattstrom C, Duraj F, Groth CG (1989) Kidney transplantation in patients between 65 and 75 years of age. Transplant Proc 21: 2018–2019
4. Geerlings W, Tufveson G, Brunner FP, Ehrich JH, Fassbinder W, Landais P, Mallik N, Margreiter R, Raine AEG, Rizzoni G, Selwood N (1991) Combinet report on regular dialysis and transplantation in Europe, XXI, 1990. Nephrol Dial Transplant 6: 5–29
5. Hourmant M, Taupin JL, Leymergie, Cantarovich D, Soulillou JP (1989) Azathioprine-cyclosporine A (CyA) double therapy versus CyA alone after the first rejection episode in kidney-transplanted patients under CyA. A randomized study. Transpl Int 2: 113–116
6. Howard RJ, Plaff WW, Scornik JC, Salomon DR, Peterson JC, Brunson ME (1990) Kidney transplantation in older patients. Clin Transplant 4: 181–186
7. INSERM, SC8, Observatoire Regional de la Santé des Pays de La Loire 1990
8. Morris GE, Jamieson NV, Small J, Evans DB, Calne R (1991) Cadaveric renal transplantation in elderly recipients: is it worthwhile? Nephrol Dial Transplant 6: 887–892

9. Ost L, Groth CG, Lindholm B, Lundgren G, Magnusson G, Tillegard A (1980) Cadaveric renal transplantation in patients of 60 years and above. Transplantation 30: 339–340
10. Park MS, Lee HB (1992) Outcome of dialysis in the elderly. Geriatr Nephrol Urol 1: 173–179
11. Pirsch JD, Stratta RJ, Armbrust MJ, D'Allessandro AM, Solinger HW, Kayaloglu M, Belzer FO (1989) Cadaveric renal transplantation with cyclosporine in patients more than 60 years of age. Transplantation 47: 259–261
12. Soulillou JP, Cantarovich D, Le Mauff B, Giral M, Hourmant M, Hirn M, Jacques Y (1990) Randomized trial of an anti-interleukin 2 receptor monoclonal antibody (33B3.1) versus rabbit antithymocyte globulin (ATG) in prophylaxis of early rejection in human renal transplantation. N Engl J Med 322: 1175–1182
13. Trochu JN, Cantarovich D, Renaudeau J, Patra O, Roscoat P du, Helias J (1991) Assessment of coronary artery disease by thallium scan in type-1 diabetic uremic patients awaiting combined pancreas and renal transplantation. Angiology 42: 302–307
14. Vivas CA, Hickey DP, Jordan ML, O'Donovan RM, Lutins J, Shapiro R, Starzl TE, Hakala TR (1992) Renal transplantation in patients 65 years old or older. J Urol 147: 990:993
15. West JC, Bisordi JE, Squiers EC, Latsha R, Miller J, Kelley SE (1992) Length of time on dialysis prior to renal transplantation is a critical factor affecting patient survival after allografting. Transplant Int 5 [Suppl 1]: S 148–S 150