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Bašić-Jukić, Nikolina; Furić Čunko, Vesna; Kes, Petar; Bubić-Filipi, Ljubica; Pasini, Josip; Hudolin, Tvrtko; Jurić, Ivana

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Outcome after renal transplantation in "senior" program – Croatian experience

Basic-Jukic Nikolina, Furic-Cunko Vesna, Kes Petar, Bubic-Filipi Ljubica, Pasini Josip, Hudolin Tvrtko, Juric Ivana.

Department of dialysis, University hospital Centre Zagreb, Zagreb, Croatia

Abstract

Background: Eurotransplant „senior“program (ESP) allocates kidneys from elderly donors to the patients who are older than 65 years. It is targeted to increase the number of renal transplantations. Kidneys are allocated locally without HLA matching to decrease the cold ischemia time. Croatia has introduced its own “senior” program based on HLA matching. Our results are compared with those from ET.

Methods: All patients who underwent first renal transplantation at the age of 65 years or older were identified and followed-up prospectively. Their HLA matching, cold ischemia time, renal function, surgical and medical complications, and duration of hospitalization were recorded.

Results: Until the October 2007, 22 elderly patients received an allograft from donors who were older than 65 years. There were 8 female and 14 male patients, with the mean age at transplantation of 67.4 years. Mean donor age was 66 years. Number of HLA-MM ranged from 1 to 5, and cold-ischaemia time from 7 to 15 hours. One-year patient survival was 95.4 %, and graft survival was 81.8 %. Delayed graft function, defined as the need for dialysis for more than 7 days after transplantation, occurred in 63.6% of patients. Older recipients required prolonged hospitalization for transplantation (45, range 16-131). Posttransplant complications were frequent and included posttransplant diabetes mellitus in one patient, delayed wound healing in 5 patients and lymphocaele in 2 patients. Maligancies occurred in three patients (neoplasm of native kidney, posttransplant lymphoproliferative disease and skin cancer). One patient experienced acute rejection that was successfully treated with steroids. Seventeen patients had 20 viral infections. There was only one serious infection (pulmonary tuberculosis). The major problems were cardiovascular complications which occurred in 40.9 % of patients after transplantation.

Conclusion: Renal transplantation in elderly patients is associated with increased incidence of posttransplant surgical and medical complications which demand prolonged hospitalization. Incidence of acute rejections in elderly patients is significantly decreased with HLA matching, without prolongation of the cold ischemia time. Good results justify renal transplantation in this group of patients.

Introduction

Renal transplantation is method of choice for treatment of patients with end-stage renal disease (ESRD) without contraindications for transplantation. It is associated with an improved life expectancy and quality of life when compared to dialysis even in elderly patients (1,2). However, because of the widening gap between demand and supply of donor organs, transplantation is infrequently offered to older persons with ESRD. The Eurotransplant Senior Program (ESP) was launched in January 1999 to increase number of transplantations in elderly patients. It allocates kidneys from donors who are older than 65 years to recipients of the same age. Only patients with low immunological risk (first transplantation and panel reactive antibodies<5%) are considered for transplantations. Kidneys are allocated locally to reduce cold ischemia time to recipients with compatible ABO-blood group with negative crossmatch. The program does not include HLA matching (3). Croatia has introduced "senior" program based on ESP, but with HLA matching. The purpose of this study was to evaluate patient and graft survival in elderly patients who received organs from elderly donors based on HLA matching and to compare these results with results from ESP.

Patients and methods

All patients aged 65 years or more at transplantation who received kidney from donor older than 65 years were included in investigation.

Pretransplant evaluation

Patients underwent extensive evaluation before placement on the waiting list for transplantation. Only patients without significant comorbidities in good overall clinical status were added to the waitlist. Patient's history was recorded with the special emphasis on cardiovascular status. Coronary heart disease, hypertension, stroke, reduced left ventricular function, cardiac arrhythmias, valvular diseases, peripheral vascular disease and history of pulmonary embolism were noted. We also recorded presence of gastrointestinal problems, different infections and history of malignancies.

Baseline characteristics were extracted from the pretransplant evaluation and included duration and modality of renal replacement therapy, vascular access for dialysis, body mass index calculated as the weight in kilograms divided by square of high in meters. Hepatitis B, hepatitis C, and cytomegalovirus (CMV) status before transplantation were noted.

Donor age, gender, cold ischemia time, and number of HLA mismatches were recorded.

Posttransplant monitoring

Patients were followed-up prospectively after transplantation. Surgical complications, delayed graft function defined as need for dialysis for longer than 7 days after transplantation, number of dialysis sessions after transplantation, length of hospitalization after transplantation, additional hospitalizations and acute rejections, with detailed information on immunosuppressive regimen for each patient were recorded. Date and reason of death or graft loss were noted.

Cytomegalovirus infection was defined as positive early antigen in blood culture or positive polymerase chain reaction assay. Cytomegalovirus disease was defined as symptomatic CMV infection. Treatment of CMV infection consisted of intravenous gancyclovir or oral valgancyclovir with concomitant reduction of immunosuppression.

Posttransplant renal allograft function was determined by measurement of serum creatinine levels and calculation of glomerular filtration rate with the Cockroft-Gault formula.

Data are reported as mean and ranges.

RESULTS

From January 2004 to October 2007, 286 patients received kidney transplant at our centre. Twenty-two patients (7.69 %) were older than 65 years at the time of transplantation and received kidney from donor older than 65.

Patient's characteristics at transplantation

There were 8 female and 14 male patients, with the mean age at transplantation of 67 years. Mean donor (45.45 % female) age was 66 years. Number of HLA-MM ranged from 1 to 5, and cold-ischaemia time from 7 to 15 hours. Detailed patients' characteristics are presented in Table 1.

Table 1.

Immunosuppressive treatment

Five patients (22.7 %) had more than 3 HLA mismatches and received daclizumab induction. Initial immunosuppression in all patients consisted of cyclosporine A (trough levels 150-200 mg/ml), mycophenolate mofetil 2x1 g, and steroids. Out of 18 patients with the functioning graft at one year, 3 patients remained on cyclosporine A and steroids, 2 patients received tacrolimus and steroids, and 3 patients were switched to sirolimus because of the malignant disease or poor allograft function. All other patients continued with the triple immunosuppressive regimen. Dose reduction of mycophenolate mofetil was necessary in 55.5 % (10/18), with complete discontinuation in 27.7% (5/18) patients (low leukocyte count, gastrointestinal side effects, CMV disease).

Short-term outcome

Delayed graft function, defined as the need for dialysis for more than 7 days after transplantation, occurred in 63.6% of patients. At two weeks posttransplant mean serum creatinine was 245 μmol/l (range 145 to 434 μmol/l). One patient died during the initial hospitalization after he suffered from stroke and severe bleeding from the gastrointestinal tract. Graftectomy was performed in two patients because of the renal vein thrombosis. Short-term posttransplant complications included posttransplant diabetes mellitus in one patient, delayed wound healing in 5 patients, and lymphocaele in 2 patients. One patient with history of diverticulosis had bowel rupture 20 days after transplantation. Prompt surgical intervention saved his life. Graft function remained stable. Complications caused prolonged hospitalizations for transplantation (45, range 16-131). Two patients had problems with arm swelling due to the subclavian vein stenosis at the side of arteriovenous fistula that, in one of them, required surgical intervention during the initial hospitalization.

Long-term outcome

Graft function

One-year patient survival was 95.4 %, and death-censored graft survival was 95 %. Overall one-year graft survival was 81.8 %. Besides the patients who lost their grafts during the initial hospitalization, one female patient underwent graftectomy 9 months after transplantation because of the bleeding during the drainage of the lymphocele. She was subsequently diagnosed with the post transplant lymphoproliferative disease (PTLD). Average creatinine clearance of patients with the functioning graft at one year was 55.4 ml/min, with serum creatinine 135.73 μmol/l.

Posttransplant complications

Short- and long-term posttransplant complications were frequent (Table 2).

Table 2.

Most operative complications were wound-related issues (fluid collections, bleeding, dehiscence and/or wound infection). Posttransplant diabetes mellitus occurred in one patient. Acute rejection occurred in only one patient 6 months after transplantation and was successfully treated with steroids. He received daclizumab induction. One patient developed serious infection (pulmonary tuberculosis) that was successfully treated.

The major problems were cardiovascular complications which occurred in 40.9 % of patients after transplantation. Cardiac arrhythmia, stroke, myocardial infarction and peripheral vascular disease complicated the posttransplantation course.

Dyslipidemia was common to all patients, with increase of total and LDL cholesterol, and decrease of HDL cholesterol in 16/18 patients with the functioning graft at three months after transplantation. Weight gain was not a problem in elderly renal transplant recipients, with majority of them maintaining their weight within the normal limits. Only two patients had body weight index above 30 mg/m^2 one year after transplantation.

Seventeen patients had 20 viral infections after transplantation (17 cytomegalovirus, 1 Epstein-Barr virus-associated posttransplant lymphoproliferative disease, 2 herpes zoster infections).

Malignancies developed in 3 patients. One patient was diagnosed with clear cell renal carcinoma of his native kidney one month after transplantation. He complained of the pain in lumbal spine. Diagnostic evaluation demonstrated that the pain was caused by metastatic renal cancer. Nephroureterectomy was performed, followed by local irradiation. Patient refused to cease immunosuppressive therapy. He was switched to sirolimus and maintained good graft function. At two years after transplantation he remained without signs of maligant disease. Female patient with PTLD in the wall of lymphocele underwent graftectomy and returned to dialysis. One patient developed basocellular skin cancer 7 months after transplantation and was switched to sirolimus.

DISCUSSION

Much controversy exists regarding the renal transplantation in elderly patients. This group is considered to have short life expectancy and higher incidence of different posttransplant complications (4-6). Ethical issues surrounding the allocation of scarce organs to patients with short life expectancy further increase the dilemma regarding the renal transplantation in elderly. Possible solution is use of the so-called marginal organs, which are not suitable for transplantation in younger patients, and would otherwise be discharged. ESP was targeted to increase the number of renal transplantations in elderly. However, only few data have been published regarding the outcome of patients who were transplanted in the ESP (3,7-12). In the present study we evaluated outcome of patients who were transplanted in Croatian senior program. This program is modification of ESP, while it includes HLA matching as the basis for organ allocation.

High incidence of delayed graft function in our patients may be attributed to the use of calcineurin inhibitors. At the time of introduction of “senior” program in Croatia, financial limits disabled regular use of interleukin -2 blockers or thymoglobulin for the induction. Our relatively poor short-term results regarding the delayed graft function clearly demonstrate superiority of protocols that include induction and delayed use of calcineurin inhibitors (CNIs) (13-16). An intriguing possibility is complete avoidance of CNIs in elderly patients what may be achieved in patients with favorable HLA matching (15). Elderly are generally considered as “immunologically low risk” patients with reduced number of naïve T cells, dysfunctional memory cells, increased sensibility to immunosuppression,

reduced T-cell receptors, defective T-cell signaling, increased T-suppressor cells, and altered cytokine profiles (4,5,17). However, rejection rate observed in ESP group of patients was 38 %, what was much higher than expected while 43 % of patients received mono- or polyclonal induction and 47 % were treated with triple immunosuppressive therapy (3). Increased incidence of acute rejections was observed also by Fritsche et al. (9) who recorded acute rejections in 43.2 % of ESP patients. Acute rejections demand the use of intensive immunosuppression. The price is high incidence and mortality from severe infections (18). High incidence of infectious complications and deaths argues against aggressive immunosuppression in elderly recipients (19-21). One year survival rate of 73 patients transplanted in the ESP was 94 % with graft survival of 87 % (22). Other studies obtained lower one-year patient and graft survival rates (86 % and 79 %, respectively) (3), (85 % and 84 %, respectively) (9). Patients transplanted in our centre in the "senior" program had comparable one-year patient (95.4 % vs. 96.3 %), but lower graft survival (81.8 % vs. 93.6 %) than younger patients transplanted according to the national allocation system.

It was previously believed that short cold ischemia time may balance the detrimental effect of immunological risk associated with HLA mismatching (23-25). However, high incidence of acute rejections in ESP demonstrated that it would be wise to include HLA matching in the protocol while this does not prolong the cold ischemia time significantly if kidneys are allocated locally (26). From August 15th 2007, Croatia has joined Eurotransplant and adopted ESP, as well as other programs that exist in Eurotransplant. However, we continued with our policy of organ allogation in "senior" program based on HLA matching. Frei et al. have recently published 5-year experience with the ESP. They conclude that shorter cold ischemia time does not fully mitigate the effect of HLA mismatching in the ESP (18). Eurotransplant currently considers introducing the Eurotransplant Senior DR-compatible Program (ESDP) (18).

In our experience, initial length of hospital stay was prolonged in elderly recipients. Besides the medical reasons, there are often logistic reasons for several additional days of hospitalization. There is no designated out-patient-stay facility in our region, and our catchment area includes whole Croatia. For this reason many patients who should otherwise be discharged, are kept in hospital because of the lack of proper surgical or medical care in their area.

The main disadvantage of our study is small sample size and single-centre experience. However, this is also an advantage, while all the patients were followed-up prospectively, and all of them underwent the same pretransplant and posttransplant evaluation. However, longer follow-up is needed to further clarify the role of HLA matching in elderly recipients and to demonstrate that elderly patients are not "immunologically inert" (23-25). It may be possible to avoid high mortality rates attributed to septic complications in the ESP with implementation of HLA matching, thus avoiding over-immunosuppression.

In conclusion, elderly patients should not be excluded from renal transplantation. Thorough pretransplant evaluation is mandatory as well as the close posttransplant follow-up. Use of organs from elderly donors solves the ethic dilemma surrounding the renal transplantation in elderly recipients. Our results demonstrate that HLA matching decrease the incidence of acute rejections in "senior" program and may improve outcome after renal transplantation.

LITERATURE

1. Wolfe RA, Ashby VB, Milford EL et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341:1725-30.
2. Oniscu GC, Brown H, Forsythe JL. How great is the survival advantage of transplantation over dialysis in elderly patients? Nephrol Dial Transplant 2004; 19:945-51.
3. Smiths JMA, Persijn GG, Houwelingen HC et al. Evaluation of the Eurotransplant senior program. The results of the first year. Am J Transplant 2002; 2:664-70.
4. Martins PNA, Pratschke J, Pascher A et al. Age and immune response in organ transplantation. Transplantation 2005; 79:127-32.
5. Meier-Kriesche HU, Ojo AO, Cibrik DM et al. Relationship of recipient age and the development of chronic allograft failure. Transplantation 2000; 70:306-10.
6. Meier-Kriesche HU, Ojo AO, Hanson JA, Kaplan B. Exponentially increased risk of infectious death in older renal transplant recipients. Kidney Int 2001; 59:1539-43.
7. Fabrizii V, Winkelmayer WC, Klauser R et al. Patient and graft survival in older kidney transplant recipients: does age matter? J Am Soc Nephrol 2004; 15:1052-60.
8. Fabrizii V, Kovarik J, Bodingbauer M et al. Long-term patient and graft survival in the Eurotransplant senior program: a single center experience. Transplantation 2005; 80:582-9.
9. Fritsche L, Horstrup J, Budde K et al. Old-for-old kidney allocation allows successful expansion of the donor and recipient pool. Am J Transplant 2003; 3:1434-9.
10. Krüger B, Zulke C, Fischereder M et al. Early experience with the ET Senior program “old-for old”: better to be number one? Transplant Int 2002; 15:541-5.
11. Giessing M, Budde K, Fritsche L et al. “Old-for-old” cadaveric renal transplantation: surgical findings, perioperative complications and outcome. Eur Urol 2003; 44:701-8.
12. Fritsche L, Hoerstrup J, Budde K et al. Kidney transplantation at the Charite: long tradition, elderly patients and the duration of hospitalization. Clin Transpl 2002; 44:171-9.

13. Danovitch GM, Gill J, Bunnapradist S. Immunosuppression of the elderly kidney transplant recipient. Transplantation 2007; 84:285-91.
14. Danovitch GM, Savransky E. Challenges in the counseling and management of older kidney transplant candidates. Am J Kidney Dis 2006; 47:S86-97.
15. Arbogast H, Hückelheim H, Schneeberger H et al. A calcineurin antagonist-free induction/maintenance strategy for immunosuppression in elderly recipients of renal allografts from elderly cadaver donors: long-term results from a prospective single-center trial. Clin Transplant 2005; 19:309-15.
16. Emparan C, Wolters H, Laukotter M, Senninger N. Long-term results of calcineurin-free protocols with basiliximab induction in "old-for-old" programs. Transplant proc 2004; 36:2646-8.
17. Lufft V, Kliem V, Tusch G, Dannenberg B, Brunkhorst R et al. Renal transplantation in older adults: is graft survival affected by age. A case control study. Transplantation 2000; 69:790-4.
18. Frei U, Noeldeke J, Machold-Fabrizii V et al. prospective age-matching in elderly kidney transplant recipients – a 5-year analysis of the Eurotransplant Senior program. Am J Transplant 2007; 7:1-8.
19. Reutzel-Selke A, Filatenkov A, Jurisch A et al. Grafts from elderly donors elicit a stronger immune response in the early period post-transplantation: a study in a rat model. Transplant Proc 2005; 37:382-3.
20. de Fijter JW. The impact of age on rejection in kidney transplantation. Drugs Aging 2005; 22:433-49.
21. de Fijter JW, Mallat MJ, Doxiadis et al. Increased immunogenicity and cause of graft loss of old donor kidneys. J Am Soc Nephrol 2001; 12:1538-46.
22. Bentas W, Jones J, Karaoguz A et al. Renal transplantation in the elderly: surgical complications and outcome with special emphasis on the Eurotransplant Senior Programme. Nephrol Dial Transplant 2008; 23:2043-51.
23. Preuschof L, Lobo C, Offerman G. Role of cold ischemia time and vascular rejection in renal grafts from elderly donors. Transplant Proc 1991; 23:1300-1.

24. Shoskes DA, Cecka JM. Effect of delayed graft function on short- and long-term kidney graft survival. Clin Transplant 1997; 297-303.
25. Klehr HU, Jacobs U, Miersch WD, Molitor D. Comparison of kidney transplantation with and without regard to HLA typing. Dtsch Med Wochencshr 1996; 121:434-41.
26. Opelz G. Very short ischaemia is not the answer. Nephrol Dial Transplant 2002; 17:715-6.

Table 1. Patients' characteristics at transplantation.

Characteristic	Mean (range)
Age (years)	67.4 (65-68)
Gender (% female)	36.7
Diabetes mellitus (%)	18.18
Duration of dialysis (months)	71 (8-152)
Dialysis modality (%)	
- hemodialysis	86.4
- peritoneal dialysis	13.6
Cardiovascular disease	27.27%
History of malignancy	0%
Number of HLA mismatches	2.8 (1-5)
Cold-ischemia time (hours)	10.4 (7-15)
Body-mass index (kg/m2)	26.9 (22.53-30.99)
Hepatitis B (% negative)	100
Hepatitis C (% negative)	100
CMV status (% IgG negative)	4.5

Table 2. Results at one year of follow-up.

Variable	
Patient survival	95.4 %
Graft survival	81.8 %
Serum creatinine (µmol/l)	135.73 (80-227)
Creatinine clearance (ml/min)	55.4 (30-93)
BMI (kg/m2)	26.63 (23.85-30.55)
Acute rejection (%)	1 (4.54%)
Readmissions (n)	11
-days of hospitalization	132
Malignancy (%)	3 (13.63 %)
PTDM (%)	1 (4.54 %)
CMV infection (%)	17 (77.27 %)
Major infections (%)	1 (4.54 %)
Cardiovascular complications	9 (40.9 %)
- myocardial infarction	1 (4.54 %)
- stroke	1 (4.54 %)
- peripheral vascular disease	2 (9.09 %)
- pulmonary embolia	2 (9.09 %)
- cardiac arrhytmia	3 (13.63 %)