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Research paper

Balancing risks for older kidney transplant recipients in the contemporary era: A single-centre observational study

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ABSTRACT

Introduction: Age-adapted immunosuppression may be warranted for older kidney transplant recipients but post-transplant risks stratified by age in the contemporary era of immunosuppression are lacking.
Materials and methods: We undertook a retrospective single-centre analysis of 1140 consecutive patients receiving kidney-alone allografts, with median follow-up 4.4 years' post-transplantation, undertaken at a single-centre between January 2007 and January 2015. All patients received standardized immunosuppression. Descriptive analyses were stratified by age groups (age: < 60, $n = 918$; age: 60–64, $n = 111$; age: 65–69, $n = 82$; age: ≥ 70, $n = 29$). Incidence of death, kidney allograft rejection, function/loss and immunosuppression-related complications was analyzed across age groups. For Cox regression analysis, older kidney transplant recipients were classified as age ≥ 60 ($n = 222$).
Results: Kidney transplant recipients had increased risk for cardiac events, cerebrovascular accidents, cancer and CMV viraemia with increasing age. Rejection rates were similar but kidney transplant recipients with increasing age were significantly less likely to develop anti-HLA antibodies. Older kidney transplant recipients progressively had worse patient survival and overall graft survival, but equivalent death-censored graft survival. In Cox regression analysis, age ≥ 60 was a strong independent risk factor for mortality in addition to preexisting diabetes, development of post-transplant cancer and development of rejection.
Conclusions: Older kidney transplant recipients have increased risk for immunosuppression-related complications (contributing to increased mortality) but rejection rates and death-censored graft losses are similar. Clinical trials for age-adapted immunosuppression are warranted for older adults but require balancing risks for cancer and rejection to achieve optimal long-term clinical outcomes.

1. Introduction

The proportion of older patients with end-stage kidney disease (ESKD) undergoing renal replacement therapy (RRT) is steadily increasing. National registry data consistently shows a trend towards increasing median ages for patients both starting dialysis and awaiting kidney transplantation on deceased-donor waiting lists. For example, national audit data from the UK Renal Registry demonstrates the median age for all incident patients commencing RRT was 64.8 years [1]. Data from the UK Transplant Registry reports 28% of transplant recipients receiving a deceased-donor kidney allograft in the last year were aged 60 and over, while 32% of the active kidney transplant waiting list is aged 60 and over [2]. With chronic kidney disease increasingly recognized as a public health epidemic, the long-term prospects are of an ESKD population with increasing age requiring kidney allografts.

While mortality risk is accepted as higher for older versus younger kidney transplant recipients [3], kidney transplantation remains the gold-standard RRT for all age groups. Despite this, older adults with ESKD have a skewed risk-versus-benefit ratio comparing kidney transplantation versus dialysis and questions the optimal RRT for older adults with ESKD [4]. However, older candidates for transplantation may be unfairly disadvantaged by receiving standard post-transplant immunosuppression which is not attenuated or tailored to their individualized risks. Older kidney transplant recipients have increased risk for infections and cancers, but decreased risk for rejection, which likely relates to age-related immunosenescence [5]. Tailored immunosuppression for older transplant recipients could attenuate post-transplant complications and improve overall graft survival [6] but no

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targeted randomized controlled trial has identified the optimal immunosuppression regimen. Before considering such a clinical trial, it is important to understand age-stratified outcomes after kidney transplantation with contemporary immunosuppression. Therefore, the aim of this study was to analyze outcomes for kidney transplant recipients stratified by age in a contemporary era of immunosuppression.

2. Methods

2.1. Study population

We undertook a retrospective analysis of all consecutive kidney-alone transplants performed at a single-center between January 2007 and January 2015. Survival analysis was censored to event or September 2015 (whichever occurred first). We excluded multiple organ transplant recipients and our cohort only included kidney-alone allograft recipients aged 18 and over; all other kidney allograft recipients were included for analysis. Data was electronically extracted by the Department of Health Informatics for every study recruit, with manual data linkage to additional electronic patient records. Patient and graft survival data was acquired and linked from NHS Blood & Transplant.

2.2. Immunosuppression protocol

All patients received the same immunosuppression with minimization of tacrolimus exposure, in line with the SYMPHONY protocol [7]. Induction therapy was with basiliximab (20 mg × 2) and methylprednisolone (500 mg). Maintenance therapy included tacrolimus (target 12-hour trough level 5–8 ng/L), mycophenolate mofetil (MMF, 2 g daily with tapering to 1 g daily after 6-months) and maintenance corticosteroids. Biopsies were indication-based in the context of transplant dysfunction (categorized as ≥ 20% creatinine rise or new-onset proteinuria). Biopsy data was classified in accordance to latest Banff criteria [8]. Episodes of acute cellular rejection were treated with a bolus of corticosteroids, with T-cell depletion therapy for steroid-resistant rejection. Antibody-mediated rejection was treated with antibody removal by plasmapheresis ± intravenous immunoglobulin. Viral serology (e.g. polyoma virus) and/or anti-HLA antibodies was checked by indication-basis based upon transplant dysfunction.

2.3. Statistical analysis

Kidney allograft recipient age was converted from a continuous to categorical variables and stratified into age < 60, 60–64, 65–69 and ≥ 70. Univariate comparisons done with χ^2 tests for categorical data, t tests or one-way ANOVA for parametric continuous data and Wilcoxon or Krustwal–Wallis tests for nonparametric continuous data. All-cause graft failure was taken as the time from transplantation to graft nephrectomy or return to dialysis, whichever was earlier, or death of the patient with a functioning graft. Survival of the patient was defined as the time from transplantation until death. Follow-up analysis of the entire transplant study cohort included all data up to September 2015.

Cox proportional hazards regression models were fitted by a stepwise variable selection method to analyze the combined effect

Table 1
Baseline demographics of kidney allograft recipients stratified by age.

Variable	Age < 60	Age 60–64	Age 65–69	Age ≥ 70	*P* value
Number	*n* = 918	*n* = 111	*n* = 82	*n* = 29	–
Mean waiting time ± SD (days)[a]	1147 ± 899	1410 ± 890	1158 ± 1019	1751 ± 1133	0.048
Mean dialysis time ± SD (days)[b]	785 ± 806	927 ± 773	693 ± 750	1291 ± 1028	0.002
Male gender	60.7%	51.4%	63.4%	51.7%	0.186
Ethnicity					
White	71.9%	65.8%	82.9%	72.3%	0.062
Black	6.4%	2.7%	1.2%	0.0%	
South Asian	17.0%	24.3%	13.4%	24.1%	
Other	4.7%	7.2%	2.4%	3.4%	
Socioeconomic deprivation					
1 (Most deprived)	33.1%	29.9%	16.7%	34.5%	0.003
2	22.0%	18.7%	12.8%	10.3%	
3	20.7%	16.8%	24.4%	20.7%	
4	13.6%	15.9%	25.6%	17.2%	
5 (Least deprived)	10.6%	18.7%	20.5%	17.2%	
First allograft	88.8%	95.5%	97.6%	96.6%	0.007
Smoking exposure	23.7%	22.5%	30.5%	20.7%	0.526
Living kidney donor	45.6%	38.2%	37.0%	18.5%	0.011
Cause of end-stage kidney disease					
Diabetes	8.9%	19.8%	12.2%	10.3%	0.004
PKD[c]	10.9%	16.2%	14.6%	6.9%	0.249
GN[d]	29.0%	26.1%	17.1%	17.2%	0.233
Mismatch (±SD)[e]	2.4 ± 1.3	2.9 ± 1.3	2.5 ± 1.4	2.4 ± 1.4	0.165
Donor CMV positive	42.0%	35.9%	38.9%	76.9%	0.162
ABO-incompatible[f]	4.8%	3.6%	4.9%	6.9%	0.891
Pretransplant cancer	1.3%	1.8%	1.2%	0.0%	0.898
Donor age	44.6 ± 13.9	54.1 ± 12.7	56.9 ± 12.3	61.5 ± 8.5	< 0.001
Donor diabetes	1.6%	1.8%	3.7%	0.0%	0.674
Cold ischemic times ± SD (hours)[g]	17.9 ± 5.9	18.1 ± 6.7	16.3 ± 4.6	17.5 ± 5.0	0.442
Recipient BMI	28.1 ± 7.2	28.4 ± 5.4	28.4 ± 7.0	27.6 ± 4.3	0.937
Recipient CMV positive	39.1%	38.5%	47.2%	61.5%	0.435

[a] Time from deceased-donor wait listing to kidney transplantation.
[b] Time spent on dialysis until kidney transplantation.
[c] Polycystic kidney disease.
[d] Glomerulonephritis.
[e] HLA mismatch based up cumulative score of mismatches to HLA-A, HLA-B and HLA-DR. Mismatch of 0 implies the best matched kidney allograft and 6 implies the worse matched kidney allograft.
[f] Blood group incompatible transplantation (performed after desensitization to specific anti-A or anti-B blood group antibodies).
[g] Refers to time between organ procurement and organ reperfusion when kidney is in cold storage and not receiving any blood supply.