Temporal Trend and Time-Varying Effect of Preemptive Second Kidney Transplantation on Graft Survival: A 30-Year Single-Center Cohort Study

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ABSTRACT

Background. There are discrepancies regarding the impact of preemptive 2nd kidney transplantation (PSKT) on graft survival. The present study aimed to determine whether the association between PSKT and outcome varies over time and whether this association is era dependent.

Methods. A total of 266 patients underwent SKT (244 non-PSKT, 22 PSKT) in our center from 1985 to 2015. Association between PSKT and graft survival (allograft failure from any cause including death) was assessed with the use of Cox models.

Results. During a median follow-up of 6.7 years, 116 events were recorded: 72 returns to dialysis and 44 deaths before return to dialysis. Survival curves diverged up to 5 years (5-year survivals: PSKT, 94.1 ± 5.7%; non-PSKT, 76.8 ± 2.9%) but they converged thereafter (12-year survivals: PSKT, 50.9 ± 15.2%; non-PSKT, 55.5 ± 3.9%). After adjustment for age and living-donor status, PSKT tended to be associated with better graft survival (hazard ratio [HR], 0.18; 95% confidence interval [CI], 0.02–1.27; $P = .08$) within the first 5 years of SKT but tended to be associated with worse outcome thereafter (HR, 2.36; 95% CI, 0.97–5.72; $P = .06$; P for interaction with time = .04). In addition, a significant interaction was identified between PSKT and SKT year (P for interaction = .04). In the multivariable model, the estimated HR for PSKT was 2.54 (95% CI, 0.88–7.35; $P = .08$) in 1990 as opposed to 0.16 (95% CI, 0.02–1.17; $P = .07$) in 2012.

Conclusions. The effect of PSKT on graft survival varies over time and according to year of the procedure. Although the benefit observed within the first 5 years of SKT appears to fade over time, overall graft survival seemingly improved in more recent years.

KIDNEY transplantation is the best treatment of end-stage renal disease [1]. It is well established that retransplantation is associated with better patient survival than a return to dialysis [2]. As a result, the number of patients waiting for retransplantation is growing worldwide [3,4].

In the setting of 1st kidney transplantation, several observational studies have reported that preemptive kidney transplantation (PKT) is associated with better patient and graft survivals [5,6]. Others have shown that patients who have been on dialysis for a longer period of time are at a higher risk of graft failure than patients who have been on dialysis for a shorter period of time [7,8]. Nevertheless, the beneficial effect of PKT on graft and patient survivals is

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0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.08.007

essentially recognized in the setting of living-donor kidney transplantation [9,10], and it remains unclear whether PKT from deceased donors is also beneficial [9].

There is also lingering debate regarding the impact of preemptive 2nd kidney transplantation (SKT) on outcome. Two studies using the American United States Renal Data System have reported conflicting results [11,12]. In the 1st report, preemptive SKT was associated with an increased risk of graft failure (hazard ratio [HR], 1.36; $P < .001$) whereas in the 2nd report it was associated with lower multivariate adjusted risk of allograft failure from any cause, including death (HR, 0.88; 95% confidence interval [CI], 0.81–0.96). The only available European study, performed in a Spanish center, recently reported a benefit from preemptive SKT on graft survival [13]. These discrepancies may be the consequence of a temporal trend of preemptive SKT treatment effect. In addition, given that mean follow-up times of earlier studies were <5 years, time-varying treatment effect was sparsely assessed.

The 2014 British Transplantation Society guidelines for management of the failing kidney transplant [14] recommend preemptive retransplantation, occurring when the estimated glomerular filtration rate (eGFR) is 10–15 mL/min. A retransplantation with a well matched living donor is the best therapeutic option according to the authors [14].

The main objectives of the present study were: 1) to evaluate whether the association between preemptive SKT and outcome varies over time after transplantation; and 2) to investigate whether this association follows a temporal trend with the use available very long-term (30-year) follow-up.

METHODS

Study Population

This single-center study included all patients aged >18 years who received an SKT from January 1, 1985, to April 30, 2015 in the Nancy University Hospital, Nancy, France. Patients were followed until July 30, 2015. Anonymized data were prospectively entered in a computerized database on day 0, at 3 months and 12 months after SKT, and annually thereafter.

A preemptive SKT was defined by the absence of dialysis between the 2 transplantations or dialysis duration <7 days before SKT. TDelayed graft function was defined by the necessity of ≥1 dialysis session in the 1st week after SKT, and primary nonfunction was defined by a return to dialysis <3 months after SKT.

During the study period, pre-transplantation immunologic status was assessed with the use of different technologies over time (CDC, enzyme-linked immunosorbent assay, or Luminex bead array). In addition, the French graft allocation scoring system also changed during this period, in part by taking into account these modifications. Thus, immunization against HLA antigen class I and/or class II was considered regardless of the test used. Of note, in July 2009, the policy for graft allocation was modified, aiming to prioritize access to transplantation for highly sensitized patients.

Statistical Methods

Statistical analyses were performed with the use of the commercially available software SPSS version 22 (IBM). Descriptive statistics are reported as percentage for categoric variables and mean ± SD for continuous variables. Comparisons of baseline characteristics were carried out with the use of t test or chi-square test as required. Graft survival (allograft failure from any cause, including death) was calculated with the use of the Kaplan-Meier method and plotted as survival curves. Association between preemptive SKT and graft survival was assessed with the use of the Cox proportional hazards model, with preemptive SKT considered as a time-dependent variable. Proportionality was assessed with the use of an interaction term between preemptive SKT and log-transformed time. Because a significant interaction with time was identified ($P = .04$), separate Cox models were fitted for ≤5 years and >5 years after transplantation. In addition, a temporal trend in treatment effect was assessed with the use of an interaction term between preemptive SKT and SKT year within multivariable Cox models. Multivariable analyses were adjusted on 2 prespecified factors well known to be associated with graft and patient survivals, namely, recipient age and donor type.

Moreover, given the study of Johnston et al [12] in which the beneficial effect of preemptive SKT was observed only in the subset of patients with a 1st graft duration of >1 year, a supplemental multivariable model was constructed and adjusted on the 1st graft duration (time between the 1st transplantation and the return to dialysis or preemptive SKT). Importantly, given the limited size of the latter group (patients with preemptive SKT: $n = 22$) and the resulting limited statistical power, no further adjustment was performed.

RESULTS

During the study period, 266 SKTs were performed (22 preemptive and 244 nonpreemptive). Patients with preemptive SKT and nonpreemptive SKT did not significantly differ regarding age, causal nephropathy, or duration of end-stage disease (duration from 1st dialysis or 1st kidney transplant [FKT]; Table 1). Of note, patients with nonpreemptive SKT were more likely to have class I anti-HLA antibodies, a shorter duration of their FKT, and a longer waiting time for SKT. In addition, patients with nonpreemptive SKT more frequently experienced delayed graft function (Table 2).

Time-Varying Effect of Preemptive SKT

During a median follow-up of 6.7 (range, 2.6–11.6) years, 116 events were recorded: 72 returns to dialysis and 44 deaths before return to dialysis. Survival curves diverged up to 5 years after transplantation (Fig 1; survivals at 5 years: preemptive SKT, 94.1 ± 5.7%; nonpreemptive SKT, 76.8 ± 2.9%), whereas they converged over time thereafter (survivals at 12 years: preemptive SKT, 50.9 ± 15.2%; nonpreemptive SKT, 55.5 ± 3.9%). Similar findings were observed for the return to dialysis only (Fig 2).

A significant interaction with time (P for interaction = .04) was also observed. To account for this interaction, associations for the 2 time periods were analyzed (Table 3, model 1). After adjustment for recipient age and living-donor status, preemptive SKT tended to be associated with better graft survival (HR, 0.18; 95% CI, 0.02–1.27; $P = .08$) within 5 years of SKT, whereas it tended to be associated with a worse outcome thereafter (HR, 2.36; 95% CI, 0.97–5.72; $P = .06$).