Risks and Benefits of Preemptive Second Kidney Transplantation

Olwyn Johnston,[1] Caren L. Rose,[1] Jagbir S. Gill,[1] and John S. Gill[1,2,3]

Background. Information to guide the timing of a second kidney transplantation is limited.
Methods. We compared outcomes of 3509 preemptive and 14,075 nonpreemptive second kidney transplant recipients in the U.S. Renal Data System between 1995 and 2007.
Results. Preemptive recipients had less acute rejection (12% vs. 16%; $P<0.0001$) and delayed graft function (8% vs. 23%; $P<0.0001$). Preemptive transplantation was associated with a lower multivariate adjusted risk of allograft failure from any cause including death (hazard ratio [HR], 0.88; 95% confidence interval [95% CI], 0.81–0.96) and death with a functioning graft (HR [95% CI], 0.76 [0.66–0.87]) but a similar risk of death-censored graft loss (HR [95% CI], 0.98 [0.88–1.08]). The benefits of preemptive transplantation were evident in all patients groups with first transplant survival equal to or more than 1 year; however, a 34% increased risk of death-censored graft loss was observed in preemptive recipients when first transplant survival was less than 1 year.
Conclusions. Benefits and risks of preemptive transplantation vary between primary and second transplant recipients. Benefits in second transplant recipients are primarily due to decreased death with a functioning graft, with no difference in death-censored graft survival. Preemptive transplantation was beneficial when first transplant survival was equal to or more than 1 year but associated with increased risk when graft survival was less than 1 year.

Keywords: Preemptive, Kidney transplantation, Second transplantation, Survival.

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Transplantation is the preferred treatment for patients with end-stage kidney disease (1). However, despite advances in immunosuppressant medications, transplantation still does not provide most patients with lifelong freedom from dialysis (2). The half-life (time to 50% failure) of a deceased-donor kidney transplantation is only 10.5 years (3). As the number of prevalent patients who received a first transplant more than a decade ago increases, the number of patients with failing transplants who must either return to dialysis or undergo second transplantation is also increasing (*3*).In fact, transplant failure is now the fifth leading cause of dialysis initiation in the United States (*3*). Failed renal transplant patients are a distinct group who have high morbidity and mortality compared with incident dialysis patients (*4–8*) and repeat transplantation is their best treatment option (*8*). Relatively few studies have examined whether factors known to impact first allograft survival have a similar impact on second transplant survival.

Among first transplant recipients, preemptive transplantation is associated with a decreased risk of allograft failure from any cause, death-censored allograft failure, and death with a functioning graft (*9–13*). The mechanisms that underlie the benefit of preemptive transplantation in first transplant recipients remain unclear, and it is possible that much of the advantage is due to selection bias, with preemptive patients being healthier, more health conscious, and adherent to treatment than nonpreemptive recipients (*10*). Fewer than one in five patients with primary transplant failure undergo second transplantation, and it is possible that the recognized benefits of preemptive primary transplantation may not be present in this selected group of patients. Further, the theoretical concern that the absence of uremia may increase the risk of rejection in preemptive transplant recipients may be heightened in second transplant patients because of prior transplantation. The existing literature suggests that preemptive repeat transplantation is

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[1] Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada.
[2] Tufts-New England Medical Center, Boston, MA.
[3] Center for Health Evaluation and Outcomes Sciences, University of British Columbia, Vancouver, British Columbia, Canada.
[4] Address correspondence to: John S. Gill, M.D., M.S., Division of Nephrology, University of British Columbia, St. Paul's Hospital, Providence 6A, 1080 Burrard Street, Vancouver, British Columbia, Canada V6Z 1Y6.
E-mail: jgill@providencehealth.bc.ca
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TABLE 1. Patient characteristics of preemptive compared with nonpreemptive second transplant recipients

Variable	Preemptive second transplantation (n=3509), n (%)	Nonpreemptive second transplantation (n=14,075), n (%)	*P*
Age at second transplantation, yr[a]			
18–39	1355 (38.6)	6033 (42.9)	<0.0001
40–54	1557 (44.4)	5664 (40.2)	
>55	597 (17.0)	2378 (16.9)	
Female sex	1589 (45.3)	5859 (41.6)	<0.0001
Race			
White	3017 (86.0)	10,335 (73.4)	<0.0001
Black	367 (10.5)	3143 (22.3)	
Other	125 (3.6)	597 (4.2)	
Cause of ESRD			
Diabetes mellitus	662 (18.9)	2241 (15.9)	<0.0001
Glomerulonephritis	1251 (35.7)	5269 (37.4)	
Hypertension	366 (10.4)	2316 (16.5)	
Other	1230 (35.0)	4249 (30.2)	
First transplant characteristics			
First donor source			
Living	1440 (41.0)	4771 (33.9)	<0.0001
Deceased	2069 (59.0)	9304 (66.1)	
Preemptive transplantation	822 (23.4)	1768 (12.6)	<0.0001
Second transplant characteristics			
Second donor source[b]			
Living	1968 (57.6)	3561 (26.9)	<0.0001
SCD	1358 (39.8)	9066 (68.6)	
ECD	8.9 (2.6)	589 (4.5)	
HLA mismatch[b]			
0	635 (19.0)	2637 (19.5)	<0.0001
1–3	1366 (40.8)	4697 (34.7)	
4–6	1346 (40.2)	6216 (45.9)	
PRA[b]			
0	1017 (38.4)	2242 (18.6)	<0.0001
1–29	978 (36.9)	3427 (28.3)	
>30	653 (24.7)	6420 (53.1)	
Immunosuppression at second transplantation			
Tacrolimus	2152 (61)	8493 (60)	0.22
Cyclosporine	940 (27)	3973 (28)	
No CNI	417 (12)	1609 (12)	
Mycophenolate mofetil	2496 (71)	10,053 (71)	<0.0001
Azathioprine	331 (9)	1614 (12)	
None	682 (20)	2408 (17)	
Induction immunosuppression			
Depleting	1274 (36.3)	6690 (47.5)	<0.0001
Nondepleting	765 (21.8)	2450 (17.4)	
Neither	1470 (41.9)	4935 (35.1)	
Year of transplantation			
1995–1998	692 (19.7)	3882 (27.6)	<0.0001
1999–2002	1099 (31.3)	4395 (31.2)	
2003–2007	1718 (49.0)	5798 (41.2)	
Duration of first graft survival, yr			
0–0.9	230 (6.6)	3509 (24.9)	<0.0001
1.0–2.9	148 (4.2)	2179 (15.5)	
3.0–4.9	244 (6.9)	2191 (15.6)	
5.0–6.9	338 (9.6)	1795 (12.7)	
7.0–9.9	599 (17.1)	2009 (14.3)	
>10	1950 (55.6)	2392 (17.0)	

[a] n (%).
[b] Missing values (second donor source n=1164 [6.5%], HLA mismatch n=687 [3.9%], and PRA n=2847 [16.2%]).
CNI, calcineurin inhibitors; ECD, expanded-criteria decease donor; ESRD, end-stage renal disease; PRA, panel reactive antibody; SCD, standard-criteria deceased donor.

associated with an increased risk of repeat transplant graft loss (*14*). The purpose of this study was to determine the association of preemptive second transplantation with second allograft survival in the current era.

RESULTS

Among 17,584 adult patients who received a second kidney-only transplant between January 1995 and September 2007, 3509 (20%) received a preemptive second transplant, including 901 who were never treated with dialysis after primary allograft failure and 2608 who received less than 7 days of dialysis before second transplantation. During the median follow-up of 3.6 years (25th and 75th percentiles, 1.5 and 6.5 years) from the date of second transplantation, 5919 (34%) transplants failed, including 2044 patients who died with a functioning graft and 3875 patients who returned to dialysis or required a third transplant.

Patient Characteristics

Patients who received a preemptive second kidney transplant were more likely to be 40 to 54 years old, of white race, female, diabetic, not on azathioprine before second transplantation, and have received their first or second transplant from a living donor (Table 1). Preemptive second transplant patients received fewer well human leukocyte antigen (HLA)–matched kidneys and less induction immunosuppression and were less sensitized. Preemptive recipients were more likely to have a second transplantation in recent years and had a longer duration of first allograft survival (Table 1).

Delayed Graft Function

Preemptive second transplant recipients had a lower incidence of delayed graft function (DGF) defined by the requirement for dialysis in the first week after transplantation (8% vs. 23%), and this was consistent irrespective of the donor source (living [3% versus 6%], standard-criteria deceased [6% versus 28%], or extended-criteria deceased [22% versus 37%]).

Acute Rejection

Overall, there was a lower incidence of acute rejection (AR) in the first posttransplantation year among preemptive

second transplant recipients (12% versus 16%; $P<0.0001$). The incidence of AR varied somewhat by the duration of first allograft survival. Among those with first graft survival less than 3 years, there was no difference in AR between preemptive and nonpreemptive recipients, with the exception of patients with panel reactive antibody (PRA) more than 30%, where preemptive patients had a higher incidence of AR ($P=0.003$; Table 2).

Allograft Survival

In univariate analysis, patient survival with a functioning graft was significantly higher in preemptive compared with nonpreemptive second transplant recipients (Fig. 1). The 3- and 5-year graft survival (including death as a cause of graft loss) was 87% and 78% for preemptive second transplant patients compared with 77% and 67% for nonpreemptive second transplant patients. In multivariate analysis, the risk of any cause including death (ACGL) was lower in preemptive than in nonpreemptive recipients (hazard ratio [HR], 0.88; 95% confidence interval [95% CI], 0.81–0.96). The multivariate adjusted risk of death with a functioning graft (DWFG) was also lower in preemptive recipients (HR [95% CI], 0.76 [0.66–0.87]); however, there was no difference in the risk of death-censored graft loss (DCGL; HR [95% CI], 0.98 [0.88–1.08]).

Duration of First Transplant Survival and Risk of Second Transplant Failure

The risk of second transplant failure in preemptive compared with nonpreemptive recipients varied significantly by the duration of first transplant survival (Table 3).

Preemptive second transplantation was associated with a lower risk of ACGL in patients with first transplant survival equal to or more than 10 years, and this was attributable to a lower risk of DWFG.

Preemptive transplantation was associated with a 34% increased risk of DCGL in patients with first graft survival less than 1 year (Table 3). In this subgroup, the mean duration of first transplant survival was only 0.33 years in preemptive recipients and 0.18 years in nonpreemptive recipients. Among patients with DCGL, the median time to DCGL in the second transplantation was 4.67 (25th and 75th percentiles, 4.24 and 5.43) years in preemptive recipients and 1.82 (25th and 75th percentiles, 1.54 and 2.11) years in nonpreemptive recipients.

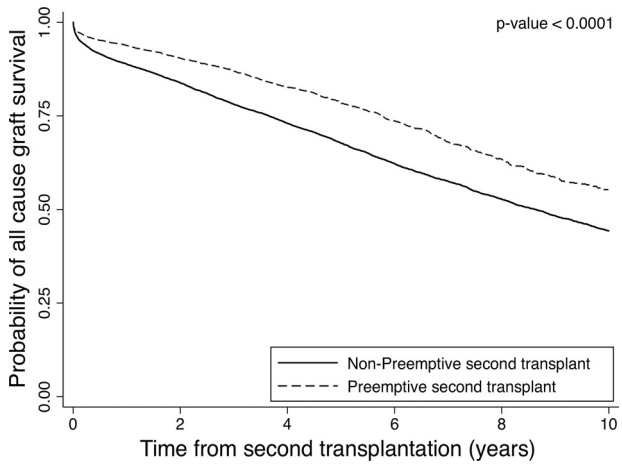

FIGURE 1. Time to all-cause graft loss.

Duration of Dialysis Between First and Second Transplantation and Risk of Death

Patients with longer durations of dialysis between first and second transplantation were at increased risk of DWFG (Table 4). Patients with dialysis exposure equal to or more than 5 years had the greatest risk.

DISCUSSION

We found that preemptive transplantation was associated with a lower risk of second transplant failure from ACGL. This benefit varied by the duration of first transplant survival: A benefit was consistently observed in patients with first graft survival 1.0 to 9.9 years and equal to or more than 10 years. The overall benefit of preemptive transplantation was driven by a lower risk of DWFG, whereas there was no benefit for the outcome of DCGL overall or in any subgroup. Importantly, an increased risk of DCGL was identified in patients with first transplant survival less than 1.0 year. These findings differ from the reported benefits in both graft and patient survival associated with

TABLE 2. AR in first year by duration of first graft survival and PRA before second transplantation

Duration of first graft survival, yr	All patients (%)		PRA 0%		PRA 1–29%		PRA >30%	
	PTX	Non	PTX	Non	PTX	Non	PTX	Non
0–0.9	22	19	21	19	25	22	33	18[a]
1–2.9	19	19	22	23	18	19	39	19[a]
3–4.9	12	15	10	11	18	16	7	17
5–6.9	9	15[b]	10	14	8	17[c]	15	15
7–9.9	10	13[c]	8	11	15	17	8	14
>10	10	11	10	9	12	13	11	12

[a] $P=0.003$.
[b] $P=0.01$.
[c] $P=0.03$.

AR was significantly lower in preemptive recipients when duration of first graft survival was ≥5 years. There was a significantly higher incidence of AR among preemptive recipients when duration of first graft survival was <3 years only when PRA was >30%.

AR, acute rejection; Non, nonpreemptive; PRA, panel reactive antibody; PTX, preemptive.

TABLE 3. Risk of preemptive second transplant failure by the duration of first graft survival

Duration of first graft survival for preemptive second transplant recipients, yr	Hazard of all-cause graft loss	Hazard of DCGL	Hazard of death with function
0–0.9 (n = 230)	1.19 (0.98–1.44)	1.341 (1.13–1.76)	0.74 (0.48–1.13)
1–2.9 (n = 148)	0.81 (0.60–1.11)	0.81 (0.56–1.17)	0.84 (0.48–1.48)
3–4.9 (n = 244)	0.93 (0.73–1.19)	1.14 (0.85–1.53)	0.61 (0.39–0.97)
5–6.9 (n = 338)	0.88 (0.69–1.13)	0.85 (0.62–1.16)	0.94 (0.64–1.38)
7–9.9 (n = 599)	0.86 (0.72–1.04)	0.93 (0.73–1.19)	0.78 (0.58–1.05)
>10 (n = 1950)	0.80 (0.69–0.91)	0.85 (0.70–1.02)	0.73 (0.60–0.90)

Adjusted for patient age at time of second transplantation, sex, race, cause of end-stage renal disease, first transplant characteristics (donor source and preemptive transplantation), propensity score for preemptive transplantation, second transplant characteristics (donor source, HLA mismatch, % PRA, and immunosuppression at second transplantation), use of induction immunosuppression, and year of second transplantation.

DCGL, death-censored graft loss; PRA, panel reactive antibody.

preemptive transplantation in primary transplant recipients (*9–13*) and also differ from a previous analysis of U.S. Renal Data System (USRDS) data, which found an increased risk of graft loss in preemptive second transplant recipients (*14*).

The reasons for the survival advantage associated with preemptive transplantation in primary transplant recipients remain uncertain. A reduced incidence of AR has been reported among preemptive living-donor but not deceased-donor primary transplant recipients (*9, 11, 15*), whereas preservation of residual native kidney function or a slower rate of kidney function decline has been refuted as mechanisms explaining the survival advantage associated with preemptive transplantation in first transplant recipients (*9*).

In this analysis, the main benefit of preemptive second transplantation was on patient survival with a significant reduction in the outcome of DWFG, even in patients with first transplant survival equal to or more than 10 years. These findings suggest that, even in patients with a long history of chronic kidney disease, continued efforts to minimize exposure to dialysis remain important. Further, given that second transplant recipients represent a highly selected population, the results indirectly suggest that the survival benefits are not simply due to a selection bias for healthier, more health conscious, or adherent patients. In contrast to studies in primary transplant recipients, we did not find improved DCGL in preemptive second transplant recipients. This is somewhat surprising given that we found an overall decreased incidence of AR in preemptive compared with nonpreemptive second transplant recipients. Further studies are needed to understand the immune and nonimmune mechanisms that diminish the allograft survival benefit of preemptive transplantation in second transplant recipients.

TABLE 4. Risk of DWFG by the duration of dialysis exposure between first and second transplantation

Duration of dialysis between first and second transplantation	Hazard of increasing dialysis durations between first and second transplantation compared with reference group preemptive second transplantation
Preemptive second transplantation (<7 days dialysis after first transplant failure)	1.00
Dialysis 7 days to 0.9 yr	1.16 (1.00–1.35)
Dialysis 1–1.9 yr	1.28 (1.10–1.52)
Dialysis 2–2.9 yr	1.39 (1.16–1.67)
Dialysis 3–4.9 yr	1.56 (1.33–1.82)
Dialysis >5 yr	2.22 (1.78–2.78)

DWFG, death with a functioning graft.

We found that preemptive second transplantation in patients with first transplant survival less than 1 year was relatively infrequent (n=230), but the outcomes were worse, with a 34% increase in the risk of DCGL in this subgroup. This finding is consistent with previous studies showing that the duration of second transplant survival is significantly modified by the duration of first graft survival (*16*). In this subgroup, the mean duration of first transplant survival was short (0.33 years in preemptive recipients and 0.18 years for nonpreemptive recipients), suggesting that many of the first transplant failures were due to perioperative events or early rejection. Unfortunately, we are not able to determine the circumstances of first transplant failure and the factors influencing the decision to proceed with second preemptive transplantation in these patients. In particular, the causes of early graft failure are not available. Similarly, the factors contributing to the increased risk of DCGL of the second transplant in this subgroup also cannot be determined. The lower incidence of DGF in preemptive repeat transplant recipients is expected and has been described previously in primary transplant recipients (*17*). The lower incidence of DGF may in part be due to residual primary allograft function. Although we did observe a numerically higher incidence of AR in preemptive second transplant recipients with short first transplant survival equal to or less than 1 year, this was only significant among those with PRA more than 30%. These findings should be interpreted with the understanding that recording of AR in the USRDS has not been validated, does not include details regarding whether the AR episodes are biopsy-proven, and does not describe AR treatment or the presence and quantification of donor-specific antibodies. Nonetheless, a conservative approach

to preemptive second transplantation in a patient with early first allograft failure may be warranted. In clinical practice, information regarding sensitization may not be obtained before initiation of discussions about a second transplant in a patient with a failing allograft, and it may be reasonable to obtain this information particularly in patients with early first transplant failure. Although early kidney transplant failure is a relatively rare event, there is little information to guide the management of this unique group of patients. We reported previously that repeat transplant outcomes after transplant nephrectomy differed in patients with first transplant survival less than 1 year compared with patients with transplant survival more than 1 year (*18*). Primary studies in which details regarding the cause of first allograft failure are known along with details regarding sensitization are needed to inform the management of this unique subgroup.

In contrast to our findings, preemptive second transplantation was associated with reduced graft survival in a previous study by Goldfarb-Rumyantzev et al. (*14*), which also used data from the USRDS between 1990 and 2000. However, that study included both adult and pediatric recipients, second, third, or higher transplant recipients, kidney pancreas recipients, and patients transplanted before 1995, whereas the current analysis includes adult, second kidney-only recipients transplanted after 1995.

With the possible exception of patients with early transplant failure, our results should not dissuade pursuit of a preemptive second transplantation in patients with a failing primary allograft. Preemptive transplantation avoids the cost (*19*) and morbidity (*20*) associated with dialysis access creation. Further, our analysis does not consider the survival of transplant failure patients on dialysis. Multiple studies have shown a high rate of morbidity (*5*) and mortality (*4–7, 21*) on dialysis after transplant failure, which may exclude patients with first transplant failure from consideration of a second transplantation.

When interpreting the results of this study, readers should consider the inherent limitations of retrospective analyses of registry data including nonrandom assignment of patients to preemptive or nonpreemptive transplantation. Although we adjusted for multiple factors known to be associated with allograft survival, the associations identified may be confounded by other factors not included in our analysis.

In summary, this study demonstrates an allograft survival advantage in preemptive second transplant recipients due primarily to a decreased risk of death with a functioning allograft and identified an increased risk of DCGL in preemptive second transplant recipients with first transplant survival less than 1 year. This information challenges concerns raised about the general use of preemptive second transplantation from an earlier USRDS-based study and highlights the potential risk of preemptive transplantation among the small subgroup with rapid first transplant failure.

MATERIALS AND METHODS

Data Source and Study Population

The study population included adult patients (≥18 years) who received a second kidney-only transplant in the USRDS between 1 January 1995 and 30 September 2007.

Definitions and Patient Follow-up

Preemptive second transplant recipients were defined as recipients of a second kidney-only transplant with more than 7 days of dialysis treatment before second transplantation. Nonpreemptive second transplant recipients received a second kidney-only transplant after 7 or more days of dialysis. Patients were followed from the date of second transplantation until death, graft failure (requirement for dialysis or third transplantation), or 30 September 2007, whichever occurred first.

Descriptive Statistics

Patients were categorized based on whether they received a preemptive or nonpreemptive second transplant and group differences were compared with the chi-square test.

Statistical Analyses

The time to all graft failure from ACGL, DCGL, and DWFG was determined in preemptive and nonpreemptive recipients by the Kaplan-Meier method and group differences were compared with the log-rank test. Cox multivariate regression models were used to determine the association of preemptive transplantation with ACGL, DCGL, and DWFG. In these models, patients were followed from the date of second transplantation until the outcome of interest (graft failure or death) or the end of follow-up. The following confounders were included in the multivariate models: patient age at time of second transplantation, sex, race, cause of end-stage renal disease, first transplant characteristics (donor source and preemptive transplantation), second transplant characteristics (donor source, HLA mismatch, % PRA, and immunosuppression at second transplantation), use of induction immunosuppression, year of second transplantation, and duration of first transplant survival. Because of the known association between the duration of first allograft survival and second transplant survival (*16*), we determined whether any association of preemptive transplantation with second allograft survival varied by the duration of first graft survival by the use of interaction terms. Because not all patients in the nonpreemptive group would be eligible for preemptive transplantation, a propensity score for preemptive second transplantation was generated using a multivariate logistic regression model adjusted for patient characteristics and kidney transplant-related characteristics that were associated with preemptive second transplantation in univariate analysis ($P<0.10$). The final logistic regression model included the following covariates: age at time of second kidney transplantation, sex, race, cause of end-stage renal disease, year of kidney transplantation, first and second kidney donor source (living or deceased), first preemptive transplantation, induction immunosuppression, HLA, PRA, and duration of first graft survival. The propensity score for preemptive transplantation generated from this model was included as an additional covariate in the Cox models above. In all models, the proportional hazards assumption was tested for using log-negative-log plots of the within-group survivor probabilities versus log-time. Patients with missing covariate information were coded as "missing" for that covariate and included in the multivariate models.

We determined the incidence of DGF (defined as the requirement for dialysis within the first 7 days after transplantation) among preemptive and nonpreemptive patients. This analysis was repeated, stratifying by donor source (living donor, standard-criteria deceased donor, and extended-criteria deceased donor). We also determined the incidence of AR in the first year after second transplantation in preemptive and nonpreemptive second transplant recipients. AR was determined if a patient had an AR event or was treated for AR coded at any of 1, 3, 6, and 12 months after second transplantation. Exact dates for AR events are not available. The incidence of AR within the first year after second transplantation was also examined in different strata of duration of first graft survival and PRA.

All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC), and figures were produced using StataMP 11 (StataCorp, College Station, TX).

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