Immunologic Long-term Outcomes of Living-Related Kidney Transplantations Depending on the Donor-Recipient Relationship

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ABSTRACT

Background. The aim of this study is to analyze the long-term immunologic outcomes of living-related kidney transplantations depending on the donor-recipient relationship.

Methods. This retrospective single-center study included adult kidney transplant recipients (KTR) transplanted between 2000 and 2014. Among 1117 KTRs, 178 patients (15.9%) received living-related donations. Those patients were further categorized according to the donor-recipient relationship: 65 transplantations between siblings, 39 father-to-child (F-t-C) and 74 mother-to-child (M-t-C) donations. Allograft biopsies were performed for clinically suspected rejections. Data analysis included patient and graft survival, biopsy proven rejections (T-cell mediated [TCMR] or antibody mediated) and development of de novo donor-specific antibody. Outcome data were assessed over a period of a maximum 14 years.

Results. There was no significant difference between the groups (F-t-C, M-t-C, and siblings) with regard to HLA-mismatches, prior kidney transplantations, time on dialysis, and cold ischemia time. Among KTRs with related donors, the type of relationship had no significant influence on graft survival. F-t-C and M-t-C pairs showed comparable incidences of TCMR at 7 years post-transplantation, both significantly exceeding the rate in sibling-to-sibling pairs (26.2% and 26.8% vs 10%, respectively; $P = .043$). A multivariate Cox regression analysis adjusted for recipient age, donor age, and HLA (A, B, DR)–mismatches identified both M-t-C- and F-t-C-donations as important independent risk factors for TCMR (hazard ratio: 8.13; $P < .001$ and hazard ratio: 8.09; $P = .001$, respectively). There was no significant difference between the groups concerning the incidence of antibody-mediated rejection and de novo donor-specific antibody.

Conclusion. Our results indicate that parent-to-child kidney donation is an independent risk factor for TCMR.

LIVING-DONOR kidney transplantation is the preferred alternative to deceased donation due to its superior graft survival and the increasing shortage of deceased-donor kidneys [1]. Despite recent enhancements in immunosuppression, immunologic events are still the leading cause of kidney graft loss [2]. There are a limited number of studies analyzing the effect of the donor-recipient relationship. Furthermore, available studies report conflicting results [3–9]. It has been assumed that a fetal-maternal microchimerism could induce some degree of immune tolerance to an organ transplanted from the mother to an offspring leading to an improved graft survival [10]. On the other hand, it has been repeatedly shown that mother-to-child (M-t-C) donations were actually associated with significantly worse graft survival in comparison to father-to-child (F-t-C) donations [3,7–9]. It has been hypothesized that the effect of the sustaining sensitization through HLA-antibodies acquired during the pregnancy overrides the possible effect of microchimerism, leading, in theory, to increased incidence of rejections in the M-t-C living-kidney donations [8]. The purpose of this study was to examine the long-term

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Table 1. Patient Characteristics

Patient Characteristics	Father-to-Child N = 39	Mother-to-Child N = 74	Sibling-to-Sibling N = 65	*P* Value
Mean recipient age, yrs (SD)	30 (8)	30 (8)	45 (11)	<.001
Mean donor age, yrs (SD)	55 (9)	54 (9)	43 (12)	<.001
Recipient male, n (%)	23 (59)	49 (66)	41 (63)	.731
Prior kidney transplantation, n	0 (0)	4 (5)	7 (11)	.079
Median time on dialysis, months (IQR)	12 (6–49)	16 (9–29)	15 (8–43)	.876
Mean cold ischemia time, hours (SD)	2.5 (1.2)	2.4 (0.8)	2.5 (0.9)	.741
Median best creatinine, mg/dL (IQR)	1.1 (0.9–1.4)	1.2 (0.9–1.5)	1.0 (0.9–1.1)	<.001
Mean HLA-mismatches, n (SD)	2.2 (0.8)	2.1 (0.9)	1.9 (1.5)	.246
Mean follow-up, yrs (SD)	7.0 (4.0)	6.8 (4.0)	5.9 (4.0)	.290

Abbreviation: IQR, interquartile ratio.

immunologic outcomes of living-related kidney transplantations depending on the donor-recipient relationship.

PATIENTS AND METHODS

This retrospective long-term single-center study included all AB0-compatible adult living-related donor kidney transplant recipients (KTR) transplanted in our center between 2000 and 2014. All included patients had negative solid-phase screenings for preformed donor-specific HLA antibodies (DSA) before transplantation. Allograft biopsies were performed for clinically suspected rejections. Follow-up DSA analyses with solid-phase assays were routinely performed [11]. Data analysis included patient and graft survival, biopsy-proven rejection episodes (T-cell mediated [TCMR] or antibody mediated [ABMR]) and development of de novo DSA. Outcome data were assessed over a period of a maximum 14 years.

Most patients initially received standard immunosuppressive protocols including induction therapy with interleukin-2 receptor antibody, calcineurin inhibitor, mycophenolate, and steroids. After the first year of transplantation, a steroid free regimen was intended if no rejection episodes had occurred.

Patient cohort characteristics and parameters were calculated as mean (and standard deviation [SD]) or as median and interquartile range. Data was analyzed using the χ^2 test and analysis of variance tests for independent variables. In cases of a nonparametric distribution, the Kruskal-Wallis test was used. Survival estimates were calculated by the Kaplan-Meier method, and survival differences were assessed by log-rank tests. Multiple Cox regression models were created to identify predictors of TCMR. The significance level was set at $\alpha = 0.05$. Statistical analysis was performed with SPSS 22 for Windows (SPSS Inc., Armonk, NY). The study was approved by the Ethics Committee of the Charité Universitätsmedizin Berlin and complied with the Declaration of Helsinki.

RESULTS

Of 1117 KTRs who underwent transplantation during the observational period, 306 patients (27.4%) received living donations. Among them, 178 KTRs (15.9%) had a living-related donor and were included in the study. Further categorization according to the donor-recipient relationship revealed 65 (36.5%) transplantations between siblings (S-t-S), 39 (21.9%) F-t-C donations, and 74 (41.6%) M-t-C donations. Patient characteristics of the cohort of KTRs with living-related donations are shown in Table 1.

There were no significant differences between the groups (S-t-S, F-t-C, and M-t-C) with regard to HLA-mismatches, prior kidney transplantations, time on dialysis, and cold ischemia time. At 7 years post-transplantation, the donor-recipient relationship had no significant influence on the death-censored graft survival (93.8%, 88.2% and 91% in F-t-C, M-t-C and S-t-S pairs, respectively; $P = .832$) (Fig 1A). Among KTRs with related donors, F-t-C and M-t-C pairs showed comparable incidences of TCMR, both significantly exceeding the rate in S-t-S pairs: 7-year TCMR rates were 26.2%, 26.8%, and 10% in F-t-C, M-t-C, and S-t-S pairs, respectively ($P = .043$) (Fig 1B).

A multivariate Cox regression analysis adjusted for recipient age, donor age, and HLA-(A, B, DR)−mismatches identified both M-t-C and F-t-C donations as important independent risk factors for TCMR (hazard ratio: 8.13; $P < .001$ and hazard ratio: 8.09; $P = .001$, respectively).

There was no significant difference between the groups in terms of ABMR: 7-year incidence of ABMR was 10.4%, 10%, and 5.8% in F-t-C, M-t-C, and S-t-S pairs, respectively ($P = .637$) (Fig 1C). In comparison to S-t-S pairs, parent-to-child donations (F-t-C and M-t-C) showed a slightly higher incidence of de novo DSA without reaching statistical significance: 7-year incidence of de novo DSA was 20.6%, 29%, and 11.7% in M-t-C, F-t-C, and S-t-S pairs, respectively ($P = .187$) (Fig 1D).

DISCUSSION

In this cohort of living-related donor KTRs, the subgroups with different donor-recipient relationships showed a comparable death-censored graft survival. These results are in contrast to previous studies reporting an inferior graft survival in M-t-C pairs in comparison to other living-related donations, and could be partially explained by the necessity of larger sample sizes to reveal smaller effects on graft survival [3,8,9]. Miles et al has assumed that the reduced graft survival of M-t-C pairs could be explained due to the sustaining sensitization acquired during pregnancy, leading to an increased incidence of rejections after M-t-C kidney donations [8]. According to our results, M-t-C donation was indeed associated with a significantly increased incidence of TCMR compared to S-t-S pairs. However, there was similar incidence of TCMR in the group of F-t-C donations in contrast to previous assumptions. Furthermore, there was no significant difference in the incidence of ABMR between