Outcome of Kidney Transplantation From Donor After Cardiac Death: Reanalysis of the US Mycophenolic Renal Transplant Registry

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ABSTRACT

Background. Kidney transplantation is limited by the shortage of donor kidneys. Donation after cardiac death (DCD) has been explored to alleviate this problem. To better understand the outcome of DCD kidney transplantation, we reanalyzed the Mycophenolic Renal Transplant (MORE) Registry.

Methods. We compared delayed graft function (DGF), biopsy-proved acute rejection (BPAR), graft loss, and patient death between DCD and donation after brain death (DBD) kidney transplantations. Recipients were further stratified into depleting and nondepleting induction groups for exploratory analysis.

Results. There were 548 patients who received kidney transplants from deceased donor in the MORE Registry. Among them, 133 received grafts from DCD donors and 415 received from DBD donors. The incidence of DGF was 29.4% and 23.5% in the DCD group and the DBD group, respectively ($P = .1812$), and the incidence of BPAR at 12 months was 9.0% and 9.9% respectively ($P = .7713$). The 1-year graft loss rate in the DCD group was higher than that in the DBD group (7.5% vs 3.1%, $P = .0283$), and the 4-year graft loss rate and patient death rate were not significantly different between the 2 groups.

Conclusions. The DCD kidney transplant group had acceptable short-term outcomes and good long-term outcomes as compared with the DBD kidney transplant group.

KIDNEY transplantation is the most successful treatment for end-stage renal disease, although it is limited severely by the current enduring critical shortage of donor kidneys. Kidney transplant candidates on the waiting list accumulate much faster than the availability of donor kidneys. In the United States, about 70,000 people died while waiting for a kidney between 2004 and 2014. This situation is even more severe in some developing countries, where there is currently no brain death legislation and the brain death concept and practice have not been the norm of local society.

Donation after cardiac death (DCD), as an alternative source of organs, has been explored to alleviate such a problem [1]. The full potential of the DCD pool was estimated to be larger than that of the donation after brain death (DBD) pool and could be double or even quadruple the number of current deceased donors [2]. In the United States, the number of DCD kidney transplants has dramatically increased, from 163 in 2000 to 1242 in 2009 (greater than 650% increase) [3].

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Long-term graft and patient survival has been reported as similar between DCD and DBD kidney transplantation. However, concerns are raised for short-term clinical events in DCD kidney transplants [4–6]. We reanalyzed the Mycophenolic Renal Transplant (MORE) Registry with data in DCD kidney transplantation. MORE Registry was a multicenter, prospective, observational study of kidney transplant recipients receiving de novo mycophenolic acid (MPA) therapy, which showed reducing or discontinuing MPA can adversely affect graft outcomes regardless of tacrolimus trough levels. Furthermore, we analyzed the effect of different induction therapy regimens on DCD kidney transplant patients.

MATERIALS AND METHODS

Study Design and Population

The MORE Registry was a 4-year, multicenter, prospective, observational study of adult kidney transplant patients receiving de novo MPA therapy either as enteric-coated mycophenolate sodium or mycophenolate mofetil under routine clinical conditions at 40 transplant centers in the United States. Recipients of multiple organ or tissue grafts (current or planned) or a prior nonkidney grafts and recipients not likely to have 3-year follow-up data for this study were excluded. Recruitment took place from June 2007 to May 2010 [7]. The study protocol and all amendments were reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each center. All enrolled patients signed the written inform consent before participating in this study. Subjects who could not read or sign the documents were not included, because they could not self- administer the required the Immunosuppressant Therapy Adherence Scale questionnaire. The MORE Registry was conducted according to the Declaration of Helsinki.

The current analysis was restricted to patients receiving a deceased donor kidney from the US Registry MORE study. Data obtained at routine clinic visits were recorded at baseline (defined as $\leq$2 weeks after transplantation); months 1, 3, 6, and 12; and annually thereafter to 4 years post-transplant, according to the local visit schedule. Delayed graft function (DGF) in MORE study was defined as patients who needed dialysis within the first week post-transplant. Counted acute rejections (ARs) were diagnosed by renal biopsies. Induction therapy was based on center practice and at the physicians' discretion.

Immunosuppression

In this analysis, all immunosuppression was administered according to the local practice, including use of induction therapy, dosing level, type of MPA therapy, and the decision of when to withdraw or continue corticosteroids. For induction therapy agents, depleting antibody was antithymocyte globulin or alemtuzumab, and nondepleting antibody was anti-interleukin-2R antibody (IL2RA).

Statistical Analysis

Categorical variables were summarized as counts and percentages and continuous variables as means with standard deviations. Categorical variables were compared with the Cochran-Mantel-Haenszel test, and continuous variables with analysis of variance. The incidence of DGF, biopsy-proven acute rejection (BPAR), 1-year graft loss, and patient death were calculated with real event numbers and evaluated using the Cochran-Mantel-Haenszel test. Incidence of 4-year graft loss and patient death was evaluated based on Kaplan-Meier estimates and the log-rank test. Cox proportional hazard regression modeling was used to estimate the risk of efficacy events for DBD and DCD kidney transplant patients after adjusting for the following baseline factors: transplant type (DBD, DCD), panel-reactive antibody (PRA), HLA mismatch, donor age, recipient age, MPA category, and induction therapy [8,9]. A logistic regression model was used to compare 1-year graft survival for the DCD and DBD groups adjusting for baseline PRA, donor sex, ABO nonidentity, and cold ischemia time (CIT). These 4 factors showed P value $< .1$ between the DCD and DBD groups at baseline. Analyses were performed using SAS statistical software (SAS Institute, Cary, NC, United States). P values $< .05$ were considered statistically significant.

RESULTS

In total, 548 patients with end-stage renal disease received kidney transplants from deceased donors in the MORE Registry. Among them, 133 received grafts from DCD donors and 415 from DBD donors. All DCD kidneys were from controlled donors (Maastricht category III or IV).

Baseline factors related to recipients, donors, and treatment in the DCD and DBD groups are shown in Table 1. In both groups, the majority of the factors were similar, except for a higher percentage of ABO nonidentical cases (12.87% vs 5.78%, $P = .004$) and male donors (72.18% vs 59.52%, $P = .009$) in the DCD group. Also, the average trough concentration of tacrolimus was a little lower in the DCD group than in the DBD group ($P = .011$).

Outcome Analysis Between the DCD and DBD Groups

The outcome of kidney transplantation for the DCD and DBD groups is shown in Table 2. The incidence of DGF and BPAR at 12 months after transplantation was comparable between the DCD group and the DBD group. The Banff classification of BPAR was listed in Table 2, and there was no significant difference in the severity of BPAR between the DCD and DBD groups. The 1-year graft loss rate was higher in the DCD group than that in the DBD group (7.5% vs 3.1%, $P = .0283$). In a logistic regression model adjusting for baseline PRA, donor gender, ABO nonidentity, and CIT (these 4 factors showed $P < .1$ between the DCD and DBD groups at baseline), the difference in graft survival was still significant ($P = .0188$). The 1-year recipient death rate was comparable in the 2 groups. When the follow-up time was extended to 4 years, graft loss rate and recipient death rate were also comparable between the DCD group and the DBD group.

To analyze risk factors of BPAR and graft loss at 12 months in kidney transplantation from deceased donors, a multivariant Cox regression analysis was performed. Donor type (DCD or DBD), PRA, HLA mismatch, donor age, MPA category, induction therapy (depleting or nondepleting), and recipient age were added to the model. Compared with the DBD group, DCD added no statistically significant additional risk for BPAR at 12 months (DBD vs DCD, hazard ratio [HR] = 0.869, $P = .688$). However, DCD