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Induction regimen and survival in simultaneous heart-kidney transplant recipients

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tacrolimus;
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propensity score;
induction therapy

BACKGROUND: Induction therapy in simultaneous heart-kidney transplantation (SHKT) is not well studied in the setting of contemporary maintenance immunosuppression consisting of tacrolimus (TAC), mycophenolic acid (MPA), and prednisone (PRED).

METHODS: We analyzed the Organ Procurement and Transplant Network registry from January 1, 2000, to March 3, 2015, for recipients of SHKT ($N = 623$) maintained on TAC/MPA/PRED at hospital discharge. The study cohort was further stratified into 3 groups by induction choice: induction ($n = 232$), rabbit anti-thymoglobulin (r-ATG; $n = 204$), and interleukin-2 receptor-α ($n = 187$) antagonists. Survival rates were estimated using the Kaplan-Meier estimator. Multivariable inverse probability weighted Cox proportional hazard regression models were used to assess hazard ratios associated with post-transplant mortality as the primary outcome. The study cohort was censored on March 4, 2016, to allow at least 1-year of follow-up.

RESULTS: During the study period, the number of SHKTs increased nearly 5-fold. The Kaplan-Meier survival curve showed superior outcomes with r-ATG compared with no induction or interleukin-2 receptor-α induction. Compared with the no-induction group, an inverse probability weighted Cox proportional hazard model showed no independent association of induction therapy with the primary outcome. In sub-group analysis, r-ATG appeared to lower mortality in sensitized patients with panel reactive antibody of 10% or higher (hazard ratio, 0.19; 95% confidence interval, 0.05–0.71).

CONCLUSION: r-ATG may provide a survival benefit in SHKT, especially in sensitized patients maintained on TAC/MPA/PRED at hospital discharge.

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Heart transplantation (HT) is a well-established treatment for patients with end-stage heart failure. Comorbid chronic kidney disease (CKD) is common among patients awaiting HT. Simultaneous heart-kidney transplantation (SHKT) has consequently seen a substantial increase during the past 10 years.[1]

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Induction immunosuppression is frequently used perioperatively to prevent acute rejection and improve graft and patient outcomes.[2] However, the use and choice of induction therapy and the selection of an optimal maintenance immunosuppression regimen for heart and kidney transplants, specifically for SHKT recipients, remain controversial. Data from the 2015 Organ Procurement and Transplant Network (OPTN) annual report show approximately 50% of the HT centers used induction therapy, out of which 50% used lymphocyte-depleting (LD) antibodies, mainly polyclonal rabbit anti-thymocyte globulin (r-ATG), and the other 50% used monoclonal antibodies directed against interleukin 2 receptor-α (IL2-RA), specifically basiliximab.[1] Similar trends have been observed in renal transplantation with more use of induction therapy (~85% of kidney transplant recipients receive induction therapy).

Given the rise in the incidence of SHKT, we sought to better understand the added survival benefit of induction therapy in this population while receiving contemporary maintenance immunosuppression with tacrolimus (TAC), mycophenolic acid (MPA), and prednisone (PRED).

Methods

The University of Texas at Dallas and the University of Texas Southwestern Medical Center Institutional Review Boards approved the study. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, candidates on the waiting list, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplant Network (OPTN). The Health Resources and Services Administration, an agency of the United States Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

This study was a retrospective cohort analysis of the OPTN registry and included the 963 adults who underwent SHKT in the United States in the SRTR data set. This database consisted of the donor, pre-operative, intraoperative, and post-operative variables that are reported to the United Network of Organ Sharing by all transplant centers in the United States. The SRTR database was queried for adult patients (age ≥ 18 years) who received transplants between January 2000 and March 2015. All patients were censored by March 4, 2016, allowing at least 1 year of follow-up. The sample size for the final analysis was 623 SHKT patients.

The study population ($N = 623$) was split into 3 groups by the induction therapy strategy at the time of transplant: no induction (232 [37%]), r-ATG (204 [33%]), and IL2-RA (187 [30%]). Separate analyses were done to evaluate the association between patient survival and induction strategy for recipients who survived more than 30 days after transplant, steroid use at 1 year, trimmed analysis (restricted analysis to inverse probability weighted [IPW] scores between 5% and 95%), age groups (aged < 60 and ≥ 60 years), race groups (white and African American), panel reactive antibody (PRA) groups (0%, >1%, and >10%), ventricular assist device (VAD) status, and dialysis at the time of transplant.

Main outcome

The primary outcome was post-transplant mortality. Patients were monitored from the date of transplant to death or the end of the study period (March 4, 2016).

Statistical analyses

Recipient characteristics are described using mean and standard deviation or frequencies. Comparisons between groups were made using the *t*-test, Kruskal-Wallis test, or chi-square test. Survival rates were estimated using the Kaplan-Meier product limit method. The log-rank test was used for comparison of the unadjusted survival curves.

The patients in the 3 induction groups were not assigned randomly; thus, the groups might consist of patients who were systematically different concerning their baseline covariate information. Because of this cohort selection bias, a propensity-score analysis using the IPW method was performed in the estimation and comparison of time to patient death among the 3 induction groups.[3–5] The typical binary logistic regression model could not be used because there were 3 induction groups. We therefore used polytomous logistic regression (Stata mlogit function) to fit the multinomial logit model for a categoric dependent variable (death).

The IPW score was constructed from the variables of recipient age, donor age, PRA, center, region, human leukocyte antigen mismatch, cytomegalovirus mismatch (donor positive and recipient negative), severe infection 2 weeks before transplant requiring intravenous antibiotics, history of malignancy, cold ischemia time (CIT), ventricular assist device (VAD), recipient race, transplant year, and sex. We compared the distribution of IPW scores between the 3 groups using box-and-whisker plots. The IPW score distributions overlapped, indicating that observations from the 3 groups were similar across the range of the IPW scores. We also performed a trimmed analysis, restricting the analysis to IPW scores that fell between the 5th percentile and 95th percentile in the cohorts to eliminate non-overlapping propensity scores. The IPW Cox proportional hazard analysis was repeated in the trimmed sample and did not result in significant change in the results. We assessed covariate balance between the groups after conditioning on the propensity score. The 3 groups were similar on the covariates (standardized mean difference), implying that for each unique value of the propensity score, the distribution of covariates was identical for the 3 groups.

Multivariable IPW Cox proportional hazard regression models were used to estimate the hazard ratios associated with mortality using no induction therapy as the reference. We assessed the proportional hazards assumption graphically by using a log-log plot of survival, Kaplan–Meier, and predicted survival plot, and Schoenfeld residuals global testing. No evidence of violations against proportionality was found. In the multivariable final Cox proportional hazard analysis, independent variables of interest were identified based on the published literature and clinical significance.[6,7] Those variables included the use of inotropes in the recipient, use of intra-aortic balloon bump, recipient diabetes status, recipient ABO type, body mass index, etiology of cardiomyopathy, renal function and total bilirubin at transplant, pulmonary artery mean pressure and pulmonary artery wedge pressure at transplant, transplant year, waiting time, medical condition (intensive care unit vs floor vs home), functional status, history of HT (prior sternotomy), candidate last listing status (1A, 1B, 2), donor weight, recipient weight, primary payer, donor desmopressin administration, and Kidney Donor Profile Index scores.

To account for missing data, which primarily consisted of 4 variables and less than 10% of the study cohort, we imputed 5 continuous variables (PRA, CIT, mean pulmonary artery pressure, pulmonary wedge pressure, and total bilirubin levels) and 2 categoric variables (human leukocyte antigen mismatch and functional status) using multiple imputation methods (a flexible,