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Original article

Posttransplant lymphoproliferative disease and survival in adult heart transplant recipients

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ABSTRACT

Background: The influence of posttransplant lymphoproliferative disease (PTLD) on long-term survival after heart transplantation (HTx) in adult recipients needs better characterization.
Methods: The United Network for Organ Sharing database was queried from 2006 to 2015 to compare survival between adult HTx recipients with and without PTLD. Cox proportional hazards models were used to analyze the primary outcome of survival, and competing-risks regression was used to analyze the outcome of PTLD development.
Results: A total of 14,487 HTx recipients who had data on PTLD were included in univariate Cox analysis and Kaplan–Meier survival function, while 10,422 were included in multivariable Cox analysis and 162 selected for a matched-pairs sample after matching on the propensity of developing PTLD. The cohort included 120 patients who were diagnosed with PTLD. Onset of PTLD, treated as a time-varying covariate, was adversely associated with survival in univariate (HR = 4.953; 95% CI: 3.768, 6.511; $p < 0.001$) and multivariable (HR = 3.849; 95% CI: 2.669, 5.552; $p < 0.001$) Cox proportional hazards models. Cox regression stratified on matched pairs of PTLD cases and non-PTLD controls confirmed the risk for death associated with PTLD onset (HR = 2.667; 95% CI: 1.043, 6.815; $p = 0.040$).
Conclusions: PTLD onset negatively influenced survival in adult HTx recipients, whereas no characteristics predisposing patients to PTLD development were identified in multivariate analysis.

Introduction

Heart transplantation (HTx) is an established treatment option for adult patients with chronic heart failure. The most recent data from the International Society for Heart and Lung Transplantation Registry reported that the survival of the 2006–June 2012 cohort was similar to patients transplanted in 2002–2005, with unadjusted 1-year survival of 84–85% [1].

Posttransplant lymphoproliferative disorder (PTLD) is a wide spectrum of lymphoid conditions ranging from benign hyperplasia to lymphoma after HTx, which is often associated with immunosuppression and Epstein–Barr virus (EBV) [2–6]. Analysis of a multi-institutional registry that included 4089 patients >15 years who underwent HTx between 1984 and 31 December 2003 found a total of 639 tumors that developed in 490 patients, with 50.7% (324) skin cancers, 9.7% (62) lymphomas, and 39.6% (253) non-cutaneous solid cancers other than lymphoma [2]. Although skin cancer and non-cutaneous solid cancer occurred more commonly after HTx, lymphoma was associated with a higher mortality rate of 70% (40/57) vs. 19% (41/212), and 62% (132/213) and a lower follow-up period of 107.1 person-years vs. 746.3 and 387.6 person-years, respectively [2]. Therefore, long-term survival may be limited for the larger cohort of recipients after HTx.

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Research addressing survival related to PTLD in adult HTx recipients is limited to single-center studies and case series [7–10]. Moreover, limited data exist on confounding variables that could be influencing survival in the setting of PTLD after HTx. Using the United Network for Organ Sharing (UNOS) Registry, we sought to investigate the impact of PTLD on survival in adults after HTx, while also addressing common and important covariates that may be influencing clinical outcomes. We hypothesized that PTLD adversely affects long-term clinical outcomes in adult HTx recipients.

Methods

Data collection

We retrospectively evaluated data from patients who were registered in the UNOS thoracic database [11]. The study was approved by the Nationwide Children's Hospital Institutional Review Board with a waiver of the need for individual consent (IRB14-00716). The UNOS thoracic database was queried for first-time adult HTx recipients between May 2006 and September 2015 from cadaveric donors with known transplant date, exclusive of duplicate entries. A total of 14,487 adult patients (≥18 years of age) were identified and included in the analysis. PTLD was identified at follow-up visits, with the reference group including patients with no recorded malignancy at follow-up, or only malignancy other than PTLD [12].

Statistical methods

All analyses were performed using Stata/IC, version 13.1 (StataCorp LP, College Station, TX, USA). Descriptive statistics for continuous variables are presented as means and standard deviations; and descriptive statistics for categorical variables are presented as proportions. For all analyses, a p-value <0.05 was considered statistically significant. The primary outcome was survival in days from the date of the transplant until the date of death or censoring. Univariate Cox proportional hazards models and Kaplan–Meier survival curves were completed to compare patients who were and were not diagnosed with PTLD. In all Cox models, PTLD was entered as a time-varying covariate equaling 0 up to the date of diagnosis or censoring, and equaling 1 after a patient was diagnosed with PTLD. A multivariable Cox proportional hazards model was used to adjust for potential confounders, which included donor and recipient gender, donor and recipient race, pulmonary hypertension, recipient–donor EBV matching, induction immunosuppression [none, basiliximab, anti-lymphocyte globulin (ALG)/anti-thymocyte globulin (ATG)/thymoglobulin, corticosteroids, and other], recipient age and body mass index (BMI), ischemic time, and transplant year.

Propensity score matching was completed to confirm increase in mortality hazard associated with the development of PTLD. The propensity of ever being diagnosed with PTLD was calculated as a logit function of the covariates included in the multivariable Cox analysis. All potentially relevant covariates were included in the propensity model to assure matching between similar PTLD and non-PTLD patients. The matching algorithm used one-to-one nearest-neighbor matching without replacement on the logit of the propensity score, with a caliper width equal to 0.2 standard deviations of the logit of the propensity score. Cox proportional hazards regression stratified on the matched pairs was used to estimate a hazard ratio (HR) of a piecewise-constant time-varying measure of PTLD. A secondary outcome was onset of PTLD, with death before PTLD onset considered a competing risk. A multivariable competing-risks regression model was fitted using all covariates described above [13].

Results

Study population

Table 1 summarizes the patient characteristics of the cohorts with and without PTLD. A total of 120 patients were diagnosed with PTLD in the contemporary cohort transplanted between May 2006 and September 2013. Comparing PTLD and non-PTLD groups, significant differences included recipient race and recipient–donor EBV matching. Recipients diagnosed with PTLD were more likely to be white than recipients not developing PTLD, whereas recipient EBV negative – donor EBV positive matches were more common in the group developing PTLD. There were no differences associated with recipient age or pulmonary hypertension. Recipients developing PTLD were, on average, transplanted one year earlier (2009 compared to 2010) than recipients who did not develop PTLD.

Univariate and Kaplan–Meier survival analysis

The cohort of 14,487 adult patients was included in the univariate Cox proportional hazards analysis (Table 2), which revealed a significant increase in the mortality hazard after PTLD onset in adult HTx recipients (HR = 4.953; 95% CI: 3.768, 6.511; $p < 0.001$). A comparison of Kaplan–Meier survival functions confirmed a survival difference between recipients who developed PTLD and those who did not (Fig. 1).

Several covariates were found to be influencing the hazard of death in the univariate Cox models. Increased risk for mortality was associated with black recipient race, donor EBV seropositivity, basiliximab induction immunosuppressant therapy, younger recipient age, higher recipient BMI, and longer ischemic time. Donor gender, donor race, pulmonary hypertension, and EBV seronegativity failed to demonstrate a statistically significant association with clinical outcomes.

Multivariable survival analysis

A total of 10,422 patients with complete data on covariates were included in the multivariable survival analysis. Adjusting for covariates, multivariable Cox proportional hazards models (Table 3) demonstrated a significant increase in the risk for mortality in HTx recipients after PTLD onset (HR = 3.849; 95% CI: 2.669, 5.552; $p < 0.001$). As with the univariate analysis, the covariates of black recipient race, younger age, higher BMI, and longer ischemic time were associated with an increased risk for mortality. Matching of EBV seropositive recipients and donors was associated with increased mortality hazard relative to matching of EBV seronegative recipients and donors, while no differences in survival by induction immunosuppression therapy were observed after adjusting for covariates.

Propensity score matching

Suitable non-PTLD controls were identified for all 81 cases of PTLD with complete covariate data (i.e. included in Table 3), leading to 162 total patients being included in the matched-pairs sample. All of the covariates shown in Table 3 were used to develop the model of propensity of being diagnosed with PTLD. A significant increase in mortality hazard was confirmed after PTLD onset (treated as a time-varying covariate) in adult HTx recipients included in the matched sample, with appropriate stratification of the analysis on the matched pairs (HR = 2.667; 95% CI: 1.043, 6.815; $p = 0.040$).

Analysis of PTLD onset

A multivariable analysis of PTLD onset was completed with death before PTLD onset considered as a competing risk (Table 4).

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