Posttransplant Lymphoproliferative Disorders in Epstein-Barr Virus Donor Positive/Recipient Negative Lung Transplant Recipients

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Background. **Epstein-Barr virus (EBV) donor positive/recipient negative (D+/R−) status is a significant risk factor for posttransplant lymphoproliferative disorder (PTLD) in lung transplant. There are, however, no studies that identify the risk factors for PTLD in the EBV D+/R− lung transplant population to guide the decision to proceed with an EBV-positive donor.**

Methods. **This was a retrospective cohort study of adults listed in the Scientific Registry of Transplant Recipients between May 5, 2005, and August 31, 2016. Cox proportional hazards models were used to assess the impact of EBV D+/R− status on the development of PTLD, the impact of PTLD on survival, and survival differences between EBV D+/R− and EBV D−/R− recipients.**

Results. **The incidence of PTLD was 6.2% (79 of 1,281) versus 1.4% (145 of 10,352) in EBV D+/R− versus all other recipients (adjusted odds ratio 4.0; 95% confidence interval: 2.8 to 5.9, $p < 0.001$). Among EBV D+/R− recipients, age less than 40 years and white race were associated with PTLD. The EBV D+/R− patients who had PTLD had increased adjusted risk of death (hazard ratio 1.91; 95% confidence interval: 1.35 to 2.71; $p < 0.001$). Compared with EBV D+/R− recipients, EBV D−/R− recipients did not have improved adjusted survival (hazard ratio 0.82; 95% confidence interval: 0.57 to 1.18; $p = 0.30$).**

Conclusions. **Despite increased rates of PTLD and associated mortality in the EBV D+/R− population, EBV seronegative patients did not have worse mortality when transplanted with lungs from EBV seropositive donors compared with lungs from EBV seronegative donors. Consideration should be given for close monitoring for PTLD among EBV D+/R− recipients, particularly those who are white and less than 40 years of age.**

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Posttransplant lymphoproliferative disorders (PTLD) are a heterogeneous group of monomorphic and polymorphic B-cell and T-cell lymphoproliferative malignancies that occur in transplant recipients. The disorders are associated with significant morbidity and mortality as well as increased rates of graft loss because of the reduced immunosuppression needed for treatment [1, 2]. Lung transplant patients appear to be at higher risk for PTLD, with an estimated incidence ranging from 3.4% to 9.4% compared with most other solid organ transplants, where the incidence ranges from 0.5% to 1.0% [3, 4]. Studies have identified Epstein-Barr virus (EBV) immune status mismatch—defined as EBV donor seropositive/recipient seronegative (D+/R−)—as the most significant risk factor for PTLD in lung transplant recipients [5, 6].

Although EBV D+/R− lung transplant recipients have a reported PTLD rate between 20% and 30%, EBV negative serologic status is not generally considered an absolute contraindication to transplant with an EBV positive donor, although some centers strongly prefer EBV negative donors for EBV negative recipients [3, 7, 8]. There are, however, few data to identify other pretransplant risk factors for and mortality from PTLD among EBV seronegative patients. Extrapolating from other solid organ transplants, younger age, white race, higher immunosuppressive load, higher human leukocyte antigen (HLA) mismatching, cytomegalovirus (CMV) serologic mismatch (CMV D+/R−), recipient human leukocyte antigen (HLA) Bw22, B18, or B21, and history of any pretransplant malignancy may increase the odds of PTLD among EBV D+/R− recipients [4, 6–10]. There are not, however, studies that identify the expected risk and survival impact of PTLD in the EBV D+/R− population to

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Abbreviations and Acronyms

CI = confidence interval
CMV = cytomegalovirus
D− = donor seronegative
EBV = Epstein-Barr virus
HLA = human leukocyte antigen
HR = hazard ratio
OR = odds ratio
PTLD = posttransplant lymphoproliferative disorder
R− = recipient seronegative
R+ = recipient seropositive
SRTR = Scientific Registry of Transplant Recipients

help guide the pretransplant decision to proceed with an EBV D+/R− lung transplant [11]. That is particularly important given the relative paucity of EBV negative donors and the potential increase in waitlist mortality when prioritizing an EBV negative offer.

The primary goal of this project was to identify pretransplant risk factors for and mortality from PTLD among EBV D+/R− lung transplant recipients. The secondary goal was to assess survival among EBV negative patients transplanted with EBV positive lungs compared with patients transplanted with EBV negative lungs. Our hypothesis was that rates of PTLD and mortality would be higher among EBV D+/R− patients compared with EBV D−/R− patients.

Patients and Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, United States Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. This was a retrospective cohort study of patients aged 18 years or more listed in the SRTR who underwent lung transplant from May 5, 2005 (the beginning of the lung allocation score era), through August 31, 2016. We excluded patients who received combined organ transplants. For patients who had multiple transplants, we only included the initial transplant and follow-up data available until retransplant, at which time they were censored.

Clinical and Sociodemographic Variables

We collected a mix of potential predictors for PTLD based on factors identified in other solid organ transplantation including donor and recipient EBV and CMV serologic status, donor and recipient ABO blood group, and recipient age, race, native lung disease, use of chronic steroids before transplant, and number of HLA donor-recipient mismatches [6–10]. We also recorded recipient sex, procedure type (bilateral or single lung transplant), the use of mechanical ventilation or extracorporeal membrane oxygenation before transplant, percent predicted forced vital capacity, and 6-minute walk distance before transplant.

Outcomes

For each patient, we recorded time to death or last status update, if alive. We also recorded whether PTLD occurred after transplant, the time from transplant to PTLD, and the time from PTLD to death or last status update, if alive.

Statistical Analysis

We used descriptive statistics to identify percentages, means and standard deviations, and medians and quartiles for selected demographic and clinical variables among EBV D+/R− patients. Because follow-up time was similar between the groups, we used a multivariate logistic regression to compare PTLD between EBV D+/R− and other patients, with age, race, native lung disease, and CMV D+/R− status treated as covariates.

We used χ^2 tests and Student's t tests (for normally distributed) or Wilcoxon rank sum tests (for nonnormally distributed) to compare demographic and clinical characteristics of EBV D+/R− patients who did and did not have PTLD after lung transplant. All variables associated with PTLD ($p < 0.20$) were then entered into a multivariate logistic regression. A backward stepwise selection procedure with a p value cutoff at 0.05 was applied to identify a set of factors associated with PTLD. We performed two additional sensitivity analyses, one using a Cox proportional hazards model to account for potential differences in follow-up time and one adding the use of cytolytic induction (antithymocyte globulin, alemtuzumab, muromonab-CD3) versus noncytolytic induction (no induction, basiliximab, dacluzumab) as covariates in the logistic regression model. The latter analysis was conducted given the association between cytolytic induction and PTLD in other solid organ transplants [11].

We conducted three survival analyses using Cox proportional hazard models. First, we examined the unadjusted and adjusted survival impact of PTLD on survival among EBV D+/R− patients. Second, we examined whether the risk factors for developing PTLD identified in our regression model were associated with increased unadjusted and adjusted risk for mortality after transplant. Third, we examined unadjusted and adjusted survival between EBV D+/R− patients and EBV D−/R− patients. We used Schoenfeld residuals to confirm the proportional hazard assumption for all models. All analyses were performed using STATA 14 (StataCorp, College Station, TX). The Institutional Review Board at Brigham and Women's Hospital approved this study.

Results

Study Cohort

There were 19,831 transplants performed during the study years, 4,476 (22.6%) of which were excluded