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Risk stratification to determine the impact of induction therapy on survival, rejection and adverse events after pediatric heart transplant: A multi-institutional study

Chesney Castleberry, MD,[a] Elizabeth Pruitt, MSPH,[b] Rebecca Ameduri, MD,[c] Kenneth Schowengerdt, MD,[d,e] Erik Edens, MD, PhD,[f] Nancy Hagin, BSN,[a] James K. Kirklin, MD,[b] David Naftel, PhD,[b] and Simon Urschel, MD[g]

From the [a]Department of Pediatric Cardiology, Washington University in St. Louis, St. Louis, Missouri, USA; [b]Department of Cardiovascular Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA; [c]Department of Pediatric Cardiology, University of Minnesota, Minneapolis, Minnesota, USA; [d]Department of Pediatric Cardiology, Cardinal Glennon Children's Hospital, St. Louis, Missouri, USA; [e]Department of Cardiology, Saint Louis University School of Medicine, St. Louis, Missouri, USA; [f]Department of Pediatrics, Division of Pediatric Cardiology, University of Iowa, Iowa City, Iowa, USA; and the [g]Department of Cardiac Sciences, University of Alberta, Edmonton, Alberta, Canada.

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BACKGROUND: Induction therapy is increasingly being used in pediatric heart transplantation. General versus risk-adapted use remains controversial. We aimed to determine the impact of induction therapy on outcomes after stratifying patients by diagnosis and risk.

METHODS: The Pediatric Heart Transplant Study (PHTS) database was used to identify patients (age $\leq$18 years) who underwent transplantation between January 1, 2001 and December 31, 2014. Patients were excluded if they survived $<$48 hours or received multiple induction agents. Patients were stratified using a multivariable model to predict 1-year mortality. Patients within the top 25% risk of predicted mortality were defined as high risk (HR) and the bottom 75% as low risk (LR).

RESULTS: Of the 2,860 patients studied, 1,370 received anti-lymphocyte antibody (ALA), 707 received an interleukin-2 receptor antagonist (IL-2RA) and 783 received no induction (NI) therapy. Overall, patients with NI had lower survival ($p < 0.01$); however, multivariable analysis did not demonstrate an association with graft loss. Freedom from rejection was greater among LR congenital heart disease (CHD) and all cardiomyopathy (CMP) patients who received induction therapy ($p < 0.01$, for both), as confirmed in a multivariable analysis for CMP patients. Frequency of graft vasculopathy was higher in LR CMP patients who received NI. Freedom from infection was lower with IL-2RA in the LR groups.

CONCLUSIONS: Pediatric heart transplant survival has improved in the recent era, in concert with increased use of induction therapy. Although induction therapy is associated with decreased rejection, it was not found to directly influence survival on multivariable analysis. Lower risk patients may benefit the most from induction therapy, particularly IL-2RA, which may be correlated with decreased infection and rejection in this cohort.

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Reprint requests: Chesney Castleberry, MD, Department of Pediatric Cardiology, Washington University in St. Louis, One Children's Place, St. Louis, MO. Telephone: 314-454-6095. Fax: 314-454-2561.
E-mail address: castleberry_c@kids.wustl.edu

Induction therapy, an intense peri-transplant immunosuppressive treatment, plays an emerging role in the post-operative management of patients requiring solid-organ

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transplantation. Currently, 74% of pediatric heart transplant patients in the United States receive induction therapy, up from 40% in 2002.[1] There are 2 agents currently being used for induction: (i) polyclonal antibody preparations, such as anti-thymocyte or anti-lymphocyte antibodies (ALA), which aim to deplete the majority of T cells; and (ii) monoclonal interleukin-2 receptor antagonists (IL-2RA), which temporarily block activation of T cells without permanently destroying them.[2] ALA are given more frequently than IL-2RA in pediatric heart transplant patients, but both are being used on an increasing basis.[3]

A recent review of registry data has demonstrated improved patient survival with use of ALA induction therapy compared with IL-2RA in adult heart transplant patients.[4] There was also improved survival in adult patients with any induction therapy in a cohort with increased risk of mortality after transplantation.[5] Despite these data, the use of induction therapy in the adult population has decreased, with only 50% of patients currently receiving induction therapy,[1] for unclear reasons, but possibly reflecting concerns about adverse impact on infections, tumors and peri-transplant management. The use of any induction therapy in the pediatric heart transplant population has been shown to correlate with a decrease in rejection during the first year after heart transplantation.[6] In addition, a recent study suggested that ALA induction was superior to IL-2RA in pediatric heart transplant patients.[7] Neither of these studies compared specific induction therapy to no induction or stratified patients based on individualized risk.

In this study we sought to determine the impact of induction therapy on post-transplant outcomes. The hypothesis was that induction therapy leads to overall improved patient and graft survival in high-risk patients, with ALA being superior to IL-2RA. Low-risk patients were expected to have similar survival with or without induction therapy and, possibly, benefit from lower rates of infection and post-transplant lymphoproliferative disorder (PTLD) without the use of induction.

Methods

The Pediatric Heart Transplant Study (PHTS) database was used to identify pediatric patients transplanted between January 1, 2001 and December 31, 2013, limiting the inclusion period to the more recent era. All patients were followed as of December 31, 2014 to provide a minimum of 1-year follow-up for all patients. The PHTS is a prospective, event-driven database that collects data from patients at 52 participating pediatric heart transplant centers (see Appendix). Era selected for the study was based on IL-2RA use in the registry. Institutional review board approval is maintained at each participating center.

Induction therapy is defined in the registry as "therapy soon after transplant not used to specifically treat known rejection." Furthermore, it is coded as a "yes" or "no" response, with specific agents listed. Patients were included in the study if they were identified as having received ALA, IL-2RA or no induction therapy (NI). Steroids are not defined as induction therapy in the registry and the use of steroids peri-operatively was not counted as induction. Patients were excluded if they were reported to have received both ALA and IL-2RA, but not if they received additional "other" immunosuppression agents ($N = 82$ for both induction agents and $N = 39$ for other induction agents). Other exclusion criteria were survival for <48 hours ($n = 15$), as there were disproportionate numbers of patients with no induction therapy, which may not reflect the intention to treat with patients dying before induction was initialized. Multi-organ transplants and retransplant patients were also excluded ($N = 215$).

Patients were then stratified into high- and low-risk groups based on predicted 1-year graft survival, calculated using the previously published multivariable logistic regression model of Schumacher et al.[8] Models are separate for patients with congenital heart disease and cardiomyopathy (C statistic = 0.63 and 0.73, respectively) and incorporate >40 donor and recipient characteristics. Characteristics included in the model equations are race, gender, diagnosis, blood urea nitrogen, panel-reactive antibody, ischemic time, donor age, donor inotropic support and year of transplant (Figure A1 in Appendix). High-risk (HR) patients were defined as those with the highest predicted 1-year mortality (top 25th percentile). All other patients were standard or low-risk (LR) and represented the lower risk quartiles with predicted 1-year mortality less than the 25th percentile. Mean predicted 1-year mortality was markedly higher in congenital heart disease (CHD) compared with cardiomyopathy (CMP) patients (7.4% for CMP, 24% for CHD; Figure A1 in Appendix). Risk stratification was validated by Kaplan–Meier survival analysis stratified by risk ($p < 0.01$ for both; Figure A2 in Appendix). This cohort partly overlapped with the training and validation cohorts from the Schumacher et al study, but differed by inclusion of a large proportion of more recent patients and exclusion of earlier patients.

The primary outcome of the study was overall graft survival. Secondary outcomes included incidence of coronary allograft vasculopathy (CAV, defined as abnormal coronary angiography), PTLD throughout the study period, rejection within the first year (defined as rejection by biopsy or other criteria leading to augmented immunotherapy) and infection within the first year (defined as evidence of an infectious process requiring intravenous therapy or a life-threatening infection requiring oral therapy).

Basic demographic information is presented as mean and standard deviation for normally distributed values or median and interquartile range when indicated. Univariate analysis was performed to determine differences in induction group with chi-square test for categorical variables and the independent t-test for continuous variables. Kaplan–Meier analysis was performed for graft survival as well as secondary outcomes, stratified by induction cohort. The log-rank test was used to determine overall and pairwise significant differences. Hazard ratio and multivariable analysis was performed to determine the impact of induction on outcomes and included variables found to be significant on univariate analysis. Early and constant phase hazard is represented separately in the multivariable analysis given the curvilinear relationship of mortality over time. Significance was set at $p < 0.05$. The analysis was performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Use of induction therapy

Among the 2,860 study patients who met the criteria, 1,370 (47.9%) received ALA, 707 (24.7%) received IL-2RA and 783 (27.4%) received NI. Overall use of induction therapy has risen in the most recent era, including increased use of both ALA and IL-2RA (60% during 2001 to 2008 vs 86%