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Outcomes in highly sensitized pediatric heart transplant patients using current management strategies

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BACKGROUND: Previous studies have suggested that children with pre-formed anti-HLA antibodies (PRA) undergoing orthotopic heart transplantation (OHT) have increased risk for rejection, coronary artery vasculopathy (CAV) and death. In 2005, our program started utilizing aggressive desensitization (including plasmapheresis, IVIg, pulse cytoxan and rituximab) with the goal of improving outcomes for these patients. The purpose of this study was to compare outcomes with this new strategy in recipients with pre-OHT high PRA (>10%) vs low PRA ≤10%).

METHODS: A retrospective study of 70 consecutive pediatric OHT patients was undertaken between January 2005 and July 2013 to identify patients with pre-OHT PRA >10% (high PRA), or PRA ≤10% (low PRA). Demographic/data information and detailed post-OHT outcomes, including rejection, 30-day and overall mortality, freedom from significant rejection, and CAV, were analyzed.

RESULTS: Fourteen (20%) patients had high PRA and 56 (80%) did not. There was a significant decrease in PRA values before and after desensitization. Thirty-day and overall mortality and the proportion of patients with rejections or CAV were lower in the high PRA group, although the difference was not statistically significant. Kaplan–Meier survival analysis revealed no significant difference in survival between the two groups. There was a significant difference in survival in our sensitized patients before 2005 vs after 2005.

CONCLUSIONS: We identified no significant differences in outcomes between high or low PRA patients. These preliminary findings may suggest improvement in OHT outcomes for high PRA patients as a result of aggressive desensitization. A larger study is warranted to confirm these findings.

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Having elevated panel-reactive antibodies (PRA) is considered a risk factor precluding orthotopic heart transplantation (OHT) at many institutions. An increase in early mortality after cardiac transplantation may be associated with donor human leukocyte antigen (HLA)-specific antibodies (DSA), elevated PRA, or positive post-transplant retrospective crossmatch. Increased frequency of acute

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allograft rejection and transplant coronary artery vasculopathy (CAV) have also been reported in sensitized patients.[1,2]

In 2004, Jacobs et al[3] described our outcomes data in pre-sensitized patients. One- and 5-year survival rates were sobering at 60% and 45%, respectively. In 2005, with the help of our regional histocompatibility laboratory (LifeLink Transplant Immunology Lab), we instituted an aggressive protocol of desensitization with the aim of improving outcomes in this subgroup of patients.

In this study we present our contemporary management strategy and outcomes data for children undergoing OHT with high PRA at All Children's Hospital/Johns Hopkins Medicine (St Petersburg, FL), after institution of the desensitization protocol.

Methods

This study was approved by the institutional review board of All Children's Hospital (IRB 13-0629). We retrospectively reviewed all cases of OHT from January 2005 to July 2013. During this period, 70 consecutive children underwent OHT. Demographic information and detailed post-transplant outcomes were analyzed. We also evaluated the incidence of opportunistic infections and infections that were severe enough to require hospitalizations. Our standard immunosuppression protocol for all patients includes induction therapy with polyclonal rabbit anti-thymocyte globulin (ATG; 0.5 to 1 mg/kg for 3 to 5 days), pulse solumedrol (7.5 mg/kg/dose every 12 hours for 4 days) and intravenous gammaglobulin (IVIg) 0.5 g/kg as a single dose. Calcineurin inhibitor therapy (usually tacrolimus) is delayed until the second or third post-operative day when renal function has normalized, and an anti-proliferative agent, usually mycophenolic acid, is started on the first post-operative day. In patients with recent infections or delayed sternal closure, we use basiliximab (interleukin-2 receptor blocker) in place of ATG. For pre-sensitized patients, the protocol is modified as follows:

1. PRA 11% to 50% with low levels of anti-HLA antibodies (mean fluorescent intensity [MFI] $<3{,}000$)—these patients receive weekly plasmapheresis and IVIg until transplant. Because effective plasmapheresis requires at least a 7Fr catheter, patients <10 kg undergo plasma exchange instead, at the time of transplant. If retrospective crossmatch is negative, we continue on the management pathway similar to that for non-sensitized patients, as described earlier. If the retrospective crossmatch is positive, we continue plasmapheresis (5 rounds) and monitor DSA levels closely. If the DSA levels are increasing rapidly, we administer rituximab. These patients continue to receive our standard immunosuppression protocol, as justr described.
2. PRA 11% to 50%, but MFI 3,000 to 7,000—from 2005 to 2009, these patients received monthly intravenous pulse cyclophosphamide 500 to 1,000 mg/m^2, weekly plasmapheresis and weekly IVIg until transplant, and 5 plasmapheresis procedures every other day post-transplant. Since 2009, we have preferred to use rituximab (375 mg/m^2 for four doses) in place of cyclophosphamide, due to the better side-effect profile and the parental anxiety regarding the use of a chemotherapeutic medication. If the retrospective crossmatch is negative and DSA is not high, we administer no further rituximab, and the patients receive the same standard protocol as the non-sensitized patients. If the retrospective crossmatch is positive, the patients completed the course of rituximab.
3. PRA $>50\%$ and/or high MFI $>7{,}000$—in these cases, in addition to the plasmapheresis and IVIg regimen noted in (2), patients also receive the 4-weekly course of rituximab.

As described in our previous report, we utilize the virtual crossmatch technique in all sensitized patients to assist in selection of an appropriate donor. A virtual crossmatch involves determination of the presence or absence of DSA in a patient by comparing the patients' HLA antibody specificities to the HLA profile of the proposed donor without carrying out a direct crossmatch, such as a flow-cytometric crossmatch (FCXM). HLA antibody specificities are determined by solid-phase assays (Luminex single-antigen beads) and, although these assays are not quantitative, laboratory-specific cut-offs are established that correlate, by themselves, or with an additive effect of multiple low-level DSA, to a positive or what we call an acceptable reactive crossmatch (ARC). In this case, there are DSA present, but at levels below the cut-off of the real crossmatch. Virtual crossmatch has allowed the expansion of donor pools, giving better access to transplant for those patients who are highly sensitized. In our program, post-transplant retrospective FCXM is also performed on all patients, regardless of PRA status. For patients on extracorporeal membrane oxygenation (ECMO), however, we accepted the first available organ, irrespective of virtual crossmatch results.

PRA is currently measured by flow cytometry using HLA Class I– and II–coated beads. Antibody specificities are determined by single-antigen Class I– and II–coated beads using Luminex technology. Rejection surveillance in these high-risk, sensitized patients is conducted by protocol endomyocardial biopsies at 2 weeks, 2 months, 4 months, 6 months, 9 months and 1 year, along with regularly scheduled echocardiograms. In our non-sensitized patients, biopsies are performed at 2 weeks, 3 months, 6 months and 1 year post-transplantation. Biopsy is also performed when the echocardiogram is suspicious for rejection. Rejection is defined as intensification of immunosuppression associated with an abnormal biopsy (International Society of Heart and Lung Transplantation [ISHLT] Grade $\geq$2R or $\geq$3A), or antibody-mediated rejection (AMR), and/or new-onset hemodynamic abnormalities confirmed by echocardiography.

Statistics

Descriptive statistics are reported as counts (percentages) for categorical variables and mean with standard deviation (SD), or median with range. Comparison between high PRA and low PRA patients was performed using Fisher's exact test for categorical variables and Wilcoxon–Mann–Whitney test for continuous variables. Kaplan–Meier survival analysis was used to evaluate the association between PRA status and overall mortality and a comparison between the curves was determined using the log-rank test. $p < 0.05$ was considered significant.

Results

Indications for transplantation included hypoplastic left heart syndrome (10 patients), cardiomyopathy (24 patients), other complex congenital heart diseases (25 patients), retransplantations (9 patients), and 1 patient with a large