Post-Transplant Malignancy after Pediatric Kidney Transplantation: Retrospective Analysis of Incidence and Risk Factors in 884 Patients Receiving Transplants Between 1963 and 2015 at the University of Minnesota

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BACKGROUND: Post-transplant malignancy (PTM) remains a concern among pediatric kidney transplant (PKT) recipients.

STUDY DESIGN: Between 1963 and 2015, 884 pediatric (age 0 to 17 years old) patients received 1,055 PKTs at our institution. Cox proportional hazards models were constructed to identify risk factors for PTM after PKT with time-to-first-PTM as a primary outcome. Secondly, the hazard of death or graft loss was calculated in patients who developed PTM.

RESULTS: Median patient survival was 33 years (interquartile range [IQR] 18.7 to 47 years); 260 patients died during the study period and 47 had been diagnosed with PTM. There were 235 PTMs that occurred in 136 (15.4%) recipients at a median age of 29 years (IQR 17.8 to 37 years). The percentages of patients with PTM were 13% at 20 years post-PKT and 26% at 30 years post-PKT. Of PTM patients who died, 63.8% died of PTM. Among those who developed PTM, there was a higher hazard of death or graft loss (hazard ratio [HR] 1.62; 95% CI 1.11 to 2.38). In multivariable proportional hazards models, factors associated with PTM were increasing age at PKT (adjusted HR [AHR] 3.14; 95% CI 1.80 to 5.48 for 14 to 17 year-olds compared with children less than 3 years), having a living unrelated donor (LURD; AHR 3.25; 95% CI 1.27 to 8.35 compared with a living related donor), or implanting an Epstein-Barr virus (EBV)-positive allograft in an EBV-negative recipient (AHR 5.66; 95% CI 1.11 to 29.0). Compared with the general population, the cancer rate for PKT recipients was 6 times higher (126 vs 21 per 100,000 person-years).

CONCLUSIONS: Pediatric kidney transplant recipients are at increased risk of PTM, which adversely affects survival. Children receiving transplants at an older age, from a LURD, or who receive an EBV-positive organ, should be monitored closely for the development of PTM. (J Am Coll Surg 2017;225:181−193. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

AHR = adjusted hazard ratio
ALG = Minnesota anti-lymphoblast globulin
ATGAM = polyclonal horse antithymocyte globulin
EBV = Epstein-Barr virus
HR = hazard ratio
IQR = interquartile range
LRD = living related donor
LURD = living unrelated donor
PKT = pediatric kidney transplant
PTLD = post-transplant lymphoproliferative disease
PTM = post-transplant malignancy
RDP = rapid discontinuation of prednisone
SEER = Surveillance, Epidemiology, and End Results

Kidney transplantation has become the standard of care for the treatment of children with end-stage renal disease. In the US, approximately 800 pediatric kidney transplants (PKT) are performed each year, and this number continues to increase,[1] especially due to the prioritization of children on the transplant waitlist through the new kidney allocation system. Given the long life expectancy for PKT recipients, long-term complications of kidney transplantation, such as malignancy, are concerning in patients who receive kidney transplants as children.

Post-transplant malignancy (PTM) is a known risk of immunosuppression, and thereby, transplantation.[2-6] Recent studies from large population registries of solid organ transplant recipients in Europe and the US have estimated the burden of PTM for transplant recipients.[7-11] Although the risk of infection-related cancers (post-transplant lymphoproliferative disease [PTLD], Kaposi's sarcoma, hepatocellular carcinoma, human papilloma virus [HPV]-related epithelial cancers, *Helicobacter pylori*-associated gastric malignancies, and some skin or lip malignancies) is especially high, noninfection-related cancers, such as kidney, colon, and lung are elevated among adult solid organ transplant recipients.[7,9-14]

In children who survive 10 years after PKT, PTM poses a significant burden of long-term morbidity and mortality.[15] It is estimated that approximately 11% to 18% of all post-PKT deaths can be attributed to PTM[16,17]—a percentage expected to rise with improvements in immunosuppression and allograft survival, exacerbated by poor global screening practices of adult cancers in PKT recipients.[18]

The most frequent PTM among PKT recipients is PTLD.[8] However, as more PKT recipients live into advanced age, they become susceptible to more adult-type, epithelium-derived cancers.[19] Therefore, understanding the incidence and the risk factors for developing PTM is paramount to improve post-transplant screening.

At the University of Minnesota, the first PKT was performed in 1963,[20] and we have prospectively maintained follow-up information on all donors and recipients. Herein, we present the incidence of PTM in our PKT population, describe the types of malignancies, and identify risk factors that may predispose patients to developing PTM.

METHODS

Participants and post-transplant outcomes

From 1963 to 2015, 884 pediatric recipients (age 0 to 17 years old) received their first solitary kidney transplant at the University of Minnesota. Complete outcomes data on first incidence of cancer after first transplant were available for 882 patients. Donor and recipient data were retrospectively reviewed using an IRB-approved database. For this study, we extracted information directly from the medical record including demographic, clinical, intraoperative, and postoperative data. Recipients (or their families) in our program are typically contacted every year and asked to provide an updated medical and psychosocial history, including development of new comorbidities and malignancies, and to send us any intervening pertinent results (laboratory, pathology) and information on new diagnoses, including malignancies. These data were used for this retrospective analysis. Patients were followed from first transplantation until last known alive date, for a median follow-up of 19.6 years (interquartile range [IQR] 9.3 to 29.8 years).

Immunosuppression protocols

Our immunosuppressive protocols have been described previously.[21-25] In brief, for the majority of the time period studied, each PKT recipient received quadruple therapy, which included a combination of an induction antibody (Minnesota anti-lymphoblast globulin [ALG], polyclonal horse antithymocyte globulin [ATGAM], or thymoglobulin); prednisone (maintenance or rapid discontinuation of prednisone [RDP]); azathioprine or mycophenolate mofetil, and cyclosporine or tacrolimus. Minnesota anti-lymphoblast globulin was given at 30 mg/kg/d for the first 14 post-kidney transplant days; ATGAM (Pharmacia—Upjohn) was given at 15 mg/kg per dose for 14 doses; thymoglobulin (polyclonal rabbit antithymocyte globulin [Genzyme Corp]) was given at 1.5 mg/kg per dose (per day) for 6 to 14 doses for recipients on steroid maintenance therapy or 5 to 7 doses for recipients undergoing RDP, with the first dose of thymoglobulin given intraoperatively. For recipients on steroid maintenance therapy, prednisone was started at