Post-transplant lymphoproliferative disease may be an adverse risk factor for patient survival but not graft loss in kidney transplant recipients

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Better prognostication of graft and patient outcomes among kidney transplant recipients with post-transplant lymphoproliferative disease (PTLD) in the rituximab era is needed to inform treatment decisions. Therefore, we sought to estimate the excess risks of death and graft loss in kidney transplant recipients with PTLD, and to determine risk factors for death. Using the ANZDATA registry, the risks of mortality and graft loss among recipients with and without PTLD were estimated using survival analysis. A group of 367 patients with PTLD (69% male, 85% white, mean age 43 years) were matched 1 to 4 to 1468 controls (69% male, 88% white, mean age 43 years), and followed for a mean of 16 years. Recipients with PTLD experienced poorer 10-year patient survival (41%, 95% confidence intervals 36-47%) than controls (65%, 63-68%). Excess mortality occurred in the first 2 years post-transplant (hazard ratio 8.5, 6.7-11), but not thereafter (1.0, 0.76-1.3). Cerebral lymphoma (2.0, 1.3-3.1), bone marrow disease (2.0, 1.2-3.3) and year of diagnosis prior to 2000 (2.2, 1.4-3.5; after 2000 reference) were risk factors of death. PTLD did not confer an excess risk of graft loss (1.08, 0.69-1.70). Thus, PTLD is a risk factor for death, particularly in the first two years after diagnosis. Cerebral or bone marrow diseases were associated with increased mortality risk, but overall survival in the rituximab era (post 2000) has improved.

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Posttransplant lymphoproliferative disease (PTLD) is a well known complication of kidney transplantation, but the impact of PTLD on long-term patient and graft outcomes is not well described. Early reports (prior to 2000)[1–3] indicated a 5-year patient survival rate after initial diagnosis of around 40%. Contemporary data from observational studies suggest that the 5-year survival rate has improved to around 50%, owing to the addition of chemotherapies, such as rituximab,[4] and other novel therapies, such as immunotherapy. However, few studies are available on whether this trend continued beyond 2010 or over extended follow-up periods.[5–7] In addition, uncertainties remain regarding site-specific survival.[2,8–10]

Comparative analyses have revealed a 14- to 17-fold greater risk of death among adult transplant recipients who developed PTLD, compared with recipients who did not develop PTLD.[11–15] However, some studies may not have accounted for lead-time bias, thereby underestimating the hazard. In addition, the matching to controls was limited to age, race, and gender (at most).[11,12] Interpretation of these results was also restricted by small sample sizes, short follow-up times, unrepresentative controls, and bias from residual confounding.

The study was designed with two goals. The primary aim was to determine the excess risk of all-cause death and allograft loss among pediatric and adult kidney transplant recipients who had PTLD. The study also aimed to determine risk factors for death after diagnosis of PTLD.

RESULTS

A total of 23,415 patients received transplants during the time period from 1969 through 2015. Of these, 395 patients developed PTLD during their first transplant, between 1990 and 2015. In total, 367 cases were matched 1:4 to 1468 controls (Supplementary Figure S1). The mean follow-up time was 16 years (SD 7.6 years), with 29,515 person-years of follow-up.

Baseline characteristics

No significant differences were found between cases and controls for the following: mean age at transplant (43 vs. 43

years); male gender (69% vs. 69%); 0–3 human leukocyte antigen mismatches (70% vs. 70%); living donor status (22% vs. 22%); recipients with comorbidities (29% vs. 29%); and race (white 85% vs. 88%). However, a greater proportion of recipients with glomerulonephritis as the cause of end-stage kidney disease (ESKD; 53% vs. 44%) and with negative Epstein Barr virus serology at transplant (40% vs. 20%) had PTLD, compared with those without (Table 1).

For those with PTLD, diagnosis occurred at a median age of 54 years (interquartile range [IQR] 41–62 years). Extra-nodal disease was most common (241 of 367; 66% [62%–72%]), with early disease (diagnosis in the first year after transplant) occurring in 53 of 367 (14% [11%–19%]), and 65 of 367 (18% [14%–22%)] having metastases at diagnosis.

Mortality for transplant patients with versus without PTLD

The overall survival rate after diagnosis of PTLD was 62.5% (57.8%–67.7%) at 1 year, 34% lower than controls (1-year survival of 96.3% [95.3%–97.2%]). At 10 years, the survival rate was 41.2% (36.0%–47.1%) in those with PTLD, 24% less than in controls (10-year survival of 65.3% [62.6%–68.2%]; Figure 1a).

Compared with controls, patients who had PTLD experienced an increased risk of mortality, which was confined to the first 2 years after diagnosis (hazard ratio [HR] 8.53 [6.65–10.9], $P < 0.001$), with no differences in mortality observed thereafter (HR 0.97 [0.76–1.24], $P = 0.81$).

Causes of death after PTLD

Of those who developed PTLD during their first transplant, 220 of 367 (60% [55%–65%]) patients died, 67% ([61%–73%], 148/220) due to cancer. The most common other causes of death were cardiovascular disease (26/220, 12% [8%–17%]) and infection (23/220, 11% [7%–15%]).

In the first 2 years after transplant, 79% ([72%–85%], 123/156) of deaths were attributed to PTLD, compared with 40% (27%–52%], 25/64) after 2 years ($P < 0.001$). Overall, death from PTLD occurred much earlier (median 3 months, IQR 0.6–12 months) than death from other causes (30 months, IQR 3–100 months). The median age at death was 61 years (IQR 48–67 years).

Site-specific mortality

For patients with nodal disease, 51% ([42%–60%], 62/122) died, with a median time to death of 9 months (IQR 1–67 months). Mortality was 65% ([60%–71%], 160/245) for extra-nodal disease, at a median time of 5 months (IQR 1–30 months). Those with bone-marrow/reticuloendothelial disease had the highest mortality (21/28, 75% [57%–87%]) and the shortest time from diagnoses until death (1 month, IQR 0–6 months; Figure 2; Supplementary Table S1).

Predictors of mortality after PTLD

Univariable hazard ratios of risk factors for mortality are presented in Supplementary Table S2. Survival was contingent on the site of PTLD, with nodal PTLD displaying the best survival rate (5-year survival of 64% [55%–73%]), and bone-marrow PTLD the worst (5-year survival of 23% [12%–46%]; Figure 2). Age at diagnosis was also a predictor on univariable analysis, with age <20 years associated with a 5-year survival rate of 91% (80%–100%) compared with 31% (23%–40%) for those aged >60 years (Figure 3). In addition, year of diagnosis was associated with poorer prognosis, with diagnosis in 1990–1999 having a 5-year survival rate of 43%

Table 1 | Characteristics of cases with posttransplant lymphoproliferative disease and their matched controls

Variable	PTLD	No PTLD	*P* value
Recipient			
Total number	367	1468	
Male	252 (69)	1008 (69)	>0.95
White	323 (85)	1253 (88)	0.20
Cause of ESKD			0.02
Glomerulonephritis	192 (53)	646 (44)	
Cystic	43 (11)	225 (15)	
Other	131 (36)	593 (41)	
EBV serology negative	75 (40)	156 (20)	<0.001
Any comorbidity	105 (29)	420 (29)	>0.95
Diabetes	52 (15)	182 (13)	
Cerebrovascular disease	17 (05)	48 (03)	
Peripheral vascular disease	25 (08)	73 (05)	
Coronary disease	50 (14)	197 (15)	
Transplant			
Age at transplant (yr)			0.93
0–19	36 (10)	129 (09)	
20–39	100 (27)	415 (28)	
40–59	179 (49)	721 (49)	
60+	52 (14)	203 (14)	
Living donor	81 (22)	324 (22)	>0.95
HLA mismatch			0.64
0–3	247 (70)	961 (70)	
4–6	105 (30)	434 (30)	
Era			>0.95
1969–1987	40 (11)	166 (11)	
1988–1993	115 (32)	446 (31)	
1994–2000	111 (30)	444 (30)	
2001–2015	101 (27)	412 (28)	
Baseline immunosuppression			0.60
Tac/MMF/Pred	39 (11)	176 (12)	
Cyc/MMF/Pred	81 (22)	350 (24)	
Cyc/Aza/Pred	153 (42)	568 (40)	
Other	89 (25)	341 (24)	
PTLD			
Age at PTLD (yr)	54 (41–62)		
Years to PTLD	8 (4–13)		
Site of disease			
Nodal	122 (34)		
Extra-nodal	241 (66)		
CNS	44 (12)		
Graft	16 (4)		
Bone marrow	28 (8)		
Extra-nodal other	153 (42)		
PTLD era			
1990–1999	90 (25)		
2000–2009	198 (54)		
2010–2015	79 (21)		
Early disease (<= 1 year posttransplant)	53 (14)		
Metastases at diagnosis	65 (18)		

Aza, azathioprine; CNS, central nervous system; Cyc, cyclosporine; EBV, Epstein Barr virus; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; MMF, mycophenolate; pred, prednisone; PTLD, posttransplant lymphoproliferative disease; Tac, tacrolimus.
Values are n (%) or median (interquartile range), unless otherwise indicated. Missing data: EBV = 854; comorbidity = 81; HLA mismatch = 101; site of disease = 4.