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Post-transplant lymphoproliferative disorder in pediatric heart transplant recipients

Cedric Manlhiot, BSc,[a] Stacey M. Pollock-BarZiv, PhD,[b] Claire Holmes, BSc,[a] Sheila Weitzman, MD,[c] Upton Allen, MD,[d] Nadia A. Clarizia, BSc,[a] Bo-Yee Ngan, MD,[e] Brian W. McCrindle, MD, MPH,[a] and Anne I. Dipchand, MD[a,b]

From the [a]Labatt Family Heart Centre, [b]SickKids Transplant Centre, [c]Division of Haematology/Oncology, [d]Division of Infectious Diseases and [e]Division of Pathology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

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Epstein-Barr virus;
antiviral prophylaxis;
induction therapy;
immunosuppression

BACKGROUND: Post-transplantation lymphoproliferative disorder (PTLD) is a major cause of morbidity and mortality after pediatric heart transplantation.

METHODS: Heart transplant recipients at The Hospital for Sick Children, Toronto, from 1990 to May 2008, were reviewed. Competing risk hazard analysis was used to model the natural history of the disease. Patients were matched for gender and duration of follow-up to identify potential covariates associated with increased risk of PTLD.

RESULTS: A total of 173 heart transplant recipients (42% <1 year old) were reviewed. Twenty-three developed PTLD at a median of 4 years post-transplantation. After transplantation, PTLD affected 9%, 15% and 28% at 3, 5 and 10 years, respectively. Freedom from death or PTLD recurrence was 72%, 58% and 50% at 1, 3 and 5 years, respectively, after PTLD diagnosis. Higher maximum Epstein–Barr viral (EBV) load (hazard ratio [HR]: 2.6, $p = 0.004$) and longer duration of induction therapy (HR: 1.7, $p = 0.02$) were associated with increased risks of PTLD. Higher cumulative cyclosporine doses over the first year post-transplantation were associated with increased risks of PTLD (HR: 1.2 per 1 mg/kg/day equivalent, $p = 0.03$), but higher tacrolimus doses were not ($p = 0.38$). Patients on cyclosporine at 6 months post-transplantation were at higher risk of PTLD than those on tacrolimus (HR: 5.2, $p = 0.003$). The use of anti-viral prophylaxis in patients with high EBV load may provide some protection (HR: 7.6 vs 15.4 with no anti-viral, $p = 0.02$).

CONCLUSIONS: PTLD is a major concern in pediatric heart transplant recipients and is associated with high morbidity/mortality. Exposure to EBV and higher intensity of immunosuppression seems to be associated with increased risk.

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Post-transplant lymphoproliferative disorder (PTLD) is a major cause of morbidity and mortality in pediatric heart transplant recipients, affecting approximately 10% of surviving patients 10 years after transplantation.[1,2] PTLD-related mortality is high, with approximately 70% of patients surviving 5 years after diagnosis. The condition confers significant risk of graft rejection and subsequent graft loss as a result of the reduced immunosuppression necessary for treatment.[2] PTLD encompasses a spectrum of malignancies occurring after solid-organ transplantation. Most often, after pediatric transplantation, these malignancies involve the proliferation of Epstein–Barr virus (EBV)-infected B cells left unchecked by EBV-specific cytotoxic T cells due

Reprint requests: Anne I. Dipchand, MD, Labatt Family Heart Centre, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada. Telephone: 416-813-6674. Fax: 416-813-7885.
E-mail address: anne.dipchand@sickkids.ca

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Table 1 Demographics and Clinical Characteristics of Heart Transplant Patients With PTLD ($n = 23$) and Without PTLD ($n = 150$)

	N	PTLD ($n = 23$)	*N*	No PTLD ($n = 150$)	*p*
Demographics					
Median age at transplantation (years)		0.6 (0.01–14.1)		2.3 (0.01–19.3)	0.05
Neonates (<30 days)		5 (22%)		12 (8%)	0.06
Infants (30 days to 1 year)		7 (30%)		49 (33%)	1.00
Children (1 year to 10 years)		7 (30%)		42 (28%)	0.81
Adolescents (>10 years)		4 (17%)		47 (31%)	0.23
Gender (male)		14 (61%)		86 (57%)	0.83
Etiology					0.82
Congenital, including EFE (1) and cardiac tumor (2)		14 (61%)		98 (65%)	
Cardiomyopathy		9 (39%)		52 (35%)	
Year of transplantation					
Before 1995		5 (22%)		8 (5%)	0.02
1995–1997		4 (17%)		32 (21%)	0.79
1998–2000		9 (39%)		33 (22%)	0.12
2001–2003		2 (9%)		35 (23%)	0.17
2004–2006		3 (13%)		42 (28%)	0.20
HLA-sensitized		1 (5%)		18 (12%)	0.48
Blood group (recipient)					
A		6 (26%)		65 (43%)	0.17
B		3 (13%)		16 (11%)	0.62
0		14 (61%)		64 (43%)	0.12
AB		0 (0%)		5 (3%)	1.00
ABO-incompatible transplantation		5 (22%)		30 (20%)	0.79
Rhesus-incompatible transplantation		3 (13%)		16 (11%)	0.72
EBV status					
<1 year old at transplantation	10		43		
Recipient-negative/donor-negative (R^-/D^-)		8 (80%)		17 (40%)	0.04
Recipient-negative/donor-positive (R^-/D^+)		2 (20%)		26 (60%)	.
>1 year old at transplantation	9		63		
Recipient-negative/donor-negative (R^-/D^-)		1 (11%)		11 (17%)	1.00
Recipient-positive/donor-negative (R^+/D^-)		1 (11%)		4 (6%)	1.00
Recipient-negative/donor-positive (R^-/D^+)		4 (44%)		14 (22%)	0.22
Recipient-positive/donor-positive (R^+/D^+)		3 (33%)		34 (54%)	0.30
EBV-positive at last follow-up	21	21 (91%)	134	81 (60%)	0.004
CMV status					
<1 year old at transplantation	12		50		
Recipient negative/donor negative (R^-/D^-)		8 (75%)		29 (58%)	0.75
Recipient negative/donor positive (R^-/D^+)		4 (25%)		21 (42%)	
>1 year old at transplantation	11		76		
Recipient-negative/donor-negative (R^-/D^-)		5 (45%)		24 (32%)	0.50
Recipient-positive/donor-negative (R^+/D^-)		1 (9%)		16 (21%)	0.68
Recipient-negative/donor-positive (R^-/D^+)		1 (9%)		24 (32%)	0.27
Recipient-positive/donor-positive (R^+/D^+)		4 (36%)		12 (16%)	0.11
Induction					
RATS		19 (86%)		86 (57%)	0.03
Median days on RATS		6 (2–23)		6 (2–26)	0.23
Thymoglobulin		4 (17%)		60 (40%)	0.04
Median days on Thymoglobulin		4 (3–6)		4 (1–18)	0.89
No induction		0 (0%)		4 (3%)	1.00
Immunosuppression and medication					
Cyclosporine at transplantation[a]		15 (65%)	137	68 (50%)	0.26
Tacrolimus at transplantation[a]		12 (52%)	137	92 (67%)	0.16
Steroids at transplantation[b]		22 (96%)	137	132 (96%)	0.55
Steroids at 1 year post-transplantation	21	15 (71%)	130	56 (43%)	0.02
Azathioprine[b]		14 (61%)	137	77 (56%)	0.82
Mycophenolate mofetil[b]		11 (48%)	137	97 (71%)	0.03
Acyclovir/gancyclovir[b]		3 (13%)	137	50 (36%)	0.10
Rituximab[b]		3 (13%)	137	15 (11%)	0.73

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