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Posttransplant Lymphoproliferative Disorder in Adults Receiving Kidney Transplantation in British Columbia: A Retrospective Cohort Analysis

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Abstract

Background: Posttransplant lymphoproliferative disorder (PTLD) is a major complication following kidney transplantation.
Objective: We undertook this study to characterize PTLD in kidney transplant patients in British Columbia with regard to incidence, patient and graft survival, histological subtypes, treatment modalities, and management of immunosuppression.
Design: Retrospective cohort analysis.
Setting: British Columbia.
Patients: All adult patients who underwent kidney transplantation in British Columbia between January 1, 1996, and December 31, 2012, were included. Patients less than 18 years of age at the time of first transplant and multiple organ transplant recipients were excluded from analysis.
Measurements: Patients with lymphoproliferative disorders that occurred subsequent to kidney transplantation were considered to have developed PTLD.
Methods: Cases of PTLD were identified by cross-referencing data abstracted from the provincial transplant agency's clinical database with the provincial cancer agency's lymphoma registry. Patients were followed up for the development of PTLD until December 31, 2012, and for outcomes of death and graft failure until December 31, 2014. Data collection was completed via an electronic chart review.
Results: Of 2217 kidney transplant recipients, 37 (1.7%) developed PTLD. Nine cases were early-onset PTLD, occurring within 1 year of transplant; of these cases, 6 were known/presumed Epstein-Barr virus mismatch, compared with only 2 of 28 late-onset cases. Patient survival for early-onset PTLD was 100% at 2 years post diagnosis. Late-onset PTLD had survival rates of 71.4% and 67.9% at 1 and 2 years, respectively. PTLD was associated with significantly decreased patient survival (P = .031) and graft survival (uncensored for death, P = .017), with median graft survival of PTLD and non-PTLD patients being 9.5 and 16 years, respectively. Immunosuppressant therapy was reduced in the majority of patients; additional therapies included rituximab monotherapy, CHOP-R, radiation, and surgery.
Limitations: Limitations to this study include its retrospective nature and the unknown adherence of patients to prescribed immunosuppressant regimens. In addition, cumulative doses of immunosuppression received and the degree of immunosuppression reduction for PTLD management were not effectively captured.
Conclusions: The incidence of PTLD in British Columbia following kidney transplantation was low and consistent with rates reported in the literature. The incidence of late-onset PTLD and its association with reduced patient and graft survival warrant further analysis of patients' long-term immunosuppression.

Abrégé

Contexte: Le syndrome lymphoprolifératif post-greffe (SLPG) est une complication grave survenant à la suite d'une transplantation rénale.
Objectif de l'étude: Nous avons mené cette étude afin de caractériser le SLPG chez les receveurs d'une greffe rénale en Colombie-Britannique en ce qui a trait à son incidence, à la survie du patient et du greffon, aux sous-types histologiques, aux modalités de traitement et à la gestion de l'immunosuppression.
Cadre et type d'étude: Il s'agit d'une étude de cohorte rétrospective effectuée en Colombie-Britannique.

Sujets: Ont été inclus dans l'étude tous les patients adultes ayant subi une transplantation rénale entre le 1er janvier 1996 et le 31 décembre 2012 en Colombie-Britannique. Les patients âgés de moins de 18 ans au moment de l'intervention et les patients receveurs de greffe de multiples organes ont été exclus.
Mesures: Tout cas de SL apparu après une greffe rénale étaient considérés comme un SLPG.
Méthodologie: Les cas de SLPG ont été répertoriés en recoupant les données extraites de la base de données cliniques de l'agence provinciale de transplantation avec les données du registre des lymphomes tenu par l'agence provinciale de lutte contre le cancer. Les participants ont été suivis jusqu'au 31 décembre 2012 pour l'apparition du SLPG et jusqu'au 31 décembre 2014 pour les issues défavorables telles que la mort du patient ou le rejet du greffon. L'examen du dossier électronique des patients a complété la collecte des données.
Résultats: Des 2 217 receveurs d'une greffe rénale répertoriés, seuls 37 (1,7 %) ont développé un SLPG. L'apparition du SLPG s'est faite de façon précoce, soit dans la première année post-greffe, pour neuf de ces patients, dont six représentaient un cas connu ou présumé de non-concordance pour le virus d'Epstein Barr (EBV). En comparaison, seuls deux des 28 patients ayant expérimenté un développement tardif du SLPG étaient présumés non-concordants pour l'EBV. Deux ans après le diagnostic, 100 % des patients ayant eu une apparition précoce du SLPG avaient survécu. Dans les cas de développement tardif de la maladie, le taux de survie passait à 71,4 % après un an et à 67,9 % après deux ans pour les patients. Le développement du SLPG a été associé avec une réduction significative de la chance de survie du patient ($p = 0,031$) et du greffon ($p = 0,017$, cas de décès non censurés). La survie médiane du greffon était de 9,5 ans pour les patients ayant développé un SLPG alors qu'elle était de 16 ans pour les autres. L'intensité du traitement immunosuppresseur a pu être réduite pour la majorité des patients. Les traitements additionnels incluaient la monothérapie au rituximab, le R-CHOP, la radiation et la chirurgie.
Limites de l'étude: La nature rétrospective de l'étude est un facteur limitant la portée de nos résultats, de même que l'absence de données sur l'adhérence des patients au traitement immunosuppressif. De plus, nous n'avons pu mesurer précisément les doses cumulatives d'immunosuppresseurs reçues, ni le degré de réduction de ces derniers dans la prise en charge du SLPG.
Conclusion: En Colombie-Britannique, l'incidence du SL post-greffe rénale s'est avérée faible et cohérente avec les taux rapportés dans la littérature. L'incidence de l'apparition tardive du SLPG et son association à un taux et une durée de survie amoindris (à la fois pour le patient et pour le greffon) justifient une analyse plus poussée de l'immunosuppression à long terme dans la population en question.

Keywords
posttransplant lymphoproliferative disorder, PTLD, lymphoproliferative disorders, kidney transplant

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What was known before

Posttransplant lymphoproliferative disorder is a complication following kidney transplantation that can seriously threaten long-term outcomes, including overall patient and graft survival.

What this adds

This research adds to the existing Canadian literature on the topic by presenting updated epidemiological data on posttransplant lymphoproliferative disorder in adult kidney transplant patients in British Columbia.

Introduction

Graft function and patient survival immediately following transplantation have improved dramatically since the early days of kidney transplantation, yet a number of complications still threaten long-term outcomes. Immunosuppression following transplantation is known to increase the risk of malignancy; posttransplant lymphoproliferative disorder (PTLD) is among the more common malignancies diagnosed.[1-3] Specifically, lymphoproliferative disorders occur greater than 10 times more frequently in kidney transplant recipients than in the general population.[4,5] PTLD is a heterogeneous disorder, ranging from very indolent to very aggressive.[3,6] Given

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this diversity, reported survival rates can be highly variable.[1] However, lymphomas in the aggregate have tended to be aggressive in nature and often poorly responsive to treatment, resulting in 5-year survival rates of less than 40%.[7]

Treatment options for PTLD vary based on the disease subtype and may include rituximab monotherapy, rituximab with concurrent or sequential chemoimmunotherapy, radiation, or surgery.[8-11] The almost universal initial step is the reduction in immunosuppression with the reported response rates ranging from 25% to 63%.[12] Balancing mortality risk with PTLD and risk of graft rejection in the setting of reduced immunosuppression is a challenge for clinicians.[13,14]

In British Columbia (BC), the incidence of lymphoproliferative disorders following kidney transplant in a cohort of patients transplanted between 1986 and 1989 was last reported to be 1.26% in the late 1980s.[15] Since then, mycophenolate has largely replaced azathioprine as the antimetabolite of choice and, whenever possible, immunosuppression intensity has been reduced. Rapid steroid elimination protocols following kidney transplant have also since been incorporated into common practice. Whether these factors have any mediating effect on PTLD in this population is not known.

The purpose of this study was to characterize PTLD in kidney transplant patients in BC with regard to incidence, patient and graft survival, histological subtypes, treatment modalities, and management of immunosuppression.

Methods

Study Population and Study Design

This retrospective database study reviewed adult patients who underwent kidney transplantation in BC between 1996 and 2012. The study protocol was approved by the University of British Columbia Clinical Research Ethics Board and the Vancouver Coastal Health Research Institute. The institutional review bodies waived the need for informed consent.

A list of all patients who received a kidney transplant between January 1, 1996, and December 31, 2012, was generated from the clinical database of the provincial transplant agency (BC Transplant). The database includes transplant-related information on all renal transplant patients who have been seen by a transplant nephrologist in BC. This time period was selected to minimize confounding of PTLD incidence and survival by era of immunosuppression, as mycophenolate became the antimetabolite of choice in immunosuppressant protocols in BC starting in 1996. Patients less than 18 years of age at the time of first transplant and multiple organ transplant recipients were excluded from analysis.

To identify patients who developed PTLD, this list was cross-referenced with the British Columbia Cancer Agency (BCCA) registry of all patients with lymphoma diagnoses. The data in this registry are obtained from a population-based provincial arm of the Canadian national cancer registry, which is certified annually by the North American Association of Central Cancer Registries. Lymphoma diagnoses throughout the study period were coded according to World Health Organization (WHO) International Classification of Diseases for Oncology criteria by trained cancer registry abstractors. Data collection was completed via an electronic chart review. Patients were considered to have developed PTLD if the date of first kidney transplant preceded the date of lymphoma diagnosis. Patients were followed up for analysis of incident PTLD until December 31, 2012, and for outcomes of death and graft failure until December 31, 2014.

Statistical Analysis

Continuous variables were analyzed using the *t* test for independent samples. Associations between categorical variables were tested for using the chi-square test and the Fisher exact test (Table 1). Results were considered statistically significant if P values were $<.05$. The aforementioned tests were conducted using XLSTAT Version 2016.05. Overall survival rates and graft survival were compared between PTLD and non-PTLD groups using Kaplan-Meier survival estimates (Figures 1 and 2). Patient survival was calculated from the date of transplant to the date of death by any cause or date of last follow-up. Graft survival was uncensored for death and calculated from the date of transplant to the date of graft failure or death. Fleming-Harrington and log-rank tests were used to compare survival distributions between PTLD and non-PTLD patients for patient and graft survival, respectively. Differences were determined to be statistically significant if P values were $<.05$. Survival analyses were performed using RStudio version 0.99.903.

Results

Of the 2217 adult patients identified by BC Transplant, 45 were identified by BCCA as also having lymphoma diagnoses within this time period. Of these patients, 7 had lymphoma diagnoses that predated their kidney transplants and did not go on to develop PTLD, and 1 patient's lymphoma diagnosis was an indolent small B-cell lymphoma. Thus, 37 of 2217 patients (1.7%) were found to have had PTLD diagnoses.

Demographic data of the 37 patients with PTLD and the 2180 patients who did not develop PTLD are summarized in Table 1. Characteristics among the PTLD patients were not statistically different from the kidney transplant patients who did not develop PTLD. Time to PTLD diagnosis ranged from 2.9 to 166 months (median 63 months) post transplant; additional characteristics of the patients who developed PTLD are presented in Table 2. Nine cases were early-onset PTLD; all others were considered late-onset cases. Of the early-onset cases, 6 were known or presumed to be EBV mismatched. Conversely, only 2 of 28 late-onset cases were EBV mismatched.

Table 1. Demographic Data of Kidney Transplant Patients Who Developed PTLD (n = 37) and Those Who Did Not (n = 2180).

Characteristic	PTLD (n = 37) n (%)	No PTLD (n = 2180) n (%)
Male gender	24 (64.9)	1330 (61.0)
Mean age at transplant, years (range)	46.6 (18-70)	49 (18-80)
Mean age at PTLD diagnosis, years (range)	52.3 (19-78)	NA
Ethnicity		
Caucasian	27 (73.0)	1437 (65.9)
Asian	7 (18.9)	402 (18.4)
Other	3 (8.1)	341 (15.6)
Serology		
EBV mismatch	6 (16.2)	100 (4.6)
Presumed EBV mismatch	2 (5.4)	25 (1.1)
Induction therapy		
Anti-IL-2-receptor antibodies	19 (51.4)	1259 (57.8)
ATG	2 (5.4)	270 (12.4)
OKT3	1 (2.7)	39 (1.8)
None	15 (40.5)	612 (28.1)
Prednisone Rx at discharge	27 (73.0)	1281 (58.8)
Donor type—deceased	15 (40.5)	1032 (47.3)

Notes. EBV serology categorized as "EBV mismatch" refers to cases in which the donor was EBV positive and the recipient EBV negative; "presumed EBV mismatch" refers to cases where no EBV serology data were available on the donor and the recipient was EBV negative. Induction therapy categorized as "none" refers to cases in which the patient did not receive ATG, OKT3, basiliximab, or daclizumab within the first 5 days post transplant. There were no significant differences between the groups. EBV = Epstein-Barr virus; PTLD = posttransplant lymphoproliferative disorder; ATG = antithymocyte globulin; OKT3 = muromonab-CD3; NA = not applicable.

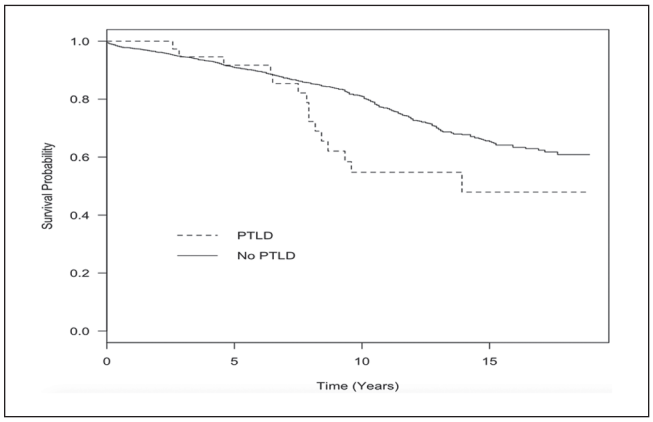

Figure 1. Kaplan-Meier survival analysis comparing overall survival from the time of transplant of patients who received at least 1 kidney transplant between January 1, 1996, and December 31, 2012, who went on to develop PTLD (n = 37) with patients who received a transplant during the same time period but did not develop PTLD (n = 2180).
Notes. Overall survival was significantly worse in patients with PTLD compared with patients without PTLD (Fleming-Harrington test, P = .031). PTLD = posttransplant lymphoproliferative disorder.

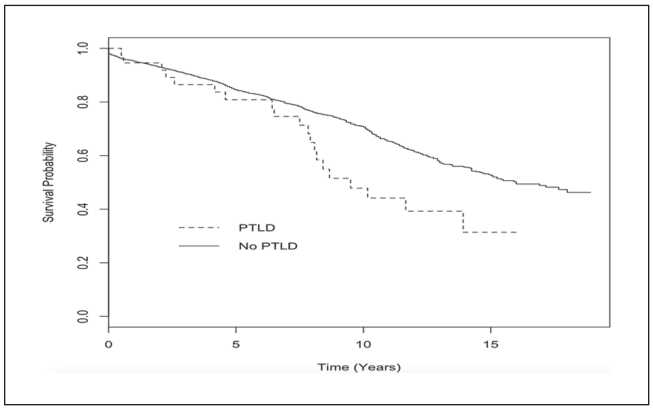

Figure 2. Kaplan-Meier survival analysis comparing graft survival from the time of transplant, uncensored for death, of patients who received at least 1 kidney transplant between January 1, 1996, and December 31, 2012, who went on to develop PTLD (n = 37) with patients who received a transplant during the same time period but did not develop PTLD (n = 2180).
Notes. Graft survival was significantly worse in patients with PTLD compared with patients without PTLD (log-rank test, P = .017). PTLD = posttransplant lymphoproliferative disorder.

The primary sites, treatment modalities, and outcomes of patients with diffuse large B-cell lymphoma (DLBCL), polymorphic PTLD, and multiple myeloma are described in Tables 3, 4, and 5, respectively. The same categories of information are presented for the patients with other types of PTLD in Table 6. For most patients, PTLD management also included a reduction of immunosuppression.

Twenty-six patients developed DLBCL, of which 23 patients were treated with rituximab. Of the patients treated with rituximab, 13 received rituximab monotherapy, and 10

Table 2. Characteristics of Kidney Transplant Patients With PTLD (n = 37).

Patient ID	Gender	Ethnicity	Primary diagnosis	Year of transplant	Age at transplant	Donor type	EBV status	Induction therapy	Age at PTLD diagnosis	Time to PTLD diagnosis (years)
1	F	Caucasian	Polycystic kidney disease	1997	52	NDD	No mismatch	OKT3	61	9.25
2	M	Caucasian	Polycystic kidney disease	2001	59	LD	No mismatch	None	67	7.92
3	M	Caucasian	Glomerulonephritis	1998	44	LD	No mismatch	None	50	6.83
4	F	Caucasian	Polycystic kidney disease	2001	62	NDD	No mismatch	None	73	11.5
5	M	Caucasian	FSGS	2009	49	NDD	No mismatch	Basiliximab	52	3.17
6	M	Caucasian	T2DM	2003	58	LD	No mismatch	Basiliximab	66	8.42
7	M	Caucasian	Polycystic kidney disease	2002	62	NDD	No mismatch	Basiliximab	66	4.58
8	F	Asian	Lupus nephritis	1999	35	LD	No mismatch	None	46	11.5
9	F	Caucasian	CKD, unknown etiology	2006	60	LD	No mismatch	Basiliximab	63	3.08
10	M	Caucasian	Hypertension	1998	52	NDD	No mismatch	None	65	12.75
11	M	Caucasian	Henoch-Schonlein purpura	1999	25	LD	Mismatch	None	26	1.25
12	M	Caucasian	FSGS	1998	19	LD	No mismatch	ATG	22	2.5
13	F	Caucasian	FSGS	1999	40	LD	No mismatch	None	54	13.75
14	F	Asian	Lupus nephritis	2003	28	NDD	No mismatch	Basiliximab	37	8.58
15	M	Asian	Hypertension	2002	42	LD	No mismatch	Basiliximab	50	8.33
16	F	Asian	IgA nephropathy	2007	56	LD	No mismatch	Basiliximab	61	5.25
17	F	Caucasian	T1DM	1998	37	NDD	Presumed mismatch	None	38	0.75
18	M	Caucasian	FSGS	1999	34	LD	Mismatch	None	43	9.67
19	M	Caucasian	Pyelonephritis/interstitial nephritis	2004	18	LD	Mismatch	Basiliximab	19	1
20	M	Asian	IgA nephropathy	2001	48	LD	No mismatch	Basiliximab	55	7
21	M	Caucasian	Hypertension	2010	41	LD	Mismatch	Basiliximab	42	0.42
22	M	Asian	IgA nephropathy	1996	33	NDD	No mismatch	None	40	7.42
23	M	Asian	IgA nephropathy	2001	37	LD	No mismatch	Basiliximab	45	7.58
24	M	Caucasian	T2DM	2006	60	NDD	No mismatch	Basiliximab	60	0.33
25	M	Caucasian	IgA nephropathy	2003	30	LD	No mismatch	Basiliximab	39	8.17
26	M	Caucasian	Glomerulonephritis	2000	58	LD	No mismatch	None	63	5.17
27	M	Caucasian	FSGS	2004	50	NDD	No mismatch	ATG	51	0.5
28	F	Caucasian	Lupus nephritis	1998	55	NDD	Presumed mismatch	None	56	0.58
29	F	Caucasian	CKD, unknown etiology	2010	51	LD	Mismatch	Basiliximab	51	0.42
30	M	Aboriginal	Hypertension	1999	40	NDD	No mismatch	None	52	12.5
31	M	Indian	Posterior urethral valves	2012	21	LD	Mismatch	Basiliximab	22	0.25
32	M	Caucasian	FSGS	2000	70	LD	No mismatch	None	78	7.5
33	M	Caucasian	Polycystic kidney disease	2009	61	LD	No mismatch	Basiliximab	62	0.67
34	F	Caucasian	Pyelonephritis/interstitial nephritis	2003	61	NDD	No mismatch	Basiliximab	66	5.17
35	F	Caucasian	CKD, unknown etiology	2004	67	NDD	No mismatch	Basiliximab	70	2.75
36	M	Aboriginal	T2DM	1998	60	NDD	No mismatch	None	68	7.75
37	F	Caucasian	Glomerulonephritis	2006	51	LD	No mismatch	Basiliximab	55	3.92

Notes. PTLD = posttransplant lymphoproliferative disorder; EBV = Epstein-Barr virus; NDD = neurological determination of death; LD = living donor; OKT3 = muromonab-CD3; FSGS = focal segmental glomerulosclerosis; T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; ATG = antithymocyte globulin; IgA = immunoglobulin A; T1DM = type 1 diabetes mellitus; NA = not applicable. EBV serology categorized as "presumed mismatch" refers to cases where no EBV serology data were available on the donor and the recipient was EBV negative. Induction therapy categorized as "none" refers to cases in which the patient did not receive ATG, OKT3, basiliximab, or daclizumab within the first 5 days post transplant.

Table 3. Primary Site, Treatment, and Outcomes of Kidney Transplant Patients With DLBCL PTLD (n = 26).

Patient ID	Pathology	Primary site	Treatment regimen	Radiation	Surgery	Outcome	Treatment of recurrence	Time to death[a]	Graft outcome	Time to graft failure[a]
1	Diffuse large B-cell lymphoma	Peritoneum	Rituximab	No	No	Death	NA	40	Failure prior to PTLD	NA
2	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Rituximab	No	No	Death	NA	95	Death with functioning graft	95
3	Diffuse large B-cell lymphoma	Liver	Rituximab	No	Adjuvant	Recurrence	CHOP-R, R-ICE, BEAM	1010	Failure	980
4	Diffuse large B-cell lymphoma	Lymph nodes	Rituximab, then CHOP-R	No	No	Remission	NA	NA	Functioning graft	NA
5	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Modified CVP-R, 1st cycle IVAC, 2nd cycle modified CODOX-R, final cycle IVAC	No	No	Remission	NA	NA	Functioning graft	NA
6	Diffuse large B-cell lymphoma	Lymph nodes, multiple regions	None (palliative)	No	No	Death	NA	9	Death with functioning graft	9
7	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Prednisone, cyclophosphamide	No	No	Death	NA	31	Death with functioning graft	31
8	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	CHOP-R	Yes	Adjuvant	Recurrence	R-ICE, BEAM autograft, GDP-R, radiation	884	Death with functioning graft	884
9	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Rituximab, then CHOP-R	No	No	Remission	NA	NA	Functioning graft	NA
10	Diffuse large B-cell lymphoma	Small intestine	Rituximab	No	Yes (resection of intestine)	Remission	NA	NA	Functioning graft	NA
11	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Rituximab	No	No	Remission	NA	NA	Functioning graft	NA
12	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Rituximab	No	No	Remission	NA	NA	Failure	638
13	Diffuse large B-cell lymphoma	Lymph nodes of head, face, and neck	Rituximab	No	No	Remission	NA	NA	Functioning graft	NA
14	Diffuse large B-cell lymphoma	Lymph nodes	Rituximab	No	No	Remission	NA	NA	Functioning graft	NA

(continued)

Table 3. (continued)

Patient ID	Pathology	Primary site	Treatment regimen	Radiation	Surgery	Outcome	Treatment of recurrence	Time to death[a]	Graft outcome	Time to graft failure[a]
15	Diffuse large B-cell lymphoma	Cecum	CHOP-R	No	No	Remission	NA	NA	Functioning graft	NA
16	Diffuse large B-cell lymphoma	Tonsil	Rituximab, then CHOP-R	No	No	Remission	NA	NA	Functioning graft	NA
17	Diffuse large B-cell lymphoma	Liver	Missing data	No	No	Remission	NA	2894	Death with functioning graft	2894
18	Diffuse large B-cell lymphoma	Small intestine	Rituximab	No	Yes (resection of intestine)	Remission	NA	NA	Failure	188
19	Diffuse large B-cell lymphoma	Lymph nodes of head, face, and neck	Rituximab	No	No	Remission	NA	NA	Functioning graft	NA
20	Diffuse large B-cell lymphoma	Vertebrae	CHOP-R	Yes	No	Remission	NA	NA	Functioning graft	NA
21	Diffuse large B-cell lymphoma	Lymph nodes, multiple regions	CHOP-R	No	No	Remission	NA	NA	Functioning graft	NA
22	Diffuse large B-cell lymphoma	Tonsil	Rituximab	No	No	Remission	NA	NA	Failure	1587
23	Diffuse large B-cell lymphoma	Liver	Rituximab + cyclophosphamide	No	No	Death	NA	13	Death with functioning graft	13
24	Diffuse large B-cell lymphoma	Cecum	Rituximab	No	No	Recurrence	Modified CHOP	837	Death with functioning graft	837
25	Diffuse large B-cell lymphoma	Lymph nodes, intra-abdominal	Rituximab, then CHOP-R	No	No	Remission	NA	NA	Functioning graft	NA
26	Diffuse large B-cell lymphoma	Small intestine	Rituximab	Yes	Yes (resection of intestine)	Recurrence	Cyclophosphamide and dexamethasone	1016	Death with functioning graft	1016

Notes. DLBCL = diffuse large B-cell lymphoma; PTLD = posttransplant lymphoproliferative disorder; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; CHOP-R = CHOP + rituximab; BEAM = carmustine, etoposide, cytarabine, melphalan; CVP-R = cyclophosphamide, vincristine, prednisolone, rituximab; IVAC = ifosfamide, etoposide, cytarabine; modified CODOX-R = cyclophosphamide, vincristine, doxorubicin, rituximab; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; GDP-R = gemcitabine, dexamethasone, cisplatin, rituximab; NA = not applicable.
[a]From PTLD diagnosis (days).

Table 4. Primary Site, Treatment, and Outcomes of Kidney Transplant Patients With Polymorphic PTLD (n = 5).

Patient ID	Pathology	Primary site	Treatment regimen	Radiation	Surgery	Outcome	Time to death[a]	Graft outcome	Time to graft failure[a]
27	Polymorphic PTLD	Liver	Rituximab	No	No	Remission	NA	Failure	574
28	Polymorphic PTLD	Lymph nodes of head, face, and neck	None	Yes	No	Remission	2207	Death with functioning graft	2207
29	Polymorphic PTLD	Lymph nodes	Rituximab	No	No	Remission	NA	Failure	38
30	Polymorphic PTLD	Lymph nodes, intra-abdominal	Rituximab	No	Yes (resection of intestine)	Remission	NA	Functioning graft	NA
31	Polymorphic PTLD	Lymph nodes of head, face, and neck	Rituximab	No	No	Remission	NA	Functioning graft	NA

Notes. PTLD = posttransplant lymphoproliferative disorder; NA = not applicable.
[a]From PTLD diagnosis (days).

Table 5. Treatment and Outcomes of Patients With Multiple Myeloma Following Kidney Transplant (n = 4).

Patient ID	Pathology	Treatment regimen	Radiation	Surgery	Outcome	Time to death[a]	Graft outcome	Time to graft failure[a]
32	Multiple myeloma	None (palliative)	Yes	No	Death	159	Failure prior to PTLD	NA
33	Multiple myeloma	None (conservative surveillance)	No	No	Stable myeloma	NA	Functioning graft	NA
34	Multiple myeloma	Melphalan and prednisone	No	No	Death	493	Death with functioning graft	493
35	Multiple myeloma	Missing data	No	No	Death	46	Failure prior to PTLD	NA

Notes. PTLD = posttransplant lymphoproliferative disorder; NA = not applicable.
[a]From PTLD diagnosis (days).

received rituximab in combination with chemotherapy, with the most common chemotherapy regimen being CHOP-R. Among the patients who received rituximab, 16 achieved remission without recurrence (Table 3).

Among all PTLD patients, the 1- and 2-year patient survival rates were 78.4% and 75.7%, respectively. Survival was excellent among early-onset cases, with 100% surviving to 2 years post diagnosis of PTLD. Survival among late-onset PTLD patients was less favorable, with 1- and 2-year survival rates being 71.4% and 67.9%, respectively. Overall survival was significantly worse in patients with PTLD than in kidney transplant patients who did not develop PTLD (Fleming-Harrington, $P = .031$; Figure 1). Overall graft survival, uncensored for death, was also significantly worse in patients with PTLD than in patients without (log-rank test, $P = .017$). Median graft survival was 9.5 years among patients with PTLD and 16 years among patients without (Figure 2).

Discussion

This study is the most recent update on incidence, characteristics, and outcomes of PTLD in BC kidney transplant patients since the 1980s.[15] Changes in immunosuppression protocols that have occurred since this time had the potential to alter the frequency with which PTLD was occurring.

PTLD occurred in 1.7% of patients who received kidney transplants between 1996 and 2012 in BC, which is consistent with the range of 1% to 2% that has been reported in the literature.[1,7,16-18] This incidence is not appreciably different from the 6 lymphoma cases Melosky et al reported out of the 478 kidney transplant patients studied between 1986 and 1989.[15] However, Melosky et al followed patients for a mean period of only 26 months, implying a number of late-onset cases were likely not captured, and that the true frequency of PTLD may have been higher than what was reported. Other Canadian literature reports that 2.5% of kidney transplant

Table 6. Primary site, Treatment, and Outcomes of Kidney Transplant Patients With PTLD, Subtype Other Than Those in Tables 1 to 3 (n = 2).

Patient ID	Pathology	Primary site	Treatment regimen	Radiation	Surgery	Outcome	Time to death[a]	Graft outcome	Time to graft failure[a]
36	Plasmacytoma	Rib, sternum, clavicle, and associated joints	None (palliative)	No	No	Death	49	Death with functioning graft	49
37	Exact diagnosis unknown (DLBCL vs Burkitt lymphoma)	Peritoneum	Hydrocortisone, prednisone, CODOX-M, IVAC-R	No	No	Remission	NA	Functioning graft	NA

Notes. PTLD = posttransplant lymphoproliferative disorder; DLBCL = diffuse large B-cell lymphoma; CODOX-M = cyclophosphamide, vincristine, doxorubicin, methotrexate; IVAC-R = ifosfamide, etoposide, cytarabine, rituximab; NA = not applicable.
[a]From PTLD diagnosis (days).

patients during this period were affected by early-onset PTLD.[19] Considering lymphomas affect kidney transplant patients at significantly higher rates than they do the general population, the frequency of PTLD among kidney transplant patients in BC, while low, remains a concerning cause of morbidity and mortality among this population.

Several studies have identified risk factors for the development of PTLD following solid organ transplantation. Among these include EBV seronegativity of recipient, Caucasian ethnicity, male gender, and age less than 18 years.[3,10,20-23] Some of these are additive, with young Caucasian males being among the highest risk of developing PTLD.[20,24] Our study appears to corroborate some of this research, as 21.6% of patients with PTLD were EBV negative (documented as either EBV mismatch or, when EBV serology data were unavailable for the donor, presumed EBV mismatch) compared with only 5.7% of patients who did not develop PTLD. Although not statistically significant, there were also a greater proportion of patients who were Caucasian (73.0% vs 65.9%) and male (64.9% vs 61.0%) in the PTLD group as compared with the non-PTLD group. The majority of reported PTLD cases are associated with EBV.[25,26] Therefore, the degree of immunosuppression received is an important risk factor for the development of PTLD as it influences the body's response to EBV.[21,22,27-29] In a study of over 145 000 cadaver kidney transplant recipients, OKT3 and ATG exposure were associated with a 3- to 4-fold higher incidence of PTLD, whereas anti-IL-2-receptor antibodies were not associated with an increased incidence of PTLD.[30] Interestingly, a greater proportion of PTLD patients (40.5% vs 28.1% of non-PTLD patients) in this study did not receive induction therapy with ATG, OKT3, basiliximab, or daclizumab within the first 5 days post transplant. Similarly, smaller proportions of PTLD patients received either anti-IL-2-receptor antibodies (51.4% vs 57.8% of non-PTLD patients) or ATG (5.4% vs 12.4% of non-PTLD patients) for induction therapy. As hypothesized, our PTLD population did consist of a greater proportion of patients (2.7% vs 1.8% of non-PTLD patients) who had received OKT3 induction therapy. Maintenance immunosuppression of individual patients was not examined in detail in this study; the evidence implicating individual maintenance immunosuppressant agents is conflicting and appears to suggest that the net effect of immunosuppression regimens post transplantation, not a particular individual agent, is more associated with the risk of PTLD.[31] Duration of immunosuppression therapy, a known risk factor for the development of late-onset PTLD,[10] was also not captured by these data.

Both adult kidney transplant programs in BC have utilized rapid steroid elimination protocols since 2003. It has been reported that steroid maintenance therapy is associated with a decreased risk of developing late-onset PTLD[3]; however, other sources suggest that steroid-free protocols do not alter the frequency with which PTLD occurs.[18,32] The overall 1.7% incidence of PTLD in our kidney transplant patients was consistent with other studies that did not specify the use of rapid steroid elimination protocols.[7,16] Given the nature of the study design, our results permit the ability to merely speculate on the effect that rapid steroid elimination may have on the risk of PTLD. In addition, the ability to capture the degree to which, if any, steroids mitigate or propagate the risk of PTLD following kidney transplantation is challenged because of other concomitant changes to immunosuppression regimens that have likely had greater bearing on the risk of PTLD.

PTLD management varies based on the subtype; however, a nearly universal initial step is reduction in immunosuppression.[1,10,11,13] The majority of our patients underwent a reduction of immunosuppression upon PTLD diagnosis; however, the degree of reduction was not studied.

In patients who fail to adequately respond to a reduction of immunosuppression, treatment options for patients with monomorphic or systemic polymorphic PTLD may include rituximab with or without chemoimmunotherapy.[11] Rituximab, an anti-CD20 monoclonal antibody not associated with treatment-related mortality, is frequently used as monotherapy after lack of response from a reduction in immunosuppression alone, or in simultaneous or sequential combination with CHOP.[9,16,27,33,34] Previously, CHOP and CHOP-R were reported to have a 31% treatment-associated mortality in immunosuppressed patients.[33] However, a more recent B-cell PTLD treatment trial reported that sequential treatment with rituximab followed by CHOP chemotherapy was associated with a much lower (11%) risk of treatment-related mortality.[9]

Of the 26 DLBCL patients, 23 were treated with rituximab, either alone or in combination with CHOP or CHOP-like chemotherapy. Supporting the notion that rituximab is a mainstay of therapy for a number of PTLD subtypes, outcomes were favorable for the majority of patients treated with rituximab, as 16 of the 23 patients treated with rituximab (69.6%) achieved remission without recurrence. Recurrence occurred in 4 patients, which may be a consequence of rituximab not altering cellular immune response to EBV, thereby not offering a long-term defense against EBV-positive B-cell proliferation once B-cell recovery following rituximab therapy occurs.[12] The recurrence rate seen following monotherapy with rituximab in BC is lower than that which has been observed in rituximab monotherapy prospective studies.[9]

Given the heterogeneity of disorders categorized as PTLD, prognosis can be highly variable. A number of factors have been reported to negatively influence a patient's prognosis, including late-onset PTLD, advanced age at diagnosis, central nervous system (CNS) involvement, monomorphic PTLD, T-cell PTLD, poor performance status, extranodal disease, and renal insufficiency.[35-41] Our data correspond with some of these prognostic factors. Late-onset cases fared worse, with 1- and 2-year survival rates of 71.4% and 67.9% in the late-onset group compared with 100% survival at 2 years in the early-onset group. Late-onset PTLD is more likely to be EBV negative, which has been associated with worse outcomes.[10,42] These findings are in contrast to results

from studies reporting no difference in survival between patients with early-onset and late-onset PTLD.[8,30]

The overall 1- and 2-year survival rates of the 37 patients diagnosed with PTLD in BC were 78.4% and 75.7%, respectively. Our overall survival data do not appear worse than what has been reported by other retrospective database studies, with 5-year survival rates among kidney transplant patients with PTLD being between 53% and 64%.[39,43] Outcomes of PTLD following kidney transplant in BC appear better in today's era of immunosuppression than they did in the 1980s, but previous data do not specify specific survival rates. Melosky and colleagues identified 6 patients with PTLD following kidney transplant; there were no survivors among the 5 patients diagnosed with non-Hodgkin lymphoma.[15] The outcome of the sixth patient, diagnosed with Hodgkin's lymphoma, was not specified.

The ability to accurately capture all cases of PTLD in a population is threatened by a number of factors, most notably the potential loss to follow-up of patients who develop late-onset PTLD and the possible omission of PTLD documentation in clinic records. One of this study's strengths is that it incorporated data from both a provincial transplant database and a provincial cancer database, increasing the likelihood that all PTLD cases were captured. Limitations to this study inherent to its design include its retrospective nature, the unknown adherence to prescribed immunosuppressants, and the reduced follow-up for patients transplanted in the latter years of the time period studied. The degree of immunosuppression reduction for PTLD management was not effectively captured, nor were cumulative doses of immunosuppression, including immunosuppression used for the treatment of rejection. Furthermore, database standards were not consistent over the time period studied, limiting the quality and quantity of data that could be retrieved.

Conclusion

This study suggests the rate of PTLD in BC following kidney transplantation is low and consistent with rates reported in literature. The incidence of late-onset PTLD and its association with reduced patient and graft survival warrant further analysis of patients' long-term immunosuppression and ongoing surveillance for the development of PTLD. Further research should focus on the treatment of PTLD, particularly given the associations between late-onset PTLD and reduced patient and graft survival.

Ethics Approval and Consent to Participate

The study protocol was approved by the University of British Columbia Clinical Research Ethics Board and the Vancouver Coastal Health Research Institute. Participant informed consent was not required for this study.

Consent for Publication

All authors consent to this manuscript being published.

Availability of Data and Materials

Not available.

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