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Original Article

Post-transplant lymphoproliferative disorders (PTLD)-from clinical to metabolic profiles-a single center experience and review of literature

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Abstract: Post-transplant lymphoproliferative disorders (PTLD) are among the most serious complications after solid organ transplantation (SOT). Monomorphic diffuse large B-cell lymphoma (DLBCL) is the most common subtype of PTLD. Historically, outcomes of PTLD have been poor with high mortality rates and allograft loss, although this has improved in the last 10 years. Most of our understanding about PTLD DLBCL is extrapolated from studies in non-PTLD DLBCL, and while several clinical factors have been identified and validated for predicting non-PTLD DLBCL outcomes, the molecular profile of PTLD DLBCL has not yet been characterized. Compartment-specific metabolic reprograming has been described in non-PTLD DLBCL with a lactate uptake metabolic phenotype with high monocarboxylate transporter 1 (MCT1) expression associated with worse outcomes. The aim of our study was to compare the outcomes of PTLD in our transplant center to historic cohorts, as well as study a subgroup of our PTLD DLBCL tumors and compare metabolic profiles with non-PTLD DLBCL. We performed a retrospective single institution study of all adult patients who underwent a SOT between the years 1992-2018, who were later diagnosed with PTLD. All available clinical information was extracted from the patients' medical records. Tumor metabolic markers were studied in a subgroup of PTLD DLBCL and compared to a group of non-PTLD DLBCL. Thirty patients were diagnosed with PTLD following SOT in our center. Median time from SOT to PTLD diagnosis was 62.8 months (IQR 7.6; 134.4), with 37% of patients diagnosed with early PTLD, and 63% with late PTLD. The most common PTLD subtype was DLBCL. Most patients were treated with reduction of their immunosuppression (RIS) including a group who were switched from calcineurin inhibitor (CNI) to mTOR inhibitor based IS, in conjunction with standard anti-lymphoma chemoimmunotherapy. Progression free survival of the PTLD DLBCL cohort was calculated at 86% at 1 year, and 77% at 3 and 5-years, with overall survival of 86% at 1 and 3-years, and 75% at 5 years. Death censored allograft survival in the kidney cohort was 100% at 1 year, and 93% at 3, 5 and 10 years. MCT1 H scores were significantly higher in a subset of the non-PTLD DLBCL patients than in a PTLD DLBCL cohort. Our data is concordant with improved PTLD outcomes in the last 10 years. mTOR inhibitors could be an alternative to CNI as a RIS strategy. Finally, PTLD DLBCL may have a distinct metabolic profile with reduced MCT1 expression compared to non-PTLD DLBCL, but further studies are needed to corroborate our limited cohort findings and to determine if a specific metabolic profile is associated with outcomes.

Keywords: PTLD, DLBCL, solid organ transplant, reduction of immunosuppression, metabolic profile

Introduction

Posttransplant lymphoproliferative disorders (PTLD) are a heterogeneous group of malignancies, which remain among the most serious complications after solid organ transplantation (SOT) [1, 2]. PTLD is the second most common malignancy in SOT recipients after non-melano-

ma skin cancers [3-5] and is the most common cause of cancer related death in SOT recipients [6]. Most PTLD are of B-cell origin, with CD20+ monomorphic diffuse large B cell lymphoma (DLBCL) being the most common subtype [1]. Risk of lymphoma in SOT recipients is estimated as 3- to 21-fold higher than that in the general population, and perhaps as much as 120-fold higher among children who receive a SOT [7, 8].

Epstein-Barr virus (EBV), a double stranded DNA gamma herpesvirus, infects up to 90% of the world's population by adulthood [9]. More than half of PTLD cases are associated with EBV, with several identified risk factors, such as age of recipient, type of organ transplanted and the pre-transplant EBV status of the recipient and donor [10-13], as strong risk factors for PTLD. SOT recipients most at risk for EBV-positive PTLD are pediatric recipients with primary EBV infection and recipients who are heavily immunosuppressed [14]. In EBV-positive PTLD, the herpesvirus serves as the pathogenic driver by inducing abnormal lymphocyte proliferation [15]. EBV can be in a latent or lytic phase in infected B-lymphocytes. In the setting of immunosuppression (IS), the latent infected B-cells undergo somatic changes, which result in progression from early lesions through polymorphic PTLD to monomorphic PTLD [16], with most cases of EBV-associated monomorphic PTLD resembling non-PTLD diffuse large B-cell lymphoma [9]. Latent EBV can undergo reactivation in the setting of immunosuppressive treatment of the SOT recipient and can originate from either the recipient or the donor allograft [17]. EBV is usually associated with early PTLD (defined as diagnosis within the first year after SOT), as opposed to late onset PTLD (diagnosed after the first year from SOT) which tends to be EBV-negative [18]. The pathological process which drives EBV-negative PTLD is not yet clear [15], but genomic profiling suggests that EBV-negative PTLD is similar to lymphoma in the immunocompetent host [19].

The current classification of PTLD is based on the 2016 revision of the World Health Organization of lymphoid neoplasms [20], which include six subtypes, and the most common subtype is monomorphic PTLD with DLBCL histology [1]. Most of our understanding about PTLD DLBCL has been extrapolated from studies in non-PTLD DLBCL, but the molecular profile of PTLD DLBCL has not yet been exhaustively characterized. Non-PTLD DLBCL can be sub-classified on the basis of the molecular features [21]. Rearrangements or high expression of MYC, along with BCL2 and/or BCL6 are associated with poor outcomes [21]. More recently, non-PTLD DLBCLs have been classified on the basis of full genome mRNA expression patterns [22, 23] although this is not yet deployed in clinical practice. However, the significance of these subgroups in PTLD DLBCL is unknown.

In addition to molecular features, several clinical factors have been identified and validated for predicting non-PTLD DLBCL outcomes [21]. These include age, Ann Arbor stage, ECOG performance status, site of disease, and the metabolic marker lactate dehydrogenase (LDH) which have been developed into prognostic indices, initially the International Prognostic Index (IPI), and subsequently the Revised-International Prognostic Index (R-IPI) and the R-IPI-24 in which higher scores are associated with poor outcomes [24]. These prognostic indices have been validated for PTLD [25], and are widely used at initial diagnosis by clinicians to predict the likelihood of response to treatment, and anticipated overall survival [26].

The importance of glycolytic metabolism as a driver of poor outcomes is clear in DLBCL, where the levels of the glycolytic enzyme LDH are one of the strongest prognostic biomarkers [24]. Also, the preferred imaging modality for staging and assessing response to treatment in DLBCL is 18-fluor 2-deoxy-glucose positron emission tomography with Computed Tomography (FDG-PET-CT), which is a glycolytic imaging technique that evaluates glucose uptake by the tumor [21]. Compartment-specific metabolic reprograming has been described in non-PTLD DLBCL with high expression of translocase of the outer mitochondrial membrane (TOMM20) and monocarboxylate transporter 1 (MCT1) in neoplastic lymphocytes, indicating a mitochondrial oxidative phosphorylation (OXPHOS) phenotype. Conversely, stromal cells in non-PTLD DLBCL samples strongly express monocarboxylate transporter 4 (MCT4), which is associated with a glycolytic phenotype [27]. In non-Hodgkin lymphoma, increased MCT1 expression in lymphoma cells and MCT4 expression in stromal cells has been associated with worse prognosis [28].

The aim of the study was to compare the outcomes of PTLD in our transplant center to historic cohorts. Since the metabolic profile of PTLD DLBCL tumors have not been delineated, we also studied a subgroup of our PTLD tumors and compared metabolic profiles with non-PTLD DLBCL.

Materials and methods

Study design

We performed a retrospective study of all adult patients who underwent a SOT between the years 1992-2018, who were later diagnosed with PTLD, and were followed at our center. For each of the patients, we performed a manual chart review using electronic medical records. All clinical data including patients' demographic characteristics, type of transplant, immunosuppressive regimen, prior rejection episode/s, diagnosis of PTLD, PTLD histological characteristics, disease location, management and patient outcomes were extracted.

The PTLD patients were stratified into 2 groups: patients with a diagnosis of monomorphic B-cell lymphoma, DLBCL subtype, since this is the most common subtype, and patients with PTLD of any other subtype.

From the PTLD DLBCL cohort, we analyzed a subgroup of consecutive patients that had recent available pathology samples (n = 6) to a consecutive cohort of patients that were diagnosed of DLBCL but without history of solid or bone marrow transplant (n = 6) to compare metabolic markers.

The study was approved by Thomas Jefferson University institutional review board (IRB # 16258).

Study population

Only the first SOT was considered in this analysis. If the patient was re-transplanted following the PTLD diagnosis, the date of relisting or documented allograft failure (which ever came first), was considered as the graft failure date.

Clinical definitions

The diagnosis of PTLD was confirmed by histology upon review by a hematopathologist. PTLD sub-classification was based on the 2016 revised WHO criteria [20]. Early PTLD was defined as that occurring in the first 12 months post-transplant and late if diagnosed thereafter. Information on staging, site of disease, standardized uptake value (SUV) and Deauville score in positron emission tomography (PET) imaging was collected. The status of genetic markers, such as MYC, BCL2 and BCL6, in the tissue biopsies was obtained, as was the Epstein Barr encoding region (EBER) status and the proliferation marker Ki67.

For the subgroup of PTLD DLBCL the revised International Prognostic Index (R-IPI), which includes age, performance status, LDH, number of extra-nodal sites and disease stage [24] was calculated as an outcome predictor.

Paraffin immunohistochemistry

For the PTLD DLBCL and non-PTLD DLBCL patients, we conducted IHC staining for MCT1, MCT4, and TOMM20. A 3-step avidin-biotin horseradish peroxidase method was used for antibody labeling using 4-micron paraffin sections. Briefly, sections were deparaffinized, rehydrated through graded ethanols and washed in deionized water. Antigen retrieval was performed in 0.01 M citrate buffer, pH 6.0 with or without 0.1% Tween-20 for 10 minutes using an electric pressure cooker. The sections were cooled to room temperature (RT) and blocked for endogenous peroxidase in 3% H_2O_2 for 15 min. An avidin-biotin kit (BioCare Medical, Concord, CA) was used to block endogenous biotin and the sections were blocked overnight with 10% goat serum in PBS at 4°C. The next day, sections were brought to RT and incubated with primary antibodies for one hour, followed by biotinylated species-specific secondary antibody (Vector Labs, Burlingame, CA) and avidin-biotin-horseradish peroxidase complex (ABC Elite Kit, Vector Labs) with washing in PBS between steps. Antibody binding was detected with 3,3' diaminobenzidine (DAB liquid substrate kit, Agilent Technologies, Carpinteria, CA). The following antibodies were used: MCT1 (SLC16A1): 19-mer peptide sequence CSPDQKDTEGGPKEEESPV-cooh affinity purified rabbit antibody (YenZym Antibodies, South San Francisco, CA); MCT4 (D-1), sc-376140 mouse monoclonal antibody (Santa Cruz Biotechnology, Dallas, TX) and Tom20 (F-10), sc-17764 mouse monoclonal antibody (Santa Cruz). H scores were assigned to IHC samples to com-

Table 1. Patients' and transplant characteristics

	Total PTLD patients (N = 30)	Treated DLBCL patients (N = 15)
Age at SOT, median (IQR)	50.4 (35.82; 58.84)	57.1 (34.1; 59.9)
Gender, N (%)*		
Female	11 (37%)	5 (33.3%)
Male	19 (63%)	10 (66.7%)
Race, N (%)		
Black	8 (27%)	6 (40%)
White	19 (63%)	9 (60%)
Other	3 (10%)	0
Type of Organ Transplanted, N (%)		
Kidney	15 (50%)	10 (66.7%)
Liver	12 (40%)	5 (33.3%)
SPK	2 (7%)	0
SLK	1 (3%)	0
Type of Donor, N (%)		
DBD	22 (73%)	12 (80%)
DCD	5 (17%)	3 (20%)
Living donor	3 (10%)	0
SOT number, N (%)		
1	28 (93%)	14 (93.3%)
2	2 (7%)	1 (6.7)

Ages are represented as median (Q1: Q3). All categorical data is presented as number (percent). *Percentages were rounded to nearest decimal point. PTLD, post-transplant lymphoproliferative disorders; DLBCL, diffuse large B-cell lymphoma; SOT, solid organ transplantation; SPK, simultaneous pancreas-kidney; SLK, simultaneous liver-kidney; DBD, donor after brain death; DCD, donor after cardiac death.

pare staining intensity between the groups. The percentage of cells at each staining intensity level is calculated using the following formula: [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]. The final score ranges from 0-300 [29, 30].

Statistical analysis

The time-to-event endpoints of overall survival (OS), allograft survival (AS) and progression free survival (PFS) are summarized using Kaplan-Meier curve as well as its 95% confidence band, for (a) the entire cohort; (b) a subgroup of patients who received only a kidney transplant or a combined kidney-pancreas transplant; and (c) a subgroup of DLBCL patients who opted to receive cancer care including treatment. Kaplan-Meier estimates of 1-year, 3-year and 5-year survival rates are reported with 95% confidence intervals. Additional clinical and demographic information are summarized using median and interquartile range (IQR), percentages and 95% exact confidence intervals. The analysis is performed using statistical software R [31] by Dr. Zhan from the Division of Biostatistics at Thomas Jefferson University.

Results

Study population-entire cohort

Thirty SOT recipients were included in our study. The majority of the patients were male, white, and were kidney alone recipients, with most organs coming from donors after brain death (DBD). Recipients and organ characteristics are outlined in **Table 1**. At time of transplant, patients who underwent kidney alone, simultaneous pancreas-kidney (SPK) or simultaneous liver-kidney (SLK) transplants received rabbit anti-thymocyte globulin (rATG) as the induction therapy, while patients who received liver transplant were induced with the anti-interleukin 2R antagonist, basiliximab, per our center's protocol. Following the transplant, kidney alone and SPK recipients were placed on a maintenance immunosuppressive regimen consisting of a calcineurin inhibitor (CNI), an anti-metabolite agent, with or without prednisone based on their sensitization profile at time of transplantation. The CNI was either tacrolimus or cyclosporine A, and the antimetabolite agent was either mycophenolate mofetil or mycophenolic acid. Eight of the orthotopic liver transplant (OLT) recipients were originally managed on a CNI and an antimetabolite agent, with the remaining seven on monotherapy with only a CNI. All IS regimens were prescribed based on our center's standard operating protocol at time of transplant.

Study population-treated DLBCL cohort

Fifteen patients with proven diagnosis of monomorphic B-cell lymphoma, DLBCL subtype, who

received one or more documented lines of treatment besides reduction of immunosuppression (RIS) were included in this sub-group analysis. Of these, 10 were male and 5 were female; 6 were black, and 9 were white. Mean age at transplant was 57.1 years (IQR 34.1; 59.9), and mean age at PTLD diagnosis was 57.6 years (IQR 48.3; 67.8). Ten of the patients received a kidney only transplant, and the remaining 5 underwent an OLT. Twelve of the donors were DBD, and 3 were donors after cardiac death (DCD). None were from living donors. Six of the kidney-only recipients were on a triple IS regimen, with the additional 4 on a CNI and an antimetabolite. Four OLT recipients were maintained on monotherapy with a CNI agent, and the remaining patient was on dual treatment with a CNI and an antimetabolite.

PTLD characteristics-entire cohort

Median time from SOT to PTLD diagnosis was 62.8 months (IQR 7.6; 134.4), with 11 of the 30 (37%) patients diagnosed within the first 12 months after transplant (i.e., early PTLD), and the remaining 19 (63%) diagnosed more than 12 months after transplant (i.e., late PTLD). Median follow up time from PTLD diagnosis to end of study was 33.2 months (IQR 9.1; 78.5). Prior to PTLD diagnosis, 4 of 24 patients for which data were available, were diagnosed and treated for rejection by escalation of their net IS. Twenty-two of patients were diagnosed with monomorphic B-cell lymphoma. Of these, 17 were diagnosed with DLBCL subtype. Further details on the PTLD features are described in **Table 2**. Of the 30 patients, we had Epstein Barr encoding region (EBER) status on biopsy for 26 of them, with 15 (58%) of them being positive. EBV viremia was detected at time of lymphoma diagnosis in 14 patients of the 25 for whom these assessments were performed (56%). For those diagnosed with early PTLD, 9 were EBER positive and one was EBER negative. Of patients diagnosed with late PTLD, 10 were EBER negative, and only 6 patients were EBER positive.

Seventeen patients, out of the 27 for which data were available, had an elevated LDH value at time of diagnosis [median 281; IQR (204; 360)].

FDG-Positron emission tomography (FDG-PET-CT) results prior to treatment initiation were available for 19 patients. Median SUV value was 15.2 (IQR 7.8; 23.5). Deauville score was available for 10 patients at diagnosis of lymphoma, with a median score of 5 (IQR 4; 5). Extra-nodal disease was detected in 12 of the patients, 10 had nodal disease and the rest had both nodal and extra-nodal involvement. Four of the patients had lymphoma involvement of their allograft.

PTLD characteristics-treated DLBCL cohort

For this cohort, consisting of 15 patients, median time from SOT to DLBCL diagnosis was 55.6 months (IQR 7.9; 123.7). Median value of LDH was 261 (IQR 206; 322), with 9 patients having elevated LDH at time of diagnosis. Site of lymphoma involvement was nodal in 5 patients, extra-nodal in 5 patients, and both nodal and extra-nodal in the remaining 5, with 2 patients having involvement of their allograft. Median SUV prior to treatment was 22.2 (IQR 13.6; 26.9). Ten patients were EBER positive on tissue biopsy. One of our patients was positive for both MYC and BCL2 expression on the tissue biopsy. Three additional patients were positive for both BCL2 and BCL6 expression on tissue biopsy, with an additional 5 positive for only BCL2 expression. The remaining had no available data. Median Ki67 proliferation score for 13 patients for which data was available was 75 (IQR 50; 90). R-IPI score was calculated [24], with 8 patients scoring 1 or 2 (good risk group), and 7 patients scoring 3-5 points (poor risk group).

PTLD treatment and outcomes-entire cohort

Median duration of follow up for the entire cohort from PTLD diagnosis until death or last follow up was 33.2 months (IQR 9.1; 78.5). All patients except one underwent reduction of their net is following PTLD diagnosis. Post-lymphoma diagnosis, the IS regimen was CNI-based in 15 (50%) patients, mTOR-based in 12 (40%) patients, one (3%) was maintained on prednisone only, and 2 (7%) patients were taken off all IS medications. Fourteen patients in our cohort received Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as their first line of chemotherapy, 3 received doxorubicin, dacarbazine, vinblastine, bleomycin (ABVD) for Hodgkin lympho-

Table 2. PTLD characteristics

	Total PTLD patients (N = 30)	Treated DLBCL patients (N = 15)
Age at PTLD diagnosis, median (IQR)	55.09 (49.1; 65.4)	57.6 (48.3; 67.8)
Time from SOT to PTLD diagnosis, N (%)*		
≤ 12 months	11 (37%)	6 (40%)
> 12 months	19 (63%)	9 (60%)
Type of PTLD, N (%)		NA (all monomorphic B-cell, DLBCL subtype)
Monomorphic B-cell	22 (73%)	
DLBCL subtype	17 (56%)	
Plasmacytoma subtype	2 (7%)	
Other	3 (10%)	
Polymorphic	3 (10%)	
Classic Hodgkin Lymphoma	3 (10%)	
Other	2 (7%)	
Site of Disease, N (%)		
Nodal	10 (33%)	5 (33.3%)
Extra-nodal	12 (40%)	5 (33.3%)
Both	8 (27%)	5 (33.3%)
Lymphoma Staging, N (%)**		
I	5 (18%)	1 (6.7%)
II	4 (14%)	1 (6.7%)
III	4 (14%)	4 (26.6%)
IV	15 (54%)	9 (60%)
ECOG at Diagnosis, N (%)**		
0	2 (7%)	1 (6.7%)
1	22 (79%)	12 (80%)
2	2 (7%)	2 (13.3%)
3	2 (7%)	0

Ages are represented as median (Q1: Q3). All categorical data is presented as number (percent). *Percentages were rounded to nearest decimal point. **N is 28 patients. PTLD, post-transplant lymphoproliferative disorders; DLBCL, diffuse large B-cell lymphoma; SOT, solid organ transplantation; ECOG, Eastern Cooperative Oncology Group.

ma and an additional 3 patients received Rituximab only. Additional treatments included rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-EPOCH), cyclophosphamide, etoposide, prednisolone, vincristine (CEOP), radiation and methotrexate, and CHOP. Three patients were never treated for their lymphoma, with palliative supportive/comfort measures and hospice implemented instead, and one additional patient was never treated and remains under surveillance due to indolent T-large granular lymphocytic leukemia. At time of last follow up, 20 of our patients were in remission, 3 were noted to have relapse of their lymphoma, and 3 had refractory disease. Of the 20 patients who were in remission at time of last follow up, 15 achieved remission after 1st line treatment, with the additional 5 patients achieving remission after 2nd line treatment. Progression free survival (PFS) estimated at 88% at 1 year, 83% at 3 years, and 76% at 5 years (**Figure 1A**). The overall survival (OS) curves reveal 81% survival at 1 and 3 years, and 75% survival at 5 years (**Figure 1B**). The three patients who were never treated were excluded from the KM PFS and OS analyses and curves.

PTLD treatment and outcomes-treated DLBCL cohort

Fourteen out of the fifteen patients with PTLD DLBCL were treated with R-CHOP following reduction of IS, with one treated with radiation, and high dose methotrexate followed by rituximab, for PTLD DLBCL with CNS lymphoma.

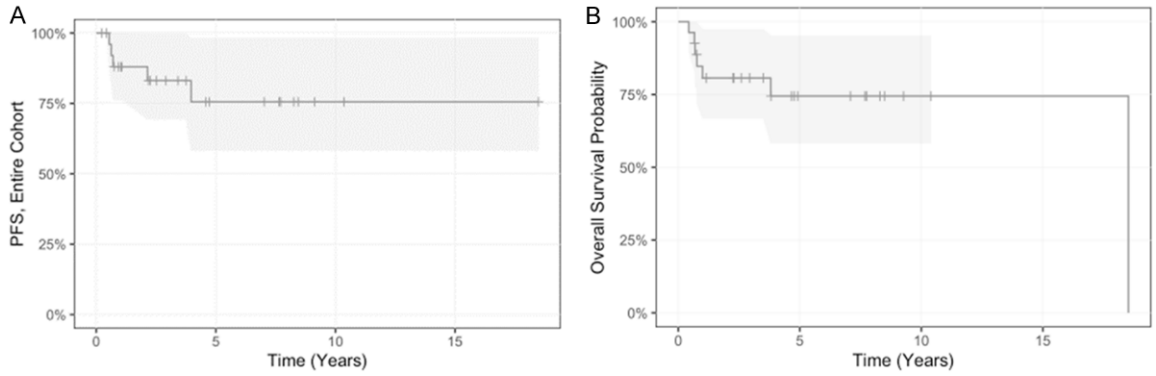

Figure 1. Progression free survival (PFS) and overall survival (OS) for entire PTLD cohort. A. KM curve describing PFS for the 27 patients who received any form of anti-lymphoma treatment. PFS at 1 year was 88% (95% CI 76-100%), 83% at 3 years (95% CI 69-100%), and 76% at 5 years (95% CI 58-98%). B. KM curve describing OS for the 27 patients who received any form of anti-lymphoma treatment. OS at 1 and 3-years was 81% (95% CI 67-97%) and 74% at 5 years (95% CI 58-95%).

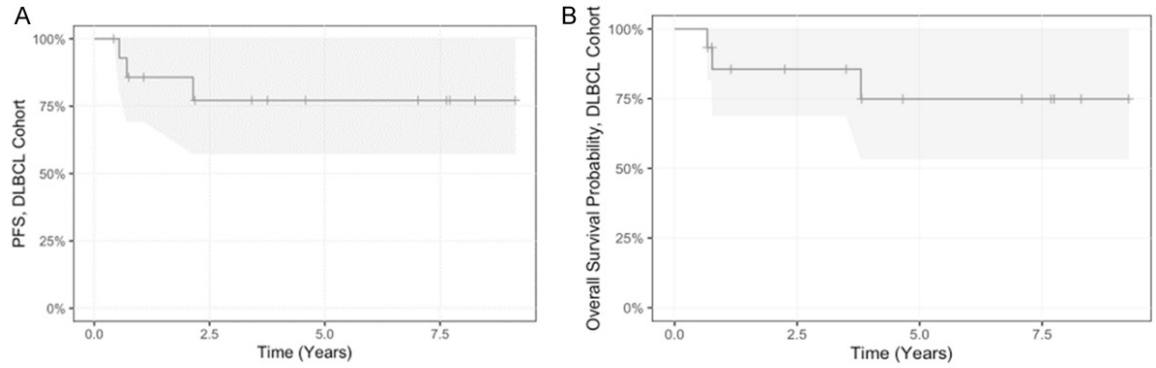

Figure 2. Progression free survival and overall survival for the PTLD DLBCL cohort. A. KM curve describing PFS for the 15 PTLD-DLBCL patients. PFS at 1 year was 86% (95% CI 69-100%), and 77% (95% CI 57-100%), at 3 and 5-years. B. KM curve describing OS for the 15 PTLD-DLBCL patients. OS was 86% (95% CI 69-100%) at 1 and 3-years, and 75% (95% CI 55-100%), at 5-years.

Twelve patients achieved remission, and 3 had relapse of their disease at a median of 8.4 months (IQR 7.5; 17.1) from diagnosis. PFS of the PTLD DLBCL cohort was calculated at 86% at 1 year, and 77% at 3 and 5-years (**Figure 2A**). All three patients who relapsed, eventually died from their lymphoma despite second line therapy, with median time from PTLD DLBCL diagnosis to death of 9.2 months (IQR 8.6; 27.4). Of note, all three patients who died were liver transplant recipients, and all were reported to have a working allograft at time of death. The OS of the PTLD DLBCL cohort was 86% at 1 and 3-years, and 75% at 5 years (**Figure 2B**).

Allograft survival-entire cohort

Three patients lost their transplanted allograft following PTLD diagnosis during follow up. One of these was a kidney transplant recipient, one was an OLT recipient, and one was a SPK recipient. Median follow up time from PTLD diagnosis to allograft failure was 66 months (IQR 44.6; 114.0). Overall graft survival since PTLD diagnosis was 81% at 1 year, 77% at 3 years and 73% at 5 years and 69% at 10 years. Death censored graft survival for the overall cohort was 100% at 1 year, 96% at 3 and 5 years and 92% at 10 years. These data highlight the fact that most of the graft loss was due to patient dying with functional allograft.

Similarly, overall kidney allograft survival (kidney and SPK transplants alone) from PTLD diagnosis was 86% at 1 year, and 78.6% at 3, 5, and 10 years. Death censored allograft survival in the kidney cohort was 100% at 1 year, and 93% at 3, 5 and 10 years again reflecting

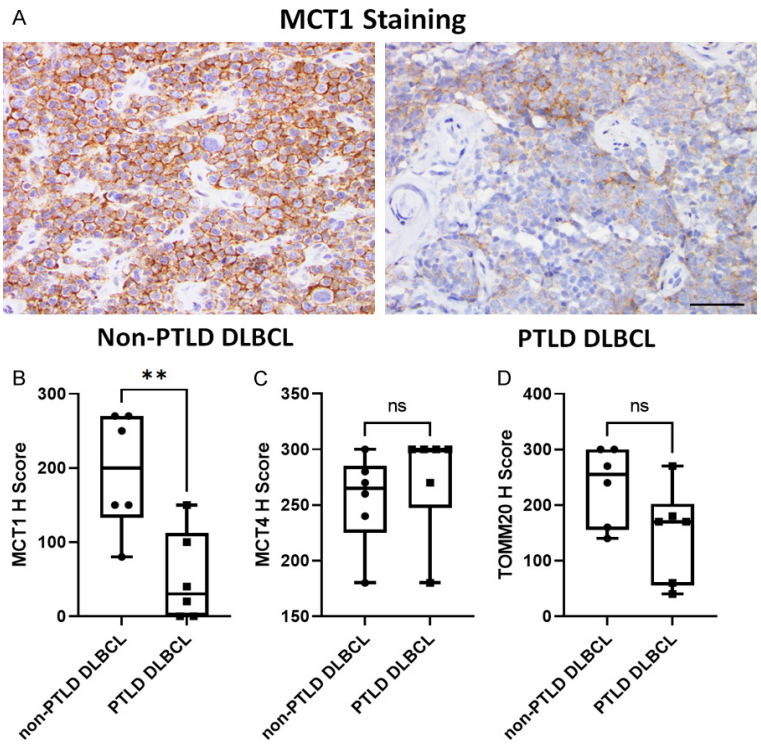

Figure 3. MCT1, MCT4, and TOMM20 expression in non-PTLD DLBCL compared to PTLD DLBCL. (A) Representative images of immunohistochemistry for MCT1 are shown (original magnification 40X). H scores as a measurement of overall staining intensity for MCT1 (B), MCT4 (C), and TOMM20 (D) was measured and compared between non-PTLD DLBCL and PTLD DLBCL. N = 6 samples, unpaired t-test with Welch's correction, $^{**}P < 0.01$. Scale bar = 50 microns.

Metabolic signatures of PTLD DLBCL tumor samples

We studied tumor glycolytic and mitochondrial OXPHOS metabolic markers in a subgroup of the PTLD DLBCL cohort that had available pathology samples and compared marker expression to a cohort of patients that were diagnosed with DLBCL but without a history of transplant and hence did not have PTLD (non-PTLD DLBCL). MCT4, MCT1, and TOMM20 expression by immunohistochemistry (IHC) were studied as markers of glycolytic versus OXPHOS metabolism. MCT1 H scores were significantly higher in the non-PTLD DLBCL patients than in the PTLD DLBCL cohort as shown in **Figure 3A**, **3B**. There were no differences in the expression of MCT4 or TOMM20 between the DLBCL subtypes (**Figure 3C**, **3D**).

Discussion

Solid organ transplantation is the treatment of choice for patients reaching end stage disease of their kidneys, liver, heart, or lung regardless of the etiology of their disease. Advances in the field of SOT have allowed prolonged and better quality of life for most patients. However, complications are common, especially as it relates to infectious and malignant processes in light of life-long immunosuppressive medications.

One of the feared complications is PTLD, with overall survival (OS) at 5 years of 53% and 59% depending on the series, with worse overall survival among patients with monomorphic PTLD [8, 32]. More recent studies have shown improved survival with 70% of patients in the PTLD-1 study achieving complete remission with median OS of 6.5 years, with the adoption of lymphoma specific protocols, specifically sequential therapy of rituximab followed by R-CHOP in patients with CD20+ PTLD [33]. In our cohort, the OS at 1 and 3 years was 81%,

that most of the kidney allograft loss was due to death with a functional graft.

Kidney function-entire cohort

For 19 of our patients, we had documented kidney function at 1-year from PTLD diagnosis, with a median serum creatinine of 1.1 mg/dL (IQR 0.9; 1.9) and median eGFR of 65 ml/min (IQR 36; 74). Kidney function data at 3-years were available for 13 patients in our cohort, with median serum creatinine of 1.2 mg/dL (IQR 1; 1.6), and median eGFR of 52 ml/min (IQR 45; 67). Median time from PTLD diagnosis to last documented kidney function was 42 months (IQR 12.8: 87.2), with median serum creatinine of 1.5 mg/dL (IQR 0.5; 3), and median eGFR of 52 ml/min (IQR 35.5; 79). Three of our patients were dialysis dependent at time of their last laboratory date, with one of them being a liver transplant recipient, and were excluded from above calculation.

and 74% at 5 years, demonstrating comparable to better than the previously published survival rates. These improved results in the modern era are most likely the result of earlier diagnosis and improved standardized treatment protocols with centralized referrals to a hematological malignancies team that specializes in the treatment of PTLD [33, 34].

Our study reveals similar outcomes with reduction of IS by means of switching from CNI based IS to mTOR inhibitor-based IS. The notion of RIS as the initial therapy dates back to observations by Starzl et al. [35] of 17 SOT recipients who developed PTLD, and has become the standard of care [36, 37]. Impaired activity of cytotoxic T-cell lymphocytes by IS induces proliferation of EBV-transformed B cells [8], and thus the goal of RIS is to reestablish T-cell function in the host. Over the years, this approach has shown a benefit mainly in a subset of patients with early disease [38], and about 60% of patients will require chemotherapy after RIS to achieve remission [36, 37]. However, this approach can also lead to increased risk of allograft rejection and a shortened allograft lifespan [39, 40]. The approach and degree of reduction of IS medications to manage PTLD remains controversial, and mostly based on older data when only CNIs were available [41-43]. In 2010, Parker et al. [44] published the British guidelines for PTLD, which stated the need to reduce the dose of CNIs by 30-50% and withdrawal of anti-metabolite therapy in patients with newly diagnosed PTLD, and this became the standard of care first step in the management of PTLD. These guidelines are based on expert opinion and no studies have demonstrated that reductions in CNIs improve outcomes. Clinical trials have adopted reduction of CNI [33] in their protocols prior to further therapy for lymphoma although it is unclear if this is of benefit to the majority of patients or only a subgroup such as EBV+ early PTLD. Another approach is to substitute CNI to mTOR inhibitor IS, which we utilized in 12 of 30 patients. Rapamycin has anti-proliferative effects in lymphoma including in PTLD cells as well as antiviral effects [45, 46]. Recent European data show that approximately 30% of solid organ transplant centers chose to switch to the mTOR inhibitor-rapamycin from a CNI, upon diagnosis of EBV positive PTLD due to its potentially beneficial properties [47]. This approach of switching to mTOR-inhibitor based IS was also highlighted in a registry-linked study of kidney transplant recipients [48], due to the potential anti-viral properties of rapamycin. However, the effect of mTOR inhibition in the pathogenesis of PTLD was still unclear with conflicting outcomes data. US data from the OPTN/UNOS database have revealed an association between the use of mTOR inhibition for maintenance IS and PTLD risk [49]. Conversely, a meta-analysis has shown a 40% decrease in risk of malignancy with mTOR inhibitor use as IS but a higher mortality in SOT patients [50]. In conclusion, the risk and benefit of any specific IS agent in PTLD is not clear, and the benefit seen with RIS may be explained by the net reduction of the immunosuppressive state of the SOT recipient, rather than being attributed to a specific IS agent. More data is needed in order to determine if reduction of CNI troughs versus conversion to an mTOR inhibitor IS regimen post-PTLD diagnosis is of benefit.

When transplant patients undergo RIS following PTLD diagnosis, they are at increased risk of losing their allograft, which is a cause of further morbidity, and increased mortality. Our cohort demonstrated favorable death censored allograft survival at 1, 3, and 5-years with reduction of IS including the switch from CNI based to mTOR inhibitor-based IS. In a study with 101 patients with PTLD, 21 lost their graft during the study period at a median follow up time of 70 months. The presence of an eGFR < 30 ml/min per 1.73 m^2 at PTLD diagnosis, biopsy-proven acute rejection following RIS, and the absence of a CNI agent as part of maintenance IS were independent risk factors for allograft loss whereas PTLD subtype or chemotherapy regimen did not affect the risk of allograft survival [40]. These results highlight that allograft outcomes post-PTLD diagnosis may be more dependent on changes of IS than to the type of cancer or the chemotherapy regimen. Conversely, Trappe and colleagues observed that treatment with R-CHOP may mitigate the risk of RIS, providing further immunosuppressive effect and decreasing the risk for graft loss to the allograft survival [51]. So, patients exposed to chemotherapy may be less likely to lose their allograft with RIS. Further studies are needed to determine the best strategies to decrease IS after PTLD in order to minimize allograft loss and facilitate PTLD remission.

Our single center study corroborates the improved PTLD outcomes specifically for the DLBCL subtype that is similar to more current outcomes series. Non-PTLD DLBCL is the most common type of NHL in the US [52], with most patients presenting with a highly aggressive disease. The standard treatment for the majority of patients with newly diagnosed DLBCL is R-CHOP [53], which leads to a cure in approximately 50-60% of cases [54]. Over the years, and based on the PTLD-1 study [34] as well as single center data, this R-CHOP treatment has been adopted for PTLD DLBCL, with improved responses and survival [1]. In our sub-cohort of 15 patients with PTLD DLBCL, 14 patients were treated with R-CHOP as first line chemotherapy treatment, with one patient receiving high dose methotrexate and dexamethasone for DLBCL with CNS involvement. Progression free survival was 86% at 1 year, and 77% at 3- and 5-years post lymphoma diagnosis, and OS in this population was of 86% at 1 and 3 years, and 75% at 5 years. Our outcome data in a limited cohort is similar to that of Lau et al. [55] and Canadian data [56] who reported improved response to treatment and survival in the modern era. The three patients in our PLTD DLBCL cohort who relapsed, later died. This is in line with previous data which have shown poor outcomes for patients in whom first line treatment failed, with a reported median OS of approximately 6 months [57]. In summary, the adoption of a more standardized treatment protocol for PTLD DLBCL subtype, which is similar to the management of non-PTLD DLBCL has been associated with improved outcomes.

Our study suggests a distinct metabolic profile in PTLD DLBCL compared to non-PTLD DLBCL. Glucose is the main substrate for cellular energetics of cancer and non-cancer cells and its metabolic fate can be glycolysis with the generation of lactate or mitochondrial OXPHOS with the generation of carbon dioxide and water [58]. Numerous studies have demonstrated increased glucose metabolism in aggressive B cell lymphomas including DLBCL [59-63]. In non-PTLD DLBCL the most common metabolic phenotype is one of metabolic coupling between non-cancer cells such as macrophages with high expression of the rate-limiting step in glycolysis MCT4 and high mitochondrial metabolism in the lymphoma cells with high MCT1 expression which is the main lactate importer and TOMM20, which allows for mitochondrial localization of nuclear encoded OXPHOS proteins [27, 28, 64]. MCT1 drives mitochondrial metabolism including OXPHOS and MCT1 expression has prognostic value in DLBCL [28, 58, 65]. Also, TOMM20 is a marker of mitochondrial metabolism, and it induces OXPHOS. Presently, studies with AZD3965, an MCT1 inhibitor, demonstrate that MCT1 inhibition increases apoptotic cell death in vitro in B cell lymphomas [28]. AZD3965 also has anticancer activity in vivo in aggressive B cell lymphomas [66]. A phase I clinical trial is underway to assess the safety and activity of AZD3965 in adults with DLBCL and Burkitt's lymphoma, which is another highly aggressive B cell lymphoma (NCT01791595). In sum, our data in a small number of PTLD DLBCL samples indicate that there could be reduced MCT1 expression in PTLD DLBCL compared to non-PTLD DLBCL. MCT1 is a prognostic biomarker in B cell lymphomas and targeting it has anticancer activity in aggressive B-cell lymphoma. Hence, future studies will need to determine if metabolic differences between PTLD and non-PTLD associated DLBCL can explain differences in outcomes between these two subtypes of DLBCL as well as to validate our findings in a larger cohort of patients.

Our study had several limitations including small sample size, a retrospective design, and the fact that some data were not available especially for subjects who underwent transplant over 20 years ago. Conversely, our transplant center has a very consistent IS protocol with little variation and patients are followed for the longevity of the allograft, which allowed us to have long-term follow up.

In summary, PTLD outcomes have improved recently with the adoption of standardized chemotherapy protocols and management by subspecialized teams. The use of mTOR inhibitors holds promise as an alternative to decreased CNI dosing as an IS strategy in the context of PTLD although further data will be needed. Finally, PTLD DLBCL may have a distinct metabolic profile, and this profile may be part of the reason that PTLD DLBCL is associated with better outcomes than non-PTLD DLBCL. Further studies are warranted to determine if metabolic targeting could be a therapeutic option for PTLD DLBCL and to corroborate our metabolic and clinical findings in a larger cohort of PTLD patients.

Disclosure of conflict of interest

None.

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