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Impact of post-transplant lymphoproliferative disorder subtype on survival

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Abstract

Introduction—Post-transplant lymphoproliferative disease (PTLD) is a life-threatening complication of solid organ transplantation (SOT). Histologic heterogeneity and lack of treatment standards have made evaluating clinical outcomes in specific patient populations difficult. This systematic literature review investigates the impact of PTLD histologic subtype on survival in a large dataset.

Methods—Case series were identified on PubMed using the search terms “post-transplant lymphoproliferative disorder/disease,” “PTLD,” and “solid organ transplantation,” with additional publications identified through reference lists. Patient characteristics, immunosuppressive regimen, treatment, survival, and follow-up time of 265 cases were extracted from 94 articles and combined with 11 cases from our institution. Patients with recorded subtype were included in Kaplan-Meier survival analysis (n=234). Cox proportional hazard regression analyses identified predictors of overall survival (OS) for each subtype and B-cell subgroup.

Results—OS differed significantly between monomorphic T-cell neoplasms (median 9 months) and polymorphic, monomorphic B-cell, and Hodgkin-type neoplasms, for which median OS was not reached (p=0.0001). Significant differences in OS among B-subgroups were not detected, but there was a trend towards decreased survival in Burkitt-type PTLD. Kidney transplant and reduction of immunosuppression were associated with increased OS in multivariable analysis in B-cell neoplasms. Immunosuppression with azathioprine was associated with decreased OS in T-cell neoplasms, while radiotherapy was associated with improved OS in that subtype.

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Conclusions—Histologic subtype represents an important prognostic factor in PTLT, with T-cell neoplasms exhibiting very poor OS. Possible lower survival in certain subsets of B-cell PTLT should be explored further and suggests the need for subtype-specific therapies to improve outcomes.

Keywords

post-transplant lymphoproliferative disorder; survival; immunosuppression; B-cell neoplasms; T-cell neoplasms

Introduction

Post-transplant lymphoproliferative disease (PTLD) comprises a group of lymphoid disorders arising in the setting of immunosuppression following solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). Reported cumulative incidences of PTLD in SOT range from 1 to 20% in SOT depending on transplanted organ, with peak incidence occurring 30–72 months after transplant^{1,2}, and 0.5 to 1.0% in HSCT³, with peak incidence 2 to 4 months post-transplant^{3,4}. Reports of PTLD-related mortality range from 30–60%, making this entity a major life-threatening complication of transplant⁵.

Accordingly, much work has been devoted to deciphering an etiologic framework for this complex disease in terms of both biology and epidemiology. However, the relative rarity of the disease has made evaluating clinical outcomes in specific patient populations difficult, since many analyses are limited by small sample size.

Morphologically and molecularly heterogeneous, PTLD is broadly categorized into four groups: early (plasmacytic hyperplasia and infectious mononucleosis-like lesions); polymorphic; monomorphic, which includes all T-cell/natural killer (NK) cell neoplasms as well as most B-cell neoplasms; and classical Hodgkin lymphoma⁶. Treatment of PTLD often varies according to subtype and from institution to institution,⁷ and is complicated by a difficult balance between the risks and benefits of reducing immunosuppression and the intensity of chemo-immunotherapy, which help to eradicate the malignancy but may increase risks of treatment-related toxicity and organ rejection. For patients with CD20+ monomorphic B-cell PTLD who do not respond to reduction of immunosuppression (RI) alone, the monoclonal CD20 antibody rituximab has emerged in the last 15 years as a viable therapeutic option when given alone,^{8–10} in combination with,^{11,12} or followed by chemotherapy with regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).¹³ Studies of PTLD outcomes in the post-rituximab era have largely been limited to the phase II trials investigating these regimens, and single-center experiences.^{14,15}

Although it seems reasonable that response to therapeutic agents and survival in certain monomorphic PTLD subgroups would mirror that of the *de novo* lymphoid malignancies they resemble (e.g., Burkitt or diffuse large B-cell lymphoma), data on subtype-specific outcomes remains limited, perhaps in part because such subgroup categorization may not be captured in epidemiologic datasets. Thus, we conducted a systematic literature review that

focused on detailed case series to investigate the impact of histologic subtype on survival in PTLTD after SOT.

Methods

Systematic literature review

Case reports and series were identified on PubMed using the search terms “post-transplant lymphoproliferative disorder/disease,” “PTLD”, and “solid organ transplantation,” generating a pool of 194 articles. Additional manuscripts identified through the reference lists of these papers were incorporated into the pool, which were assessed by inclusion criteria for suitability as shown in Figure 1. Inclusion criteria were: 1) articles published in English between January 1, 1974 and July 1, 2016 with pathology diagnosis and survival details; 2) adult cases following SOT.

A total of 306 cases were extracted from 94 articles (listed in Supplemental Table) and combined with 11 cases from our institution. Data abstracted included patient characteristics (age and gender), transplanted organ(s), immunosuppressive regimen, histologic subtype, initial PTLTD treatment, response to treatment, time interval between transplant and PTLTD diagnosis (in months), time interval between PTLTD diagnosis and death (in months), and length of follow-up after PTLTD diagnosis (in months). Based upon the description in the primary publication, histologic subtypes were coded as polymorphic, monomorphic B-cell, monomorphic T-cell, or Hodgkin-like (HL); there were no early PTLTD cases identified in our review of published cases. Monomorphic B-cell neoplasms were also further subdivided into four subgroups: diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, plasmacytoid, and other/unspecified.

Statistical analysis

Univariate association of each covariate described above with each of four major subtypes (polymorphic, monomorphic B-cell, monomorphic T-cell, and HL neoplasms) and with four subgroups of B-cell neoplasms was assessed using the chi-square test for categorical covariates and ANOVA for numerical covariates.

Patients with recorded subtype information and reported survival on follow-up were included in survival analysis (n=234). Univariate and multivariable Cox proportional hazard regression analyses were performed to identify predictors of overall survival (OS) for each subtype and B-cell subgroup. OS was defined as time from diagnosis to death or last follow-up, where those still alive were censored at last follow-up. The multivariable model was fit by a backward variable selection method, applying a level of significance (α) of 0.10 as removal criteria. Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test. To evaluate the impact of changes in standard therapy over time on survival, we divided cases into eras by year of publication: 1974 to 1999 to reflect the years before widespread rituximab use, and 2000–2016, by which time rituximab was commonly used to treat other B-cell malignancies and the first retrospective analyses of its use in CD20+ PTLTD had been reported.^{16,17}

A level of significance (α) of 0.05 was considered statistically significant. All statistical analyses were conducted using SAS Version 9.4, with SAS macros and software developed at the Biostatistics and Bioinformatics Core at Winship Cancer Institute.¹⁸

Results

Table 1 depicts baseline characteristics and treatment information for the entire cohort of cases ($n = 234$). Of these, 52.1% were B-cell monomorphic neoplasms (of which DLBCL was the most frequent subtype [$n=59$, 48.3% of B neoplasms]), 28.6% were T monomorphic neoplasms, 10.6% were HL, and 4.3% were polymorphic. Compared to other subtypes, HL-PTLD patients were younger at diagnosis (mean age of 37, $p = 0.001$), and among B-cell monomorphic PTLD, Burkitt-type PTLD patients were significantly younger (mean age of 37, $p < 0.001$), mirroring incidence patterns seen in corresponding *de novo* lymphoma types. As might be expected, polymorphic cases were more likely to be treated with surgery and less likely to receive chemotherapy than most other subtypes. Compared to other B-cell subgroups, treatment with chemotherapy was significantly more common in Burkitt-type PTLD (92.9%, $p = 0.014$). Univariate comparisons of variables between PTLD subtypes and among B-cell subgroups are shown in Tables 2 and 3, respectively.

In survival analysis, OS was significantly different between histological and immunophenotypic subtypes. Monomorphic T-cell neoplasms had worse survival (median 9 months), while median OS was not reached for polymorphic, monomorphic B-cell, and HL PTLD (log-rank $p=0.0001$, Figure 2a). Two-year OS with 95% confidence intervals for each subtype were as follows: 35% (23.4–46.9%) in monomorphic T cell, 70.0% (32.9–89.2%) in polymorphic, 60.6% (50.6–69.2%) in monomorphic B cell, and 76.5% (51.9–89.7%) in HL neoplasms. Significant differences in OS among B-subgroups were not detected, but there was a trend towards decreased survival in Burkitt-type PTLD (Figure 2b). We found that while survival outcomes appeared to improve for all histologic subtypes in the “modern,” post-rituximab period, prognosis for T-cell neoplasms remained poor regardless of treatment era (Figure 3). The greatest improvement in survival was seen in Hodgkin-like subtype: 2-year overall OS was 100% in the 2000–2016 era, compared to 67.5% (38.4–85.1%) in the 1974–1999 era. The small number of total monomorphic B-cell cases in the pre-rituximab era ($n=23$) precluded us from comparing outcomes for B-cell subgroups between treatment eras. As shown in Table 4, kidney transplant and treatment with reduction of immunosuppression were associated with increased OS in multivariable analysis in B-cell neoplasms. Immunosuppression with azathioprine was associated with decreased OS in T-cell neoplasms, while treatment with radiotherapy was associated with improved OS in that subtype. (Table 5).

Discussion

To investigate outcomes in specific PTLD subtypes, our systematic review sought to increase representation of relatively rare subgroups by aggregating clinical and survival data from published case series. This unconventional approach helped to mitigate the dual problem of small sample size, which often limits analyses derived from single-center experiences, and the lack of pathologic specificity that plagues many larger epidemiologic

databases. The potential limitations of our study include those inherent to carrying out any systematic review, including publication bias and study selection bias. Specifically, we suspect that the higher-than-expected frequency of monomorphic T-cell neoplasms in our dataset may be due to publication bias towards presentation of more unusual cases. We performed a comprehensive systematic review of the literature including a search of relevant publications cited by each source to address these issues where possible. Given our focus on case series, our approach was also limited by publications that lacked central pathology review or provided inadequate data for inclusion in survival analyses. Specifically, missing or incomplete data on EBV association (27%) hindered our ability to reliably assess this as a factor in subtype-specific survival. Comprehensive prospectively collected data in large cohort studies that include patients with PTLT are needed to meaningfully capture these clinical factors and assess their impact on survival. Nevertheless, our approach represents a large retrospective dataset assembled to examine PTLT subtype-specific clinical factors, treatment patterns, and outcomes, and provides provocative data for future investigation.

Our finding that patients with monomorphic T-cell PTLT exhibited poor survival compared to other subtypes is supported by a recent meta-analysis that examined T-cell PTLT alone. In that study, which included pediatric cases, median OS for all 156 cases was only 6 months, with subgroup-specific (i.e., hepatosplenic, anaplastic, primary cutaneous anaplastic, or peripheral T cell lymphoma, not otherwise specified) OS ranging from 2 to 18 months.¹⁹ T-cell subtype was also found to be a negative prognostic factor for OS in a Swedish study of 135 PTLT cases (of which 15 were T-cell neoplasms), with a hazard ratio (HR) of 3.52 ($p < 0.001$) in multivariable Cox regression analysis.²⁰

Although not statistically significant, a trend towards decreased survival in Burkitt-type monomorphic B-cell PTLT seen in our study merits investigation in larger datasets. The concept that Burkitt-type PTLT should be considered a discrete entity within B-cell PTLT, with clinicopathologic features that also distinguish it from sporadic, endemic, and immunodeficiency-associated Burkitt lymphomas, has been posited in the pediatric setting.²¹ Interestingly, although cases in that particular series uniformly exhibited aggressive clinical behavior, none of the patients who died during follow-up exhibited evidence of unresponsive and/or progressive disease at time of death.

Potential factors underlying subtype-specific outcomes in PTLT

Given that 50 to 70% of PTLTs are Epstein-Barr virus (EBV)-related, current understanding of PTLT development uses the model of malignant transformation of EBV-infected B-cells in the setting of reduced T-cell control that results from immunocompromise and/or immunosuppression^{2,22–24}. However, such models do not account for the significant proportion of PTLT cases in which the role of EBV is not readily apparent, such as in neoplasms arising from T- or NK-cells—although presence of EBV DNA in T-cell PTLT tumor cells has been described.²⁵ Disparities in timing of peak incidence between SOT and HSCT suggest differences in etiologic pathways as well. In fact, typical SOT-related PTLTs develop from recipient cells, while most HSCT-associated PTLTs arise from donor cells, further adding to the complexity of characterizing oncogenesis in this heterogeneous disease.

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Perhaps unsurprisingly, other major risk factors for PTLT development relate to modulations of the immune milieu. Reported risk factors in SOT include transplantation of lymphoid-rich organs such as lung and intestine, and transplantation from EBV-seropositive donor to EBV-seronegative recipient, whereas risk factors in HSCT include T cell-depleted graft, HLA mismatch, and primary immunodeficiency^{26,29}. Estimation of the intensity of pharmacological immunosuppression between individual patients and across clinical SOT protocols is challenging, and associations between immunosuppression and PTLT have been derived only indirectly from registry analyses and observational studies.³⁰ In both SOT and HSCT, T-cell-depleting agents such as anti-thymocyte globulin (ATG) and the anti-CD3 monoclonal antibody OKT3 are associated with PTLT development.^{15,31–33} Interestingly, increased PTLT risk has not been observed with alemtuzumab,³⁴ a monoclonal antibody directed against the CD52 marker present on both B- and T-cells, leading some to speculate that that drug's additional B-cell-depleting effect could serve to reduce the risk of B-cell PTLT. In the maintenance setting, the calcineurin inhibitor tacrolimus has been associated with increased PTLT risk in several large studies,^{31,32,35,36} but mycophenolate mofetil does not appear to exert this same effect.^{15,35,37–40} Although the mechanisms underlying these differences in risk remain unclear, it is worth noting that mycophenolate acts to suppress both B- and T-cells, while tacrolimus' immunosuppressive effect is more T-cell-specific.

Conversely, prophylactic anti-viral use following transplantation may reduce risk of PTLT development up to 83%, depending on the anti-viral agent⁴¹. The combination of monitoring serum EBV-DNA load and adjusting immunosuppression is similarly associated with lower incidence of PTLT after SOT^{42,43}. Indeed, RI is a frequently used initial approach for PTLT that can reconstitute cytotoxic T-cell function against uncontrolled lymphoproliferation, with response rates reported as high as 45%⁴⁴.

It is difficult to evaluate the role of individual immunosuppressive agents and RI strategies in PTLT risk and outcomes, especially since transplant patients may receive a variety of drug combinations during induction, maintenance, and/or treatment for graft rejection.⁴⁵ Although the relatively small sample size in our multiple variable regression models limits their power, our results indicate that RI is associated with improved OS in B-cell but not T-cell PTLT. These findings suggest subtype-specific differences in susceptibility to cytotoxic T-cell effects, which may in turn reflect etiologic differences in pathogenesis (e.g., EBV-induced malignant transformation in B-cell but not T-cell neoplasms). Moreover, the association of azathioprine with decreased OS in T-cell PTLT may implicate particular immunosuppressive agents as barriers to eradication of certain PTLT subtypes. Our findings are supported by a large study of 230 cases from the French Registry of PTLT occurring after renal transplant, which identified azathioprine as a factor associated with poor overall survival, but that study did not show a subtype-specific association or survival differences based on histologic factors.⁴⁶ Although azathioprine's inhibition of purine nucleotide biosynthesis with suppression of DNA and RNA synthesis has been well described, the specific mechanism(s) by which it down-regulates B-cell and T-cell function to induce immunosuppression are less well characterized. *In vitro* and *in vivo* data suggest that azathioprine may interfere with CD28 costimulation of alloreactive T cells by blocking the GTPase Rac1, which results in activation of apoptotic pathways upon CD28-mediated signaling.⁴⁷ Furthermore, azathioprine may preferentially induce apoptosis in CD45RO

memory T-cells through suppression of expression of the anti-apoptotic protein BCL-XL, thus offering a possible explanation for azathioprine's ability to induce tolerance to foreign antigen (e.g., of an organ graft). However, it remains unclear how elimination of this T-cell population might contribute to worse prognosis in T-cell PTLD. To answer this and other complex questions surrounding the impact of immunosuppressive regimen on subtype-specific outcomes, prospective epidemiologic studies are needed to link detailed clinical information with data from biologic specimens, including tumor tissue and longitudinally collected peripheral blood samples.

As in *de novo* lymphoid malignancies, subtype-specific survival in PTLD may also depend on response to immunochemotherapeutic regimens. Importantly, better survival in B-cell PTLDs may in part reflect improved treatment responses seen with rituximab treatment, unavailable to PTLD subtypes without CD20 expression. In a retrospective multicenter analysis of 80 SOT-related PTLD patients who received reduction of immunosuppression, those who received concomitant frontline rituximab-based therapy experienced improved 3-year progression free survival and OS (70% and 73%, respectively), compared to those who did not (21% and 33%).⁴⁸ However, that study did not differentiate between subtypes of monomorphic PTLD. Three prospective phase II trials provided evidence that rituximab monotherapy has efficacy in CD20-positive PTLD, but all of these demonstrated relatively short time-to-progression intervals.^{8–10} Accordingly, the prospective multicenter PTLD-1 trial investigated a sequential treatment approach with 4 weeks of rituximab followed by chemotherapy with CHOP in SOT-related CD20-positive PTLD failing to respond to RI.⁴⁹ Sixty percent of patients (42/70) achieved either a complete response (CR) or partial response (PR) after rituximab monotherapy, with response rate improving to 90% (53/59) with CR rate of 68% upon completion of sequential therapy. Median survival in responders was not reached at time of analysis, and response to rituximab prior to chemotherapy was predictive of time to progression and OS. EBV-associated disease was also found to be favorable in terms of time to progression, further emphasizing rituximab's role in PTLD outcomes.

Although we used the advent of widespread rituximab use as a cut-point to analyze changes in subtype-specific survival over time, the most striking difference in survival between treatment eras occurred among HL-PTLD, a CD20-negative subtype that does not benefit from rituximab treatment. Sample sizes are admittedly small, but it is unclear what factors led to this apparent increase over time. Notably, none of the articles reported treatment with newer agents such as the CD30-targeting antibody-drug conjugate brentuximab vedotin. It is possible that this may reflect a shift in supportive care or diagnostic knowledge, but it may also lend support to the findings of Rosenberg *et al.* that patients with HL-PTLD who received chemotherapeutic regimens traditionally used in Hodgkin lymphoma experienced improved survival.⁵⁰ That recent retrospective analysis utilized the Scientific Registry for Transplant Recipients (SRTR) and Surveillance Epidemiology and End Results (SEER) databases to compare outcomes between HL-PTLD and *de novo* Hodgkin lymphoma, highlighting several interesting ideas pertaining to PTLD subtype. For HL-PTLD patients, receipt of any chemotherapy was associated with decreased hazard of death (HR = 0.36, $p < 0.001$), and patients who received nontraditional Hodgkin regimens had increased hazard of death (adjusted HR = 2.01, $p = 0.04$) compared to those who received Hodgkin-specific

chemotherapy regimens. To account for the fact that patients with HL-PTLD would be more likely to die of non-lymphoma causes than patients without prior SOT (e.g., graft failure), the authors calculated cumulative incidence curves of lymphoma-specific mortality, treating other causes of death as competing risks. HL-PTLD patients exhibited a 5-year lymphoma-specific mortality rate of 23%, compared to 13% for patients with *de novo* ($p < 0.001$). Taken together, these findings suggest that subtype-directed therapy remains an important consideration in PTLD, but lymphoma-specific survival for HL PTLD remains worse for than its *de novo* counterpart. Additional studies utilizing large datasets are needed to determine whether such conclusions hold true for other rare subgroups of monomorphic PTLD. Improved understanding of the underlying differences in the pathogenesis of PTLD subtypes and outcomes for subtype-directed therapies compared to their *de novo* counterparts will be necessary to tailor appropriate treatments for each subtype.

Conclusions

Our work lends credence to the emerging concept that PTLD subtype carries major implications in terms of both prognosis and treatment options. Importantly, we show that patients with monomorphic T-cell PTLD suffer inferior survival compared to all other subtypes. Possible lower survival in certain subsets of monomorphic B-cell PTLD should also be explored further and suggests the need for subtype-specific therapies to improve outcomes. Multi-institution collaborative efforts could evaluate these associations in a larger number of cases with the necessary level of histologic discrimination. In general, performing meaningful studies of subtype-specific disparities in PTLD in the future will require collection of biological specimens as well as clinical data to examine the effect of PTLD subtype on differences in disease presentation, treatment selection, and patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selection strategy for articles included in meta-analysis.

Figure 2. Overall survival in patients with PTLD by histologic subtype (A) and in patients with B-cell PTLD by B-cell subgroup (B)

Abbreviations: B, monomorphic B-cell; T, monomorphic T-cell; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin-like.

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Figure 3. Overall survival in patients with PTLD by histologic subtype by treatment era

(A) 1974 – 1999. (B) 2000 – 2016. Abbreviations: B, monomorphic B-cell; T, monomorphic T-cell; HL, Hodgkin-like.

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Table 1

Baseline and treatment characteristics of post-transplant lymphoproliferative disorder (PTLD) cases with available survival data from systematic review. Abbreviations: post-transplant lymphoproliferative disorder (PTLD); diffuse large B-cell lymphoma (DLBCL); standard deviation (SD).

Variable	Total n = 234 (%)
Age at diagnosis	
Mean years $\pm$ SD	47 $\pm$ 14
Sex	
Female	59 (25.5%)
Male	172 (74.5%)
Missing	3
Histologic subtype	
B-cell monomorphic	122 (52.1%)
T-cell monomorphic	67 (28.6%)
Hodgkin-type	25 (10.7%)
Polymorphic	10 (4.3%)
Not otherwise specified	10 (4.3%)
<i>B-cell monomorphic subgroups</i>	<i>n = 122</i>
DLBCL	59 (48.4%)
Burkitt lymphoma	14 (11.5%)
Plasmacytoid	27 (22.1%)
Other/unspecified	22 (18%)
Transplanted organ(s)	
Heart or Heart-Lung	51 (21.8%)
Kidney or Kidney-Pancreas	130 (55.6%)
Lung or Small Bowel	14 (6%)
Liver or Liver-Kidney or Liver-Small Bowel	39 (16.7%)
Immunosuppressive regimen at diagnosis	
Calcineurin inhibitors	
None	11 (0.5%)
Cyclosporine	157 (71.4%)
Tacrolimus	50 (22.7%)
Cyclosporine and tacrolimus	2 (0.9%)
Missing	14
Anti-metabolites	
None	51 (23.1%)
Azathioprine	106 (48%)
Mycophenolate mofetil	64 (29%)
Missing	13

Variable	Total n = 234 (%)
Steroids	
Yes	159 (77.2%)
No	47 (22.8%)
<i>Missing</i>	28
<i>PTLD treatment</i>	
Reduction of immunosuppression	
Yes	168 (74%)
No	59 (26%)
<i>Missing</i>	7
Chemotherapy	
Yes	131 (57.5%)
No	97 (42.5%)
<i>Missing</i>	6
Rituximab	
Yes	46 (19.8%)
No	186 (80.2%)
<i>Missing</i>	2
Radiotherapy	
Yes	45 (19.6%)
No	185 (80.4%)
<i>Missing</i>	4
Surgical resection	
Yes	26 (11.2%)
No	207 (88.8%)
<i>Missing</i>	1

Table 2

Univariate associations by histologic subtype of post-transplant lymphoproliferative disorder. Abbreviation: standard deviation (SD).

Variable	B-cell monomorphic n = 122 (%)	T-cell monomorphic n = 67 (%)	Hodgkin-type n = 25 (%)	Polymorphic n = 10 (%)	p-value
Age at diagnosis					
Mean years $\pm$ SD	48 $\pm$ 14	49 $\pm$ 14	37 $\pm$ 12	43 $\pm$ 7	0.001
Sex					
Female	31 (26.1)	18 (26.9)	4 (16)	1 (10)	0.480
Male	88 (73.9)	49 (73.1)	21 (84)	9 (90)	
Transplanted organ(s)					
Heart or Heart-Lung	30 (24.6)	16 (23.9)	3 (12)	1 (10)	0.022
Kidney or Kidney-Pancreas	54 (44.3)	43 (64.2)	18 (72)	6 (60)	
Other	38 (31.1)	9 (11.9)	4 (16)	3 (30)	
Calcineurin inhibitors					
None	1 (0.8)	5 (8.6)	3 (12)	2 (22.2)	<0.001
Cyclosporine	86 (72.9)	39 (67.2)	21 (84)	4 (44.4)	
Tacrolimus	31 (26.3)	14 (24.1)	1 (4)	2 (22.2)	
Cyclosporine and tacrolimus	0	0	0	1 (11.1)	
Anti-metabolites					
None	30 (25.4)	12 (20.3)	6 (24)	1 (11.1)	0.091
Azathioprine	49 (41.5)	33 (55.9)	15 (60)	2 (22.2)	
Mycophenolate mofetil	39 (33.1)	14 (23.7)	4 (16)	6 (66.7)	
Steroids					
Yes	88 (79.3)	45 (83.3)	19 (76)	2 (66.7)	0.064
No	23 (20.7)	9 (16.7)	6 (24)	4 (33.3)	
Reduction of immunosuppression					
Yes	88 (72.7)	42 (66.7)	21 (87.5)	7 (70)	0.269
No	33 (27.3)	21 (33.3)	3 (12.5)	3 (30)	
Chemotherapy					
Yes	63 (52.1)	41 (65.1)	20 (80)	3 (33.3)	0.016
No	58 (47.9)	22 (34.9)	5 (20)	6 (66.7)	
Rituximab					

Variable	B-cell monomorphic n = 122 (%)	T-cell monomorphic n = 67 (%)	Hodgkin-type n = 25 (%)	Polymorphic n = 10 (%)	p-value
Yes	36 (29.5)	2 (3.1)	2 (8)	3 (30)	<0.001
No	86 (70.5)	63 (96.9)	23 (92)	7 (70)	
Radiotherapy					
Yes	100 (82)	14 (22.2)	9 (36)	0	0.077
No	22 (18)	49 (77.8)	16 (64)	10 (100)	
Surgical resection					
Yes	10 (8.2)	3 (4.5)	8 (32)	2 (20)	0.002
No	112 (91.8)	63 (95.5)	17 (68)	8 (80)	

Univariate associations by subgroup of monomorphic B-cell post-transplant lymphoproliferative disorder. Abbreviations: diffuse large B-cell lymphoma (DLBCL); standard deviation (SD).

Table 3

Variable	DLBCL n = 59 (%)	Burkitt-type n = 14 (%)	Plasmacytoid n = 27 (%)	Other/NOS n = 22 (%)	p-value
Age at diagnosis					
Mean years $\pm$ SD	45 $\pm$ 13	37 $\pm$ 11	55 $\pm$ 11	52 $\pm$ 15	<0.001
Sex					
Female	17 (28.8)	2 (14.3)	8 (29.6)	4 (21.1)	0.704
Male	42 (71.2)	12 (85.7)	19 (70.4)	15 (78.9)	
Transplanted organ(s)					
Heart or Heart-Lung	21 (35.6)	2 (14.3)	3 (11.1)	4 (18.2)	0.206
Kidney or Kidney-Pancreas	21 (35.6)	7 (50)	14 (51.9)	12 (54.5)	
Other	17 (28.8)	5 (35.7)	10 (37)	6 (27.3)	
Calcineurin inhibitors					
None	1 (1.7)	0	0	0	0.26
Cyclosporine	47 (79.7)	9 (64.3)	16 (59.3)	14 (77.8)	
Tacrolimus	11 (18.6)	5 (35.7)	11 (40.7)	4 (22.2)	
Anti-metabolites					
None	12 (20.3)	7 (50)	8 (29.6)	3 (16.7)	0.073
Azathioprine	29 (49.2)	4 (28.6)	6 (22.2)	10 (55.5)	
Mycophenolate mofetil	18 (30.5)	3 (21.4)	13 (48.2)	5 (27.8)	
Steroids					
Yes	42 (79.2)	8 (57.1)	20 (76.9)	18 (100)	0.018
No	11 (20.8)	6 (42.9)	6 (23.1)	0	
Reduction of immunosuppression					
Yes	46 (79.3)	7 (50)	20 (74.1)	15 (68.2)	0.16
No	12 (20.7)	7 (50)	7 (25.9)	7 (31.8)	
Chemotherapy					
Yes	28 (48.3)	13 (92.9)	12 (44.4)	10 (45.5)	0.014
No	30 (51.7)	1 (7.1)	15 (55.6)	12 (54.5)	
Rituximab					

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Variable	DLBCL n = 59 (%)	Burkitt-type n = 14 (%)	Plasmacytoid n = 27 (%)	Other/NOS n = 22 (%)	p-value
Yes	18 (30.5)	7 (50)	2 (7.4)	9 (40.9)	0.014
No	41 (69.5)	7 (50)	25 (92.6)	13 (59.1)	
Radiotherapy					
Yes	6 (10.2)	3 (21.4)	9 (33.3)	4 (18.2)	0.066
No	53 (89.8)	11 (78.6)	18 (66.7)	18 (81.8)	
Surgical resection					
Yes	3 (5.1)	1 (7.1)	6 (22.2)	0	0.028
No	56 (94.9)	13 (92.9)	21 (77.8)	22 (100)	

Table 4

Multivariable analysis of overall survival in monomorphic B-cell post-transplant lymphoproliferative disorder. Number of observations in the original data set = 122. Number of observations used = 111. Backward selection with an alpha level of removal of 0.10 was used. The following variables were removed from the model: age, sex, calcineurin inhibitors, anti-metabolites, steroids, chemotherapy, rituximab, and surgical resection. Abbreviations: hazard ratio (HR), confidence interval (CI).

Covariate	Level	HR (95% CI)	HR p-value
Organ graft	Lung or Small Bowel	4.83 (1.38–16.96)	0.014
	Liver or Liver-Kidney or Liver-Small Bowel	2.77 (1.06–7.27)	0.038
	Heart or Heart-Lung	5.57 (2.31–13.44)	<0.001
	Kidney or Kidney-Pancreas	-	-
Reduction of immunosuppression	Yes	0.44 (0.23–0.84)	0.013
	No	Ref	-
Radiotherapy	Yes	0.41 (0.15–1.13)	0.085
	No	-	-

Table 5

Multivariable analysis of overall survival in monomorphic T-cell post-transplant lymphoproliferative disorder. Number of observations in the original data set = 67. Number of observations used = 45. Backward selection with an alpha level of removal of 0.10 was used. The following variables were removed from the model: sex, transplanted organs, reduction of immunosuppression, steroids, chemotherapy, rituximab, and surgical resection. Abbreviations: hazard ratio (HR), confidence interval (CI).

Covariate	Level	HR (95% CI)	HR p-value
Calcineurin inhibitor	Tacrolimus	0.08 (0.01–0.76)	0.028
	Cyclosporine	0.33 (0.11–1.04)	0.058
	None	Ref	-
Anti-metabolite	Mycophenolate mofetil	1.20 (0.13–11.42)	0.875
	Azathioprine	3.12 (1.10–8.86)	0.032
	None	Ref	-
Radiotherapy	Yes	0.32 (0.11–0.92)	0.034
	No	Ref	-
Age	-	0.97 (0.94–1.00)	0.079