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Management and Outcomes of Diffuse Large B-cell Lymphoma Post-transplant Lymphoproliferative Disorder in the Era of PET and Rituximab: A Multicenter Study From the Australasian Lymphoma Alliance

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Abstract

There are limited data on post-transplant lymphoproliferative disorder (PTLD) in the era of positron emission tomography (PET) and rituximab (R). Furthermore, there is limited data on the risk of graft rejection with modern practices in reduction in immunosuppression (RIS). We studied 91 patients with monomorphic diffuse large B-cell lymphoma PTLD at 11 Australian centers: median age 52 years, diagnosed between 2004 and 2017, median follow-up 4.7 years (range, 0.5–14.5 y). RIS occurred in 88% of patients. For patients initially treated with R-monotherapy, 45% achieved complete remission, rising to 71% with the addition of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) for those not in complete remission. For patients initially treated with R-CHOP, the complete remission rate was 76%. There was no difference in overall survival (OS) between R-monotherapy and R-chemotherapy patients. There was no difference in OS for patients with systemic lymphoma (n = 68) versus central nervous system (CNS) involvement (n = 23) (3-y OS 72% versus 73%; $P = 0.78$). Treatment-related mortality was 7%. End of treatment PET was prognostic for patients with systemic lymphoma with longer OS in the PET negative group (3-y OS 91% versus 57%; $P = 0.01$). Graft rejection occurred in 9% (n = 4 biopsy-proven; n = 4 suspected) during the entire follow-up period with no cases of graft loss. RIS and R-based treatments are safe and effective with a low likelihood of graft rejection and high cure rate for patients achieving complete remission with CNS or systemic PTLD.

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) represent a heterogeneous group of lymphoid proliferations due to immunosuppression in solid organ transplant recipients.[1] The incidence depends on the type of transplant ranging from 0.5%

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to 10% and is rising due to a greater number of transplants and increasing age of the recipient.[2,3]

PTLDs represent a spectrum from polyclonal proliferations (polymorphic PTLD) that are usually Epstein-Barr virus (EBV) positive to lymphoid cancers indistinguishable to those seen in nonimmunosuppressed populations (monomorphic PTLD).[4] The majority of monomorphic PTLDs are histologically diffuse large B-cell lymphoma (DLBCL).[4–7] Iatrogenic immunosuppression results in a reduction in T-cell immune surveillance enabling an EBV-driven B-cell proliferation to occur that may result in malignant transformation. The pathogenesis of EBV-negative PTLD is less clear.[1]

Rituximab is a monoclonal antibody directed against CD20 and is effective in CD20+ B-cell PTLD.[8–11] The international PTLD-1 trials have shaped current treatment approaches. In the first, a sequential treatment approach was used with 4 cycles of weekly rituximab followed by cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy.[5] In the extension of this trial, risk-stratified sequential treatment was used where complete remission to rituximab induction identified a group with favorable progression-free survival (PFS) who only required additional rituximab monotherapy, while R-CHOP consolidation for those who did not achieve complete remission with rituximab alone appeared safe and effective.[6] Consequently, guidelines recommend initial RIS, followed by rituximab and then either R-CHOP chemotherapy for persistent or progressive disease or rituximab monotherapy for those in complete remission.[12] Patients with central nervous system (CNS) involvement were excluded from the PTLD-1 trials, and there remains limited data regarding their outcomes in the era of rituximab.

The management of PTLD requires a balance between preserving the graft and delivering effective lymphoma therapy to achieve cure. A reduction in immunosuppression (RIS) restores EBV-specific and anti-tumor immunity, yet this may increase the risk of graft rejection. The incidence of graft rejection with RIS is difficult to define. Current recommendations for RIS are based on guidelines developed in the early 2000s for renal transplant recipients and recommend: stop antimetabolites (mycophenolate and azathioprine), reduce calcineurin inhibitors (tacrolimus and cyclosporine) by 25%–50% and maintain or reduce corticosteroids.[13] Although these represent common clinical practice, there is limited evidence to guide this practice and variation exists based on type of organ transplant.

There are limited data describing outcomes in PTLD in the era of rituximab and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET). The purpose of this study was to assess the management practices and outcomes in a population-based cohort in the era of PET and rituximab. We focused on monomorphic DLBCL PTLD as this is the most common histological subtype for which treatment is likely to be most standardized.

Methods

Patients

We conducted a multicenter, retrospective study involving 11 Australian tertiary referral centers. The study protocol was reviewed and approved by each institutional regulatory committee. Inclusion criteria were[1]: aged ≥ 18 years with a known solid organ transplant[2]; diagnosis of monomorphic DLBCL PTLD between January 2004 and December 2017[3]; and staged by PET. Patients with PTLD post allogeneic stem cell transplantation were excluded. We collected data on[1]: baseline demographics including transplant type and immunosuppression at the time of diagnosis[2]; patterns of RIS with PTLD treatment[3]; the incidence of graft rejection during and after lymphoma treatment (defined as early <1 year; late ≥1 year from diagnosis) based on clinical suspicion or biopsy[4]; treatment delivered; and[5] lymphoma response and survival outcomes. Central pathology review was not performed.

We examined responses according to treatment. Rituximab primary (R-primary) was defined as patients managed with initial rituximab monotherapy followed by response assessment. Patients in remission would undergo observation or receive further rituximab monotherapy versus patients with persistent or progressive disease receiving rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP). Rituximab-chemotherapy (R-chemotherapy) was defined as patients receiving rituximab-based chemotherapy at diagnosis. The chemotherapy regimens were grouped into R-CHOP, reduced-intensity regimens, intensive treatment (non-CNS-directed), and CNS-directed treatment. Imaging modality selected for restaging was per physician discretion. Staging and response assessment was defined by sites according to international lymphoma criteria (negative—complete remission—Deauville score 1–3, where available).[14]

Statistical analysis

PFS was defined as the time from diagnosis until progressive disease, relapse, or death from any cause. Overall survival (OS) was defined as the time from diagnosis until death from any cause. Disease-specific survival (DSS) was defined as the time from diagnosis until death from lymphoma or treatment-related toxicity. Treatment-related mortality (TRM) was defined as death due to toxicity from lymphoma treatment during or within 3 months from the completion of treatment. Comparisons between groups were performed using chi-square test for categorical variables. The Kaplan-Meier method was used to estimate OS, PFS, and DSS and survival curves were compared using the log-rank test. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression analysis. Variables that showed different distribution across groups ($P < 0.1$) were included in the Cox regression models that used OS as the dependent variable to identify potential independent prognostic factors. A landmark analysis at 6 months post-diagnosis was performed to assess the prognostic value of end of treatment PET in systemic PTLD cases.

Results

Patient characteristics

A total of 91 patients fulfilled the inclusion criteria (Figure 1). The baseline characteristics for all patients are shown in Table 1.

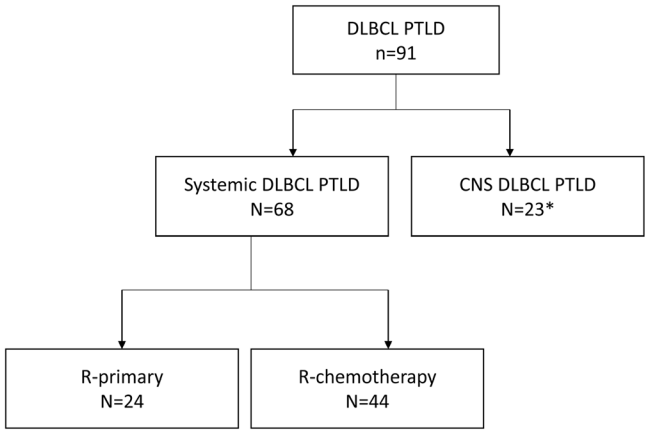

Figure 1. Overview of all study patients. R-primary is defined as patients initially managed with rituximab monotherapy. R-chemotherapy is defined as patients initially managed with rituximab-based chemotherapy. *Includes 2 patients with systemic and CNS involvement. CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; PTLD = post-transplant lymphoproliferative disorder.

Table 1.

Baseline Characteristics for 91 Patients With Monomorphic DLBCL PTLD.

Characteristic	N (%)
Median age at PTLD diagnosis (range)	52 y (18–81 y)
Median time from organ transplantation to PTLD (range)	7.1 y (0.16–36 y)
Age ≥60 at PTLD diagnosis	29/91 (32)
Less than 12 mo from transplantation to PTLD	18/91 (20)
Male gender	57/91 (63)
Organ transplanted	
Heart	6/91 (7)
Lung	13/91 (14)
Liver	23/91 (25)
Kidney only	41/91 (45)
Multiple[a]	8/91 (9)
ECOG performance status	
0–1	60/81 (74)
≥2	21/81 (26)
Stage	
1	3/91 (3)
1E	28/91 (31)
2	6/91 (7)
3	3/91 (3)
4	51/91 (56)
IPI score	
0–1	30/76 (40)
2–3	33/76 (43)
4–5	13/76 (17)
Tumor EBV status (EBER ISH pos)	52/87 (60)
B symptoms present	29/82 (35)
Nodal involvement	49/91 (54)
Extranodal involvement	
Gastrointestinal	33/91 (36)
Central nervous system	23/91 (25)
Bone	20/91 (22)
Liver	12/91 (13)
Bone marrow	9/91 (10)
Nodal involvement only	9/91 (10)
Graft	7/91 (8)
Other[b]	28/91 (31)
≥1 extranodal site	32/91 (35)
Bulky disease (>10 cm)	4/87 (5)
Raised LDH	47/84 (56)
Hypoalbuminemia (<35 g/L)	47/89 (53)
Raised beta 2 microglobulin	19/28 (68)

[a]Patients with more than 1 solid organ transplantation: 4 kidney/pancreas, 1 kidney/liver, 1 heart/lung, 1 heart/kidney, and 1 heart/lung/liver transplant recipients.

[b]Other extranodal involvement: mesentery (n = 6), pharynx (n = 5), thyroid (n = 3), spleen (n = 2), pleura (n = 2), and 1 case each of skin, muscle, kidney, adrenal, pancreas, pericardium, vulva, parotid gland, base of tongue, and orbit involvement.

DLBCL = diffuse large B-cell lymphoma; EBER ISH = Epstein-Barr encoding region in situ hybridization; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PTLD = post-transplant lymphoproliferative disorder.

The median follow-up was 4.7 years (range, 0.5–14.5 y). The median age at PTLD diagnosis was 52 years (range, 18–81 y). The median time from transplantation to PTLD diagnosis was 7.1 years (range, 0.16–36 y).

Treatment and outcomes

Immunosuppression

Immunosuppression at time of PTLD diagnosis was known for 86 (95%) patients (See Supplementary Table 1, http://links.lww.com/HS/A202). This included a calcineurin inhibitor for 74 patients [86%] plus a second agent in 58 [67%] of these patients). The commonest regimens were tacrolimus/mycophenolate (n = 30, 35%), tacrolimus/azathioprine (n = 13, 15%), and tacrolimus monotherapy (n = 13, 15%). Almost all patients were also taking maintenance prednisolone.

No patients had RIS as the sole strategy. Seventy-two (79%) patients had data available to evaluate degree of RIS. RIS occurred in 63 of 72 patients. Given the heterogeneity in patterns of RIS and types of transplant, we elected to define 3 groups of RIS[1]: Cessation of immunosuppression: calcineurin inhibitor and second agent ceased entirely (n = 20; 28%)[2]; Moderate RIS: 50% or more reduction of the calcineurin inhibitor (n = 22; 31%)[3]; and Minimal RIS: documented RIS but either to a level of <50% reduction in calcineurin inhibitor dose or reduction of the second agent only (n = 21; 29%). Nine patients (12%) did not have any RIS. All patients received rituximab or rituximab-based chemotherapy concurrently with, or shortly after RIS, rather than being restaged after RIS alone. There was a higher incidence of moderate RIS or cessation of immunosuppression in patients receiving R-chemotherapy compared to R-monotherapy (See Supplementary Table 4, http://links.lww.com/HS/A202).

Patients with systemic PTLD—rituximab primary strategy

For patients with systemic lymphoma (ie, no CNS involvement) (n = 68), rituximab monotherapy was administered first-line in 24 patients (35%), including those with stage IV disease (n = 14; 58%) and high international prognostic index (IPI ≥ 3 n = 10; 48%) (Figures 1 and 2). For the 20 patients with PET assessments, 9 (45%) achieved complete remission and did not receive subsequent chemotherapy, of which, 8 remained in remission. Other responses were: partial remission n = 7, stable disease n = 2, progressive disease n = 2; 8 of these patients subsequently received R-CHOP chemotherapy. For all 24 patients, 11 subsequently received R-chemotherapy (10 R-CHOP, 1 rituximab, cyclophosphamide, prednisolone) and responses were: complete remission n = 6, stable disease n = 2, progressive disease n = 1, TRM n = 2. The complete remission rate increased to 71% after the addition of R-CHOP for patients not in complete remission after rituximab monotherapy.

Patients with systemic PTLD—initial R-chemotherapy strategy

Of the 44 systemic PTLD patients treated with initial R-chemotherapy, 37 received R-CHOP. Responses were: complete remission n = 28 (76%), partial remission n = 3, progressive disease n = 2 (TRM n = 2, not performed n = 1, missing n = 1). The median number of cycles was 6. For the remaining 7 patients, there was heterogeneity in regimens (dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab, cyclophosphamide, vincristine, prednisolone, rituximab, cyclophosphamide, etoposide, vincristine, prednisolone, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine (Hyper-CVAD), and rituximab, dexamethasone, cytarabine, carboplatin), and we categorized these as reduced-intensity regimens intensive treatment (non-CNS directed or CNS directed) (See Supplementary Table 2, http://links.lww.com/HS/A202).

Patients with CNS involvement

There were 23 patients with CNS involvement: primary CNS lymphoma (n = 21) and systemic plus CNS involvement (n = 2) (Table 2 and Figure 3). The median age at PTLD diagnosis was 55 years (range, 22–80 y). The median time from transplantation to PTLD diagnosis was 8.5 years (range, 0.5–36 y). Nineteen of the cases occurred in renal transplant recipients. The proportion of cases with CNS involvement was higher in renal transplant recipients compared to other transplant recipients (41% versus 9%; $P < 0.001$). Tumor EBV in situ hybridization was positive in 86%.

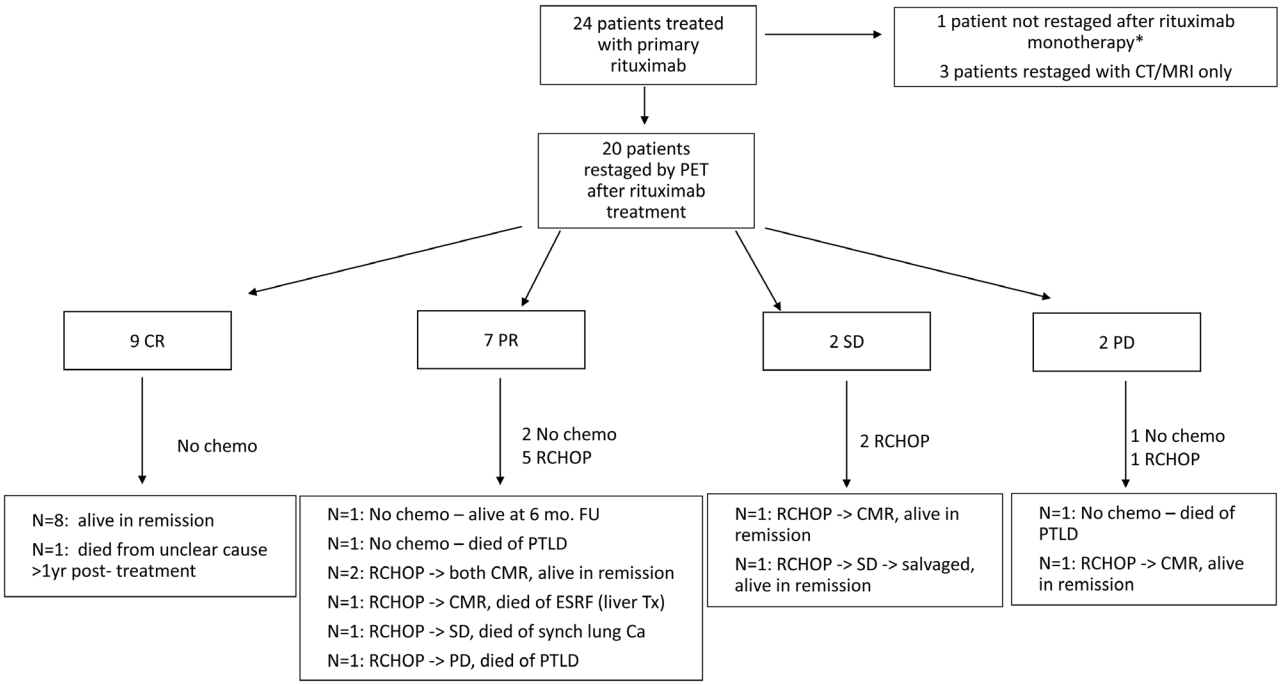

Figure 2. Outcomes for patients with systemic lymphoma receiving rituximab-primary treatment. *Pt did not undergo imaging after R-monotherapy but achieved CR after R-CP. Three pts restaged with CT or MRI only: One pt had PD on CT with rituximab monotherapy and died of TRM with R-CHOP. One pt had SD on CT with rituximab monotherapy and died of TRM with R-CHOP. One pt achieved CR with rituximab monotherapy only and was restaged with MRI only (stage IE—orbital disease). Ca = cancer; CMR = complete metabolic remission; CR = complete remission; CT = computed tomography; ESRF = end-stage renal failure; FU = follow-up; PD = progressive disease; PET = positron emission tomography; PR = partial remission; PTLD = post-transplant lymphoproliferative disorder; R-CP = rituximab, cyclophosphamide, prednisolone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SD = stable disease; TRM = treatment-related mortality; Tx = transplantation.

As first-line therapy, RIS occurred in 13 of 14 patients for whom data was available. Five patients had minimal RIS, 6 patients had moderate RIS and 2 patients had complete cessation of immunosuppression. No patient had RIS as a sole treatment modality. Rituximab was used in 21 of 23 patients. For the 2 patients who did not receive rituximab, one died of progressive disease and the other had resection and radiotherapy alone and achieved complete remission. Rituximab monotherapy was initiated in 5 patients. Four of these patients also received radiotherapy with the following responses: complete remission n = 1, stable disease n = 1, progressive disease n = 2. The patient who did not receive radiotherapy achieved a partial remission with rituximab monotherapy and then received CNS-directed chemotherapy and achieved a partial remission and remained alive at last follow-up.

Table 2.

Baseline Characteristics for 23 Patients With Central Nervous System Involvement With Monomorphic DLBCL PTLD.

Characteristic	N (%) (n = 23)
Median age at PTLD diagnosis (range)	55 y (22–80 y)
Median time from organ transplantation to PTLD (range)	8.54 y (0.53–36.1 y)
Organ transplanted	
Heart	2/23 (9)
Lung	1/23 (4)
Liver	1/23 (4)
Kidney	19/23 (83)
ECOG PS	
0–1	17/22 (77)
≥2	5/22 (23)
EBV positive	19/22 (86)
Deep region of the brain[a]	9/22 (41)
CSF flow cytometry positive	1/14 (7)
CSF cytology positive	2/16 (12)
CSF protein raised	10/17 (59)
Elevated LDH	9/20 (45)

[a]Deep region defined as any involvement of basal ganglia, corpus callosum, brain stem, or cerebellum.

CSF = cerebrospinal fluid; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; LDH = lactate dehydrogenase; PTLD = post-transplant lymphoproliferative disorder.

A total of 18 patients received rituximab-based chemotherapy: 2 initially received rituximab monotherapy (as above) and 15 received CNS-directed therapy up front. CNS-directed regimens incorporated high-dose methotrexate with or without cytarabine: rituximab, methotrexate, procarbazine, vincristine n = 3, rituximab, carmustine, teniposide, prednisolone n = 4, rituximab, methotrexate, procarbazine, vincristine, cytarabine n = 3, R-Hyper-CVAD n = 2, Rituximab plus high-dose methotrexate n = 6 (See Supplementary Table 2, http://links.lww.com/HS/A202). The average number of cycles received was 5.0. For these patients, outcomes were complete remission n = 14 (82%), partial remission n = 3. The remaining patient initially received R-CHOP for systemic plus CNS PTLD and was analyzed as such. This patient died from a complication of treatment after the first cycle of CNS-directed chemotherapy and was the only TRM event (4%) in the CNS PTLD cohort. Ten patients received radiotherapy in total (consolidative n = 6).

End of treatment PET in systemic PTLD

Of the 68 patients with systemic PTLD, 53 had end of treatment PET imaging. Reasons for not performing imaging were (n = 15): TRM n = 5, lymphoma deaths n = 2, or missing data n = 8. In a 6-month landmark analysis, achieving complete remission at end of treatment PET was predictive of OS (3-y OS PET negative 91% versus PET positive 57%; $P = 0.01$) (Figure 4). For patients achieving complete remission, only 3 (7%) patients subsequently relapsed.

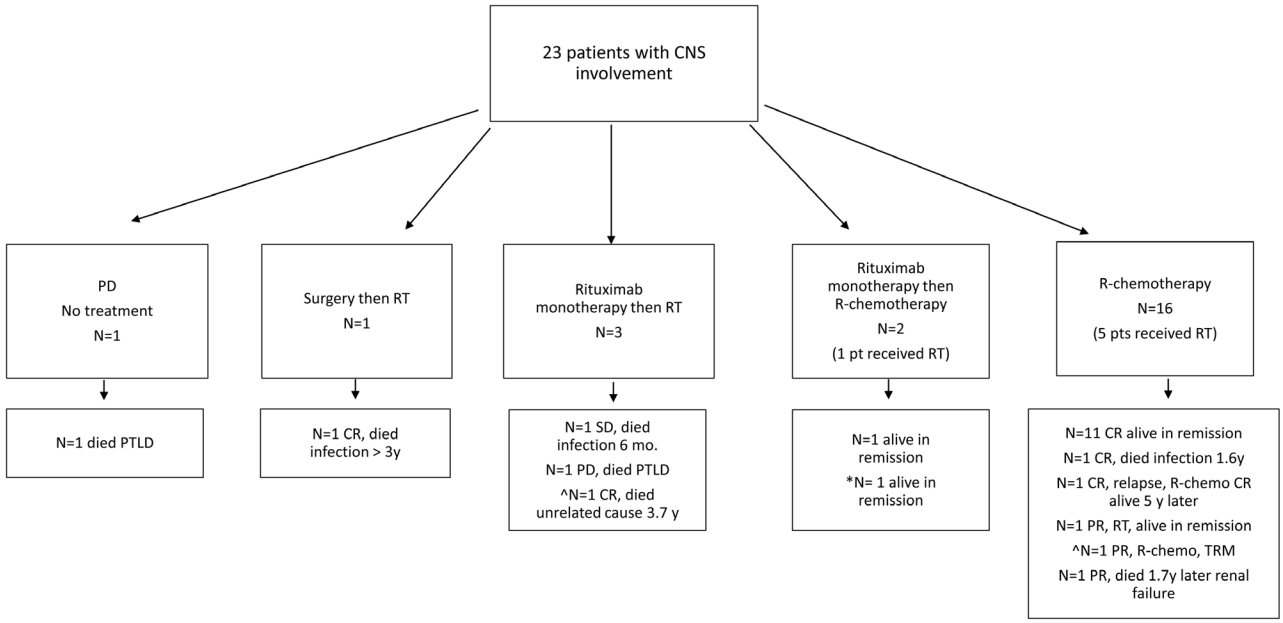

Figure 3. Treatment received and outcomes for 23 patients with CNS PTLD. *Also received EBV cytotoxic T lymphocytes + ibrutinib. ^Two patients with systemic and CNS involvement. CNS = central nervous system; CR = complete remission; EBV = Epstein-Barr virus; PD = progressive disease; PR = partial remission; PTLD = post-transplant lymphoproliferative disorder; RT = radiotherapy; SD = stable disease; TRM = treatment-related mortality.

Survival

A total of 30 patients (33%) died. TRM was 7%. All treatment-related deaths were due to sepsis with 3 occurring in the first cycle of R-CHOP, 1 occurring in the second cycle of R-CHOP and the remaining 2 occurring later in treatment regimens involving R-Hyper-CVAD. There were 10 deaths due to lymphoma: 8 patients died with refractory lymphoma (median OS 7.4 mo), while only 2 patients relapsed beyond 1 year and died (relapse at 4.2 and 8.4 y postdiagnosis, respectively). Eleven deaths were unrelated to PTLD and due to infection (n = 7), renal failure (n = 2), lung cancer (n = 1), or graft failure (liver) (n = 1). The cause of death was unknown in 3 cases.

For patients with systemic lymphoma, we examined outcomes in patients receiving rituximab monotherapy (n = 24) compared with rituximab-chemotherapy (n = 44) as initial treatment. There were no significant differences in baseline characteristics between groups (Table 3). There was no significant difference in OS (P = 0.13), PFS (P = 0.49), or DSS (P = 0.69) between the 2 groups (Figure 5A–C). For the entire cohort, 3-year and 5-year OS rates were 72.7% and 66.4%, respectively; 3-year and 5-year PFS rates were 69.2% and 60.9%, respectively. EBV tumor status was available in 65 of 68 (n = 33 positive; n = 32 negative) patients with systemic PTLD. There was no significant difference in OS (3 y OS EBV pos 75% versus EBV neg 64%; P = 0.42) or PFS (3 y EBV pos 75% versus EBV neg 67%; P = 0.33) based on EBV status.

For patients with CNS involvement, 3-year PFS and OS rates were 73.1% and 73.1%, respectively. There was no significant difference in OS or PFS comparing patients with CNS involvement to patients with systemic lymphoma (OS 73.1% versus 72.5%; P = 0.78 and PFS 73.1% versus 70.3%; P = 0.85) (Figure 6A and B).

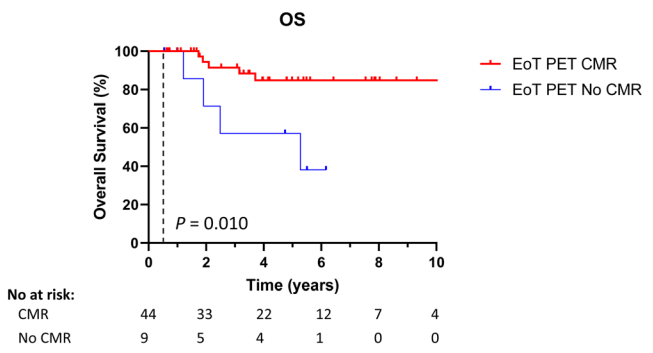

Figure 4. Six-month landmark analysis of OS for systemic lymphoma patients based on EOT PET. CMR = complete metabolic remission; EOT = end of treatment; OS = overall survival; PET = positron emission tomography.

Prognostic features

In a univariate analysis for all patients, the following baseline characteristics were significant predictors of worse OS and were included in the multivariate analysis: age ≥ 60 (P = 0.001), serum albumin <35 g/L (P = 0.044), bone marrow involvement (P = 0.001), Eastern Cooperative Oncology Group (ECOG) score ≥2 (P = 0.006), elevated lactate dehydrogenase (LDH) (P = 0.004), stage III/IV disease (P = 0.017), presence of B

Table 3.

Baseline Characteristics for Patients With Systemic Lymphoma Treated With Rituximab Monotherapy Versus Rituximab-chemotherapy As Initial Treatment.

Baseline Characteristic	Rituximab Monotherapy (n = 24) (%)	Rituximab chemotherapy (n = 44) (%)	*P*
Median age (y)	50.8	50.6	0.82
Age >60	9/24 (38)	11/44 (25)	0.28
ECOG ≥2	7/21 (33)	9/38 (24)	0.43
Stage III/IV	17/24 (70)	33/44 (75)	0.71
IPI 3–5	10/21 (48)	23/36 (64)	0.23
EBV positive	12/24 (50)	21/41 (51)	0.92
B symptoms	7/21 (33)	20/39 (51)	0.18
Raised LDH	13/23 (57)	25/41 (61)	0.73
Bulky disease (≥10 cm)	0/24 (0)	4/41 (10)	0.29

EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group performance status; IPI = International Prognostic Index; LDH = lactate dehydrogenase.

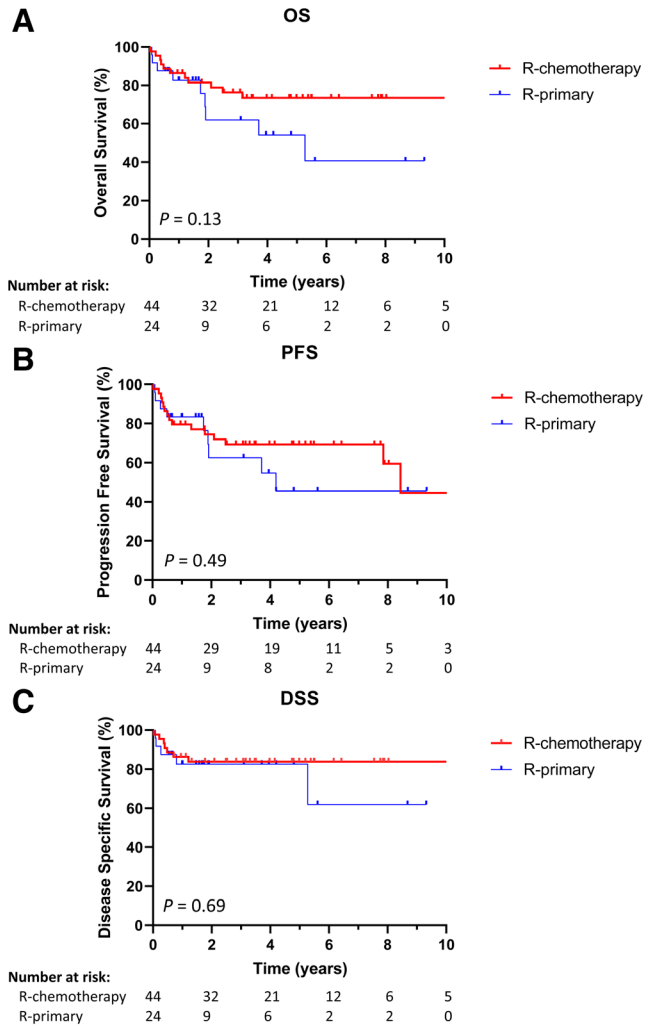

Figure 5. Survival for patients with systemic lymphoma treated with rituximab monotherapy vs rituximab-chemotherapy as initial treatment: OS (A); PFS (B); DSS (C). DSS = disease-specific survival; OS = overall survival; PFS = progression-free survival.

symptoms (P = 0.073), and thoracic organ transplant (heart or lung) (P = 0.074) (See Supplementary Table 3, http://links.lww.com/HS/A202). Multivariate analysis demonstrated only elevated LDH (HR, 3.58; P = 0.025; 95% CI, 1.17-10.8) and ECOG ≥2 (HR, 3.46; P = 0.006; 95% CI, 1.43-8.33) remained significant predictors of worse OS. In a univariate analysis for patients receiving rituximab monotherapy, IPI (HR, 5.44; P = 0.045; 95% CI, 1.03-28.55) and response to rituximab induction (HR, 10.75; P = 0.027; 95% CI, 1.31-90.9) were prognostic for OS.

Incidence of graft rejection

Graft rejection was uncommon with suspected rejection occurring in 8 patients (9%), which was confirmed by biopsy in 4 patients (4%) during follow-up (See Supplementary Table 4, http://links.lww.com/HS/A202). Only 1 patient had biopsy-proven rejection during treatment (R-CHOP). Another patient had biopsy-proven rejection in complete remission 9 months from PTLD diagnosis. A third patient was clinically suspected of having rejection during treatment but not biopsied. The remaining 2 biopsy-proven graft rejections occurred more than 2 years from PTLD diagnosis (both kidney transplant recipients with histological evidence of chronic graft rejection). Four patients had clinically suspected graft rejection. RIS (no reduction versus any reduction) was not a risk

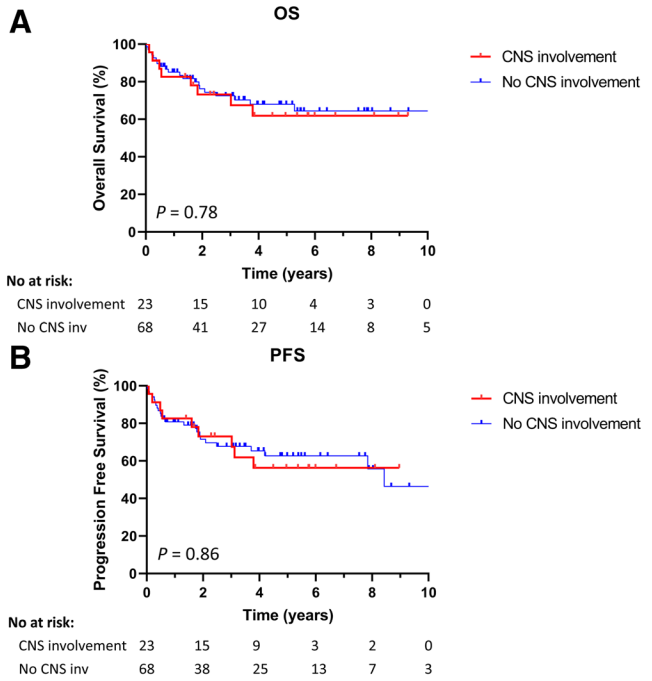

Figure 6. OS (A) and PFS (B) based on the presence or absence of CNS involvement at diagnosis. CNS = central nervous system; OS = overall survival; PFS = progression-free survival.

factor for development of suspected graft rejection (P = 0.26) or biopsy-proven graft rejection (P = 0.44). There were no cases of transplant loss due to rejection. There were no differences in the incidence of graft rejection between patients managed with a rituximab primary versus initial R-chemotherapy strategy (See Supplementary Table 4, http://links.lww.com/HS/A202).

Discussion

This is the largest assessment of patients with DLBCL PTLD staged with PET and managed in the rituximab era. Our data demonstrate similar response rates, OS and TRM to the PTLD-1 risk-stratified sequential treatment trial. The rituximab-primary approach appeared safe and effective compared to an initial rituximab-chemotherapy approach. The OS of patients with CNS involvement appeared similar to patients with systemic lymphoma. The incidence of graft rejection was lower than previously reported. End of treatment PET was prognostic for OS. Taken together, these data support that current practices with RIS and rituximab-based treatments are safe and effective with a low likelihood of graft rejection and high cure rate for patients achieving complete remission with CNS or systemic PTLD.

The PTLD-1 trial defined current practices with RIS and risk-stratified sequential treatment beginning with rituximab monotherapy.[6] Our results are broadly comparable to the PTLD-1 trial (complete remission rate to rituximab 25%, overall response rate to chemotherapy 88%, 3-y estimated response duration and OS 82% and 70%, respectively) and other studies.[7,15] For our patients initially treated with rituximab monotherapy (rituximab-primary), 45% achieved complete remission with no TRM, rising to 71% after the addition of R-CHOP for those not in complete remission. For patients treated with initial R-CHOP, the rate of complete remission was 76%. Our 3-year PFS and OS rates were 69.2% and 72.7%, respectively. Outcomes for patients requiring chemotherapy in routine practice were comparable to the trial setting.

Consistent with recent reports,[15,16] our outcomes for patients treated with a rituximab-primary approach were similar to rituximab-chemotherapy as an initial approach. These data demonstrate that a minority of patients can be cured with RIS and rituximab monotherapy without exposing them to chemotherapy and supports the current practice of risk-stratified sequential treatment. This avoids the high TRM rate (~30%) previously seen with initial CHOP chemotherapy after failure to respond to RIS.[17] The PTLD-1 trials reported a TRM rate of 11% with rituximab induction followed by CHOP,[5] and the risk-stratified sequential therapy trial reported a rate of 8% where granulocyte colony stimulating factor and antibiotic prophylaxis were mandated.[6] Our data demonstrated a TRM rate of 7%, which is higher than ~2% in immunocompetent DLBCL patients receiving combination rituximab-chemotherapy.[18]

The limited data available suggest that DLBCL PTLD with CNS involvement has been associated with a poor prognosis, the frequency is higher (~15%) than the immunocompetent population and the disease is almost always EBV positive.[19–22] A large assessment of CNS PTLD reported 3-year PFS and OS rates of 32% and 43%, respectively; however, this study included other PTLD subtypes and not all patients received rituximab.[20] Our data demonstrated 25% of patients had CNS involvement with a high proportion in renal transplant patients and 86% of cases were EBV positive. Most patients (16/23) did not receive RIS and rituximab monotherapy but rather RIS with initial CNS-directed rituximab-based chemotherapy with only 1 treatment-related death. In the univariate analysis, the presence of CNS involvement was not prognostic. While numbers are small, surprisingly, the 3-year OS was comparable to patients with systemic lymphoma (73.1% versus 72.5%). These results are considerably better than historical series, although favorable outcomes for patients treated with rituximab have been reported.[22] These findings may be due to RIS protocols, the almost universal use of rituximab, the use of CNS-directed chemotherapy regimens, radiotherapy, or improved supportive care.

CNS DLBCL PTLD is almost universally EBV positive and patients receive immunosuppression to prevent graft rejection that impairs EBV-specific T-cell immunity. In this setting, rituximab may exert a direct and indirect anti-lymphoma effect. Rituximab depletes circulating B-cells, the principle reservoir of EBV, regardless of whether they are EBV-infected or not. RIS enables restoration of EBV-specific T-cell immunity that is a critical step that occurs in conjunction with rituximab.

RIS has been the cornerstone of PTLD management for decades, yet concerns remain regarding graft rejection. RIS has had variable responses (40%–70%) and rejection rates (5%–30%).[23–25] The only prospective study of RIS was conducted prior to rituximab and reported responses in only 12% and rejection in 37%.[26] We assessed the incidence of graft rejection, both clinical and biopsy-proven, with current practices of RIS and the availability of rituximab. Almost all (88%) patients underwent RIS (29% minimal, 31% moderate, and 28% cessation) and 80% of all patients received chemotherapy. Graft rejection occurred in 8 patients (9%), which was confirmed by biopsy in only 4 patients (4%) during follow-up. Only 1 patient had biopsy-proven rejection during treatment. Importantly, there were no cases of transplant loss due to rejection. Increased awareness and monitoring for early signs of rejection would have led to alterations in immunosuppression to avoid overt rejection. We and others have previously demonstrated that RIS during and after rituximab ± chemotherapy does not lead to a deterioration in renal graft function.[27,28] Our data suggest that graft rejection may be lower in the modern era with RIS when used with rituximab ± concurrent or sequential chemotherapy, which provides significant immunosuppression by itself. Prospective trials are needed to determine the optimal approach to RIS in PTLDs.

Although PTLDs are FDG-avid lymphomas,[29] there is limited data regarding the prognostic value of end of treatment PET in PTLD.[30] The PTLD-1 trials were conducted with CT imaging. We performed a 6-month landmark analysis to explore the value of end of treatment PET in systemic PTLD. End of treatment PET was prognostic with OS significantly longer for patients achieving complete remission. Only 3 (7%) patients achieving complete remission subsequently relapsed. This demonstrates that most PTLD patients achieving complete remission will be cured. Our data confirm the findings of a previous report regarding the prognostic value of end of treatment PET.[31]

The typical limitations of retrospective nonrandomized design apply to this study. Treatment was based on physician preference and there may have been reasons why a rituximab-primary or rituximab-chemotherapy approach was chosen (ie, patient-related or lymphoma-related variables). We analyzed monomorphic DLBCL and compared outcomes with the PTLD-1 trial. Monomorphic DLBCL comprised ~75%–80% of patients in the PTLD-1 trials, yet other histologies, with variable management practices and prognoses, were included. This limits the application of our data to non-DLBCL PTLD histologies. Furthermore, during this study period (2004–2017), management practices evolved, largely driven by data from the PTLD-1 trials. As this is a retrospective study, imaging modality selected for restaging was per physician discretion.

In the largest assessment of PET staged patients managed in the era of rituximab, this real-world data demonstrate significant improvements in survival in recent decades and provides valuable insights in management. Future clinical trials are necessary to determine the optimal patterns of RIS and to improve survival with the addition of effective novel agents that can be safely delivered to immunocompromised transplant recipients. The rarity and complexity of PTLD are barriers to conducting prospective trials and future international collaboration to address these issues will be essential.

Disclosures

AB received conference sponsorship from Roche. DT received honoraria from Roche, Janssen, Takeda, Amgen; she received research funding from Roche, Janssen; and she received advisory boards from Amgen, Janssen and Roche. NH received Honoraria/Speaker's fees from Abbvie and Novartis. EAH received Honoraria/Speaker's fees from Roche, Janssen, Takeda, Bristol-Myers Squibb; she received advisory boards from Janssen, Celgene, Merck Sharp Dohme, Roche; she received research funding from Bristol-Myers Squibb, Celgene, Merck Sharp Dohme, Astra Zeneca; and she received travel expenses from Takeda, Roche, Janssen. AJ received honoraria from Janssen; he received advisory boards from Roche, Janssen, Merck Sharp Dohme; and he received travel support from Roche. CYC received Honoraria/Consulting/Advisory board from Roche, Janssen, MSD, Gilead, Ascentage Pharma, Acerta, Loxo Oncology, TG therapeutics; he research funding from Celgene, Roche, Abbvie; and he received travel expenses from Roche. SIS received honoraria or advisory board participation from Gilead Sciences, Bayer Healthcare, Ipsen, Eisai, MSD, Bristol-Myers Squibb, Roche, AbbVie, CSL Behring, Astra Zeneca, Novartis, Astellas. PM received Janssen Membership on an entity's Board of Directors or advisory committees and Research Funding; he received membership on an entity's Board of Directors or advisory committees from BMS/Celgene, Amgen, Takeda, Pfizer, Caelum Membership. GH received advisory board from Roche. All the other authors have no conflicts of interest to disclose.

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