Post-transplantation Burkitt lymphoma: a retrospective study of 55 patients

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of conditions that involve uncontrolled proliferation of lymphoid cells developing as a consequence of extrinsic immunosuppression after solid organ or hematopoietic stem cell transplantation.[1] The 2022 World Health Organization (WHO) classification distinguishes lymphomas from other proliferations arising in the setting of immune deficiency and further categorizes them as in immunocompetent patients, the most frequent being diffuse large B-cell lymphoma (DLBCL).

Based on several phase II trials,[2,3] rituximab-based therapy following reduction of immunosuppressive therapy (RIS) is now standard of care for most CD20$^+$ PTLD. Sequential therapy (4 weekly courses of rituximab either completed by 4 more courses of rituximab in responders [complete remission [CR] and low-risk partial remission [PR] group: 25-26%] or by 4 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days [R-CHOP-21] in patients not responding to rituximab monotherapy sufficiently [74-75%]) showed encouraging results for CD20$^+$ B-cell PTLD with 7-8% treatment-related-mortality (TRM), 2-year progression-free survival (PFS) of 56-67% and 2-year overall survival (OS) of 68-72%.[4,5] Current PTLD guidelines encourage sequential therapy in CD20$^+$ polymorphic and monomorphic DLBCL-type PTLD that fail to respond to upfront RIS or if RIS is not feasible.[6]

Burkitt lymphoma (BL) PTLD (BL-PTLD) is a rare subtype of post-transplant lymphoma representing less than 10% of adult PTLD.[7] Its immune-competent counterpart is characterized by a highly aggressive clinical course, frequent involvement of bone marrow (BM) and central nervous system (CNS), and is biologically hallmarked by *MYC* gene translocation to an immunoglobulin locus. Due to the reduced number of BL-PTLD cases, their clinical characteristics, outcome, and most adequate therapeutic options are not well established.[8–10] We conducted a multicenter retrospective study in order to better characterize these elements.

Our study included adult patients diagnosed with BL-PTLD between 1989 and 2022 who were identified using the French registry of PTLD after kidney transplantation, the K-Virogref network, the Lymphopath database and the prospective German PTLD registry. After the review of medical and pathological records, 55 patients treated in 20 French and eight German centers were included. The study was approved by national (CNIL 913611) and local (CPP Ile-De-France PP 13-022) ethics committees. Diagnosis of BL-PTLD followed criteria from the 2022 revised edition of the WHO classification,[11] taking into account morphology, immunohistochemistry (CD20, CD10, BCL2, BCL6, MUM-1, Ki67 data) and cytogenetics (C-*MYC*, *BCL2*, *BCL6* in fluorescence *in situ* hybridization [FISH] and/or karyotype). Association with Eppstein Barr virus (EBV) was assessed by *in situ* hybridization for Epstein Barr-encoded small RNA (EBER). Among different therapeutic options, the most frequently used chemotherapies were: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone), COPADEM (vincristine, methotrexate, cyclophosphamide, doxorubicin, prednisone 60 mg/m^2) and hyperCVAD (hyperfractioned cyclophosphamide, vincristine, doxorubicin, dexamethasone). Response to treatment followed standard international criteria.[12,13] Subgroup comparisons were performed using X^2 of Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. Time-to-event outcomes were estimated using Kaplan-Meier curves, and were compared using the log-rank test. The level of significance in all analyses was set at $P<0.05$. Statistical analysis was performed using R Studio 2021.09.1.

The study population comprised 55 patients, with a median age at diagnosis of 40.3 years and the most frequently transplanted organs were kidney (n=37) and liver (n=10) (Table 1). Median time from transplant to BL-PTLD diagnosis was 5.4 years (range, 0.2-24). Most patients presented with an aggressive and advanced stage of disease at diagnosis: Eastern Cooperative Oncology Group (ECOG) score ≥2 in 44.6% (n=21/47 cases), elevated lactate dehydrogenase (LDH) in 84% (n=41/49), Ann Arbor stage IV in 84% (n=46/55) patients. Extranodal disease was frequent (n=49, 89%), with the digestive tract being the most frequently involved organ (n=29, 53%). CNS infiltration was observed in seven patients (13%). BL-PTLD tumor samples were all CD20$^+$, CD10$^+$, BCL2$^-$, expressed Ki67 in more than 90% of cells and harbored *MYC* rearrangement detected by FISH. EBER was positive in 12 of 29 samples (41%) and LMP was positive in one of nine (11%).

Fifty-three patients received curative-intended therapy while two patients received supportive care only. RIS never was proposed as a unique initial strategy but was performed in 42 of 53 (79%) patients. Fourteen of 53 (25%) patients were treated according to sequential strategies. These patients received up to four weekly courses of rituximab followed either by: (i) rituximab consolidation (4 3-weekly courses) in a single case of CR (1/14, 7%) or (ii)

Table 1. Baseline characteristics of Burkitt lymphoma post-transplantation lymphoproliferative disorder patients.

Patient characteristics, N=55	
Median age in years (IQR)	40.3 (29.9-54.1)
Median time from transplant to BL-PTLD diagnosis in years (IQR)	5.4 (3.5-9.1)
Male sex, N (%)	45 (80.7)
Type of transplant, N (%)	
Heart	1 (1.8)
Liver	10 (18.2)
Bone marrow	1 (1.8)
Lung	2 (3.6)
Kidney	37 (67.3)
Kidney + pancreas	2 (3.5)
Kidney + liver	1 (1.8)
Kidney + heart	1 (1.8)
ECOG score, N/N (%)	
0	11/47 (23.4)
1	15/47 (31.9)
2	14/47 (29.8)
3	7/47 (14.9)
Elevated LDH, N/N (%)	41/49 (83.7)
Ann Arbor score, N (%)	
I-II	9 (16.3)
IV	46 (83.7)
Enlarged lymph nodes, N (%)	41 (74.6)
Supradiaphragmatic	22 (40.3)
Infradiaphragmatic	25 (45.6)
Spleen involvement, N (%)	3 (5.5)
Extranodal disease, N (%)	49 (89.1)
Digestive tract	29 (52.7)
Liver	14 (25.5)
Lungs	3 (5.5)
Kidney	2 (3.6)
Bone	12 (21.8)
CNS involvement	7 (12.7)
Pleural/peritoneal	5 (9.1)
Graft	4 (7.3)
Bone marrow	23 (41.8)
Immunosuppressive regimen at diagnosis, N (%)	
Cyclosporine	19 (34.5)
Tacrolimus	37 (67.3)
Mycophenolate mofetil	28 (50.9)
Corticosteroids	24 (43.6)
Azathioprine	8 (14.6)
Everolimus	2 (3.6)

BL-PTLD: Burkitt lymphoma post-transplantation lymphoproliferative disorder; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; CNS: central nervous system; IQR: interquartile range.

subsequent chemo(immuno)therapy (C(I)T) (n=13/14, 93%): CHOP (n=2), R-CHOP (n=9, including one with concomitant high dose methotrexate [MTX]), R-COPADEM followed by R-CYM (n=1), unknown (n=1). Seven (13%) patients received frontline polychemotherapy (CT) (COPADEM [n=6] and CHOP [n=1]) and 32 (60%) were treated with CIT (R-COPADEM [n=12], R-CHOP [n=13, 7 without MTX, 6 with sequential or concomitant MTX], R-EPOCH [n=5], R-hyperCVAD [n=1], rituximab with whole brain radiotherapy [WBRT] and 90Y-ibritumomab tiuxetan [n=1]) (*Online Supplementary Figure S1*). There was no significant difference between patients who had received sequential therapy or frontline CT/CIT, except that patients with CNS involvement were all treated with CT/CIT and those treated with sequential therapy had a lower ECOG score (*Online Supplementary Table S1*).

Median follow-up was 7.5 years (95% confidence interval [CI]: 5.8-10.5). Median OS and PFS were 7.1 (95% CI: 1.7-not applicable [NA])and 4.9 years (95% CI: 0.7-NA) respectively (Figure 1A, B). Thirty-eight patients (70%) attained CR after first-line treatment, including four of seven (57%) who received CT, 25 of 32 (78%) after CIT, and nine of 14 (64%) after completing sequential treatment. With sequential treatment, the overall response rate (CR + PR) to four doses of rituximab was 21% (1 CR, 2 PR). Among patients receiving frontline CIT, CR rates were 61%, 100% and 83% for patients treated with R-CHOP, R-EPOCH and R-COPADEM respectively, without significant statistical difference (P=0.26). Relapses occurred in four patients who had attained CR after a median of 6 months. Two had received upfront CIT and two sequential therapy. Out of these, only a patient relapsing after sequential therapy containing R-CHOP was successfully rescued by another CIT regimen. Three-year OS and PFS for the whole cohort were 58% (95% CI: 45.8-73.1) and 54% (95% CI: 41.9-68.9), respectively. For patients receiving upfront CIT, 3-year OS and PFS were 59% (95% CI: 42.9-80.1) and 58% (95% CI: 43-78.5). For patients receiving sequential therapy, 3-year OS and PFS were 64% (95% CI: 43.5-95.0) and 50% (95% CI: 29.6-84.4) (Figure 1C, D). OS and PFS after CIT and sequential therapy were not statistically different. There was no significant difference in PFS or OS between patients receiving upfront R-CHOP or R-COPADEM regimens (Figure 1E, F). Patients with CNS involvement (n=7) were treated with intrathecal (n=3) or high-dose intravenous MTX (n=2) or both (n=1) or WBRT (n=1) and five of them achieved CR. Twenty-two of 48 (46%) patients without CNS involvement received CNS prophylaxis during first-line therapy (either by intrathecal or systemic chemotherapy containing cytarabine or MTX). CNS prophylaxis had no impact on OS or PFS (*data not shown*).

Twenty-nine deaths occurred during follow-up mainly due to progressive disease (n=11, 38%). Treatment-related deaths (n=7, 24%; including sepsis, n=6; cerebral hemorrhage, n=1) occurred during frontline CIT treatment in five patients and in the relapse setting in two patients (*Online Supplementary Table S2*).

Univariate analysis showed that age over 50 years, ECOG score and BM involvement were significant predictors for poorer OS whereas complete response to first-line therapy

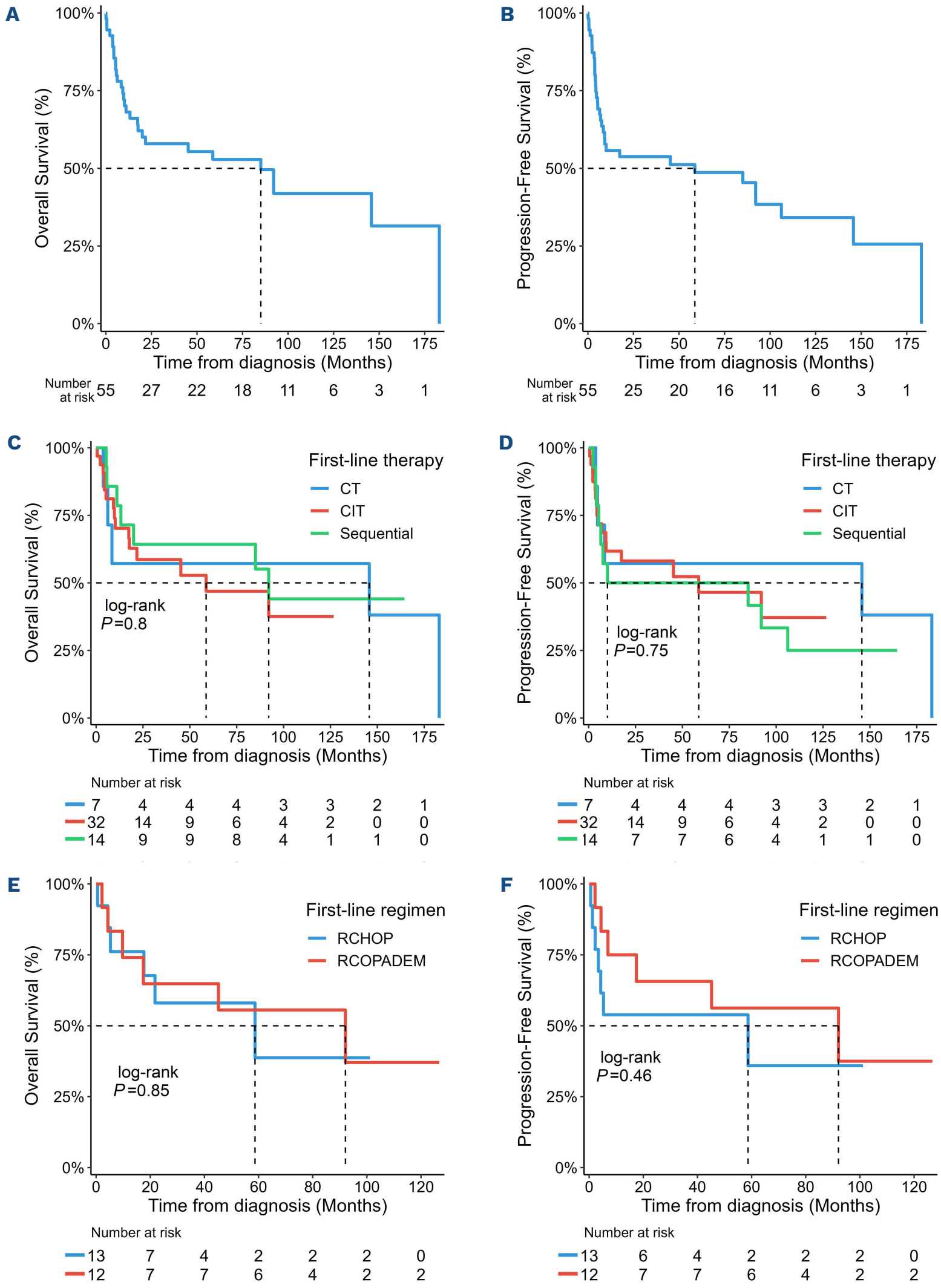

Figure 1. Survival for the whole cohort, according to the type of therapy and according to the type of chemoimmunotherapy. (A) Overall survival (OS) and (B) progression free-survival (PFS) for the whole Burkitt lymphoma post-transplantation lymphoproliferative disorder (BL-PTLD) cohort. The dashed lines indicate the respective times of median survival. (C) OS and (D) PFS by type of therapies used: chemotherapy (CT, N=7) (blue line), chemoimmunotherapy (CIT, N=32) (red line) and sequential therapy (sequential, N=14) (green line). (E) OS, (F) PFS according to the type of CIT regimen: R-CHOP (N=13) (blue line), R-COPADEM (N=12) (red line). R-CHOP: cyclophosphamide, doxorubicin, prednisone, rituximab and vincristine; R-COPADEM: rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin, and methotrexate.

was associated with longer survival and was the only variable retaining significance in multivariate analysis (Table 2). Complete response to first-line therapy was not significantly associated with other variables (i.e., age, transplanted organ, EBER, ECOG score, LDH levels, stage, BM or CNS involvement, or type of treatment).

To our knowledge, this is the largest retrospective series of BL-PTLD to date. BL-PTLD is a late-onset PTLD (like -PTLD[5]) with an aggressive presentation, frequent advanced disease, altered performance status and CNS involvement. In our series, EBV association (41%) appears to be similar to what is observed in DLBCL-PTLD (around 50%) and differs from previous series of BL-PTLD,[7,9] in keeping with publications suggesting that late-onset PTLD are more frequently EBV-negative.[1] Reflecting the lack of consensus, our retrospective BL-PTLD cohort used a variety of therapeutic approaches, ranging from high-dose chemotherapy and R-CHOP-based regimens to rituximab monotherapy. In a sequential strategy setting, the CR rate after the first four courses of rituximab monotherapy was very low (7%), but subsequent CIT provided disease control similar to the frontline CIT strategy (similar CR rate, OS and PFS). Although rituximab monotherapy does not appear to be a valuable option in BL-PTLD, sequential therapy could be discussed to avoid early complications associated with upfront C(I)T, considering the relatively high TRM observed in this series (13%). R-CHOP-based regimens yielded similar CR rates, PFS and OS compared to more dose-intensive regimens such as R-COPADEM and represent a valuable option in BL-PTLD, even with only four cycles as part of sequential therapy. In univariate analyses, age, ECOG score and BM involvement were significantly associated with poorer OS as in the immunocompetent BL cohort from which the BL-IPI was derived,[14] while complete response to first-line therapy was the strongest prognostic factor for longer OS in univariate and multivariate analyses. One

Table 2. Predictors of overall survival (Cox model, univariate and multivariate).

Variable	Hazard Ratio	95% CI	*P*
Univariate analysis			
Age in years, <50 *vs.* ≥50	3.65	1.67-7.97	0.01
Time from transplant to PTLD, late *vs.* early*	0.41	0.17-1.03	0.06
Transplanted organ, kidney *vs.* other	1.37	0.6-3.13	0.45
EBER status, positive *vs.* negative	0.68	0.28-1.66	0.40
ECOG score, ≥2 *vs.* <2	3.46	1.46-8.2	0.01
LDH levels, elevated *vs.* normal	0.15	0.02-1.09	0.06
Ann Arbor stage, I-II *vs.* III-IV	0.26	0.06-1.11	0.07
Extranodal disease, yes *vs.* no Digestive tract Liver Lung Kidney Bone CNS Pleural/peritoneal Bone marrow	6.14 1.45 1.74 1.89 1.3 1.4 1.68 2.77 2.27	0.82-4.59 0.69-3.08 0.75-4 0.44-8.12 0.3-5.63 0.59-3.32 0.64-4.47 0.81-9.52 1.07-4.82	0.08 0.33 0.20 0.39 0.72 0.44 0.29 0.10 0.03
Complete response after first-line therapy**	0.12	0.05-0.29	0.01
Multivariate analysis			
Age in years, <50 *vs.* ≥50	1.47	0.6-3.65	0.40
ECOG score, ≥2 *vs.* <2	1.56	0.56-4.3	0.39
Bone marrow involvement, yes *vs.* no	2.44	0.9-6.61	0.08
Complete response after first-line therapy**	0.15	0.06-0.42	0.01

*Late and early were defined as BL-PTLD occurring before and after 12 months post-transplantation respectively. **For sequential strategy, response was evaluated at the end of the procedure (which means after CIT in case of insufficient response to initial rituximab monotherapy). CI: confidence interval; PTLD: post-transplantation lymphoproliferative disorder; EBER: Epstein Barr-encoded small RNA; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; CIT: chemoimmunotherapy; CNS: central nervous system.

of the main limitations of our work is its retrospective nature and the use of different sources for patient selection. The fact that the majority of cases occurred after kidney transplantation is probably partly related to selection bias, but also to the fact that kidney transplantation is by far the most frequent transplantation in adults. This may partly explain the contrast between our data and a recently published pediatric cohort of BL-PTLD,[15] in which most patients had received heart or liver transplantation, although other elements (such as higher EBV association) may suggest a different disease biology.

In conclusion, our study confirms that BL-PTLD is an aggressive, late-onset PTLD with frequent extranodal and CNS localization. Although initial rituximab monotherapy is not as effective as for non-Burkitt PTLD, sequential strategy was as effective as frontline CIT regimens among which R-CHOP and more dose intensive regimens showed similar outcomes.

Authors

Pierre Walczak,[1] Sylvain Choquet,[1] Jacques Dantal,[2] David Boutboul,[3] Felipe Suarez,[4] Marine Baron,[1] Véronique Morel,[1] Thomas Cluzeau,[5] Mohamed Touati,[6] Michelle Elias,[7] Emmanuel Bachy,[8] Emmanuelle Nicolas-Virelizier,[9] Roch Houot,[10] Geoffroy Venton,[11] Caroline Jacquet,[12] Marie-Pierre Moles-Moreau,[13] Fabrice Jardin,[14] Eric Durot,[15] Noureddine Balegroune,[1] Laure Ecotière,[16] Romain Guièze,[17] Nassim Kamar,[18] Loïc Ysebaert,[19] Lionel Couzi,[20] Hugo Gonzalez,[21] Louise Roulin,[22] Kevin Ou,[23] Sophie Caillard,[24] Heiner Zimmermann,[25,26] Ralf Ulrich Trappe,[26,27] and Damien Roos-Weil[1] for the K-VIROGREF study group

[1]Sorbonne Université, Service d'Hématologie Clinique, Hôpital Pitié-Salpêtrière, APHP, Paris, France; [2]Institut de Transplantation Urologie Néphrologie (ITUN), Service de Néphrologie et Immunologie clinique, CHU Nantes, Nantes, France; [3]Service d'Immunologie Clinique, Hôpital Saint-Louis, APHP, Paris, France; [4]Service d'Hématologie Clinique, Hôpital Necker, APHP, Paris, France; [5]Service d'Hématologie Clinique, CHU de Nice, Nice, France; [6]Service d'Hématologie Clinique, CHU Limoges, Limoges, France; [7]Service de Néphrologie, Hôpital Saint-Louis, APHP, Paris, France; [8]Service d'Hématologie Clinique, Hospices Civils de Lyon, Pierre-Bénite, France; [9]Service d'Hématologie, Centre Léon Bérard, Lyon, France; [10]Service d'Hématologie, CHU Rennes, Université de Rennes, INSERM U1236, Rennes, France; [11]Service d'Hématologie et Thérapie Cellulaire, Hôpital universitaire de la Conception, Marseille, France; [12]Service d'Hématologie, CHU de Nancy, Vandoeuvre les Nancy, France; [13]Service d'Hématologie, CHU d'Angers, Angers, France; [14]Service d'Hématologie, Centre Henri Becquerel, Rouen, France; [15]CHU Reims, Hématologie Clinique, Reims, France; [16]Service de Néphrologie, Hémodialyse et Transplantation Renale, Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [17]Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Clermont-Ferrand, Clermont-Ferrand, France; [18]Service de Néphrologie et Transplantation d'Organes, CHU Rangueil, Toulouse, France; [19]Service d'Hématologie, Institut Universitaire du Cancer Toulouse-Oncopole, Toulouse, France; [20]Service de Néphrologie, Transplantation, Dialyse et Aphérèses, CHU Bordeaux, France; [21]Service d'Hématologie, Centre Hospitalier René-Dubos, Pontoise, France; [22]Service Unité Hémopathies Lymphoides, Groupe Hospitalo-universitaire Chenevier Mondor, APHP Créteil, France; [23]Service de Néphrologie et Transplantation Rénale, Hôpital Foch, Suresnes, France; [24]Service de Néphrologie et Transplantation Rénale, CHU de Strasbourg, Strasbourg, France; [25]Department of Internal Medicine-Oncology, Carl v. Ossietzky University of Oldenburg, Pius-Hospital, Oldenburg, Germany; [26]Department of Hematology and Oncology, DIAKO Ev. Diakonie-Krankenhaus Bremen, Bremen, Germany and [27]Department of Internal Medicine II: Hematology and Oncology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

Correspondence:
D. ROOS-WEIL - damien.roosweil@aphp.fr.

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Disclosures

No conflicts of interest to disclose.

Contributions

PW, SC and DRW designed the research. PW and DRW analysed data and wrote the manuscript. PW, SC, JD, DB, FS, MB, VM, TC, MT, ME, EB, ENZ, RH, GV, CJ, MPM, FJ, ED, NB, LE, RG, NK, LY, LC, HG, LR, KO, SC, HZ, RT and DRW recruited patients. All authors reviewed and approved the manuscript.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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