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Baseline ^{18}F-FDG Metabolic Tumor Volume Predicts Response to Rituximab Induction in Post-transplant Lymphoproliferative Disorders: A Multi-institutional Retrospective Study

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ABSTRACT

Post-transplant lymphoproliferative disorder (PTLD) is a rare complication of immunosuppression. Sequential treatment is commonly proposed, combining induction with rituximab (R-induction) followed by either continuation of treatment or addition of chemotherapy depending on response. Response to R-induction, often assessed by CT scan, is a major predictor of overall survival (OS). The aim of the study was to analyze predictive factors of R-induction response, including total metabolic tumor volume (TMTV), and investigate the role of ^{18}F-FDG PET/CT in response assessment. This retrospective multicenter study is based on patients with PTLD included in the K-VIROGREF cohort. Only patients treated by R-induction with a baseline ^{18}F-FDG PET/CT were included. Response to R-induction was assessed by ^{18}F-FDG PET/CT. The optimal threshold of TMTV for rituximab response was determined using receiver operating characteristic curves. Univariate and multivariate analyses were conducted to identify predictive factors of response. A total of 67 patients were included. Survival characteristics were similar to those previously reported: the complete response rate to R-induction was 30%, the 3-year OS estimate was 66%, and the treatment-related mortality was 4%. The optimal threshold for TMTV to predict R-induction response was 135 cm^3. The response rate to R-induction was 38% in the 21 patients with TMTV ≥ 135 cm^3 and 72% in the 46 patients with TMTV < 135 cm^3. TMTV was a significant predictor of response, both at univariate and multivariate analyses (odd ratios = 3.71, P = 0.022). Baseline TMTV is predictive of response to R-induction. Early assessment of patient response is feasible with ^{18}F-FDG PET/CT.

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a rare and serious complication of immunosuppression after organ transplantation and represents the second most frequent malignancy after skin cancers in immunosuppressed patients.[1,2] These lymphoproliferations constitute a well-defined entity in the World Health Organization (WHO) 2016 classification[3] with non-destructive, polymorphic, and monomorphic forms corresponding to aggressive lymphomas and Hodgkin's lymphomas.

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The treatment of PTLD is based in the first place on a reduction of immunosuppressive treatment. Formerly, PTLD were treated like their de novo counterparts. However, the use of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy in these fragile patients was associated with a high treatment-related mortality (TRM), estimated at 31%.[4] The first part of the PTLD-1 trial, consisting of sequential treatment with 4 weekly cycles of rituximab (R-induction) followed by 4 cycles of CHOP chemotherapy every 3 weeks, reported a median overall survival (OS) of 6.6 years and apparent lower treatment-related toxicity.[5] Response to R-induction therapy was prognostic for OS. These data were confirmed in the second part of the PTLD-1 trial in which a risk-stratified sequential therapy (RSST) was used[6]: patients who achieved a complete response (CR) after R-induction were treated by rituximab alone afterwards instead of (R)-CHOP chemotherapy. The median OS was 6.6 years with a TRM of 8%. In this study, responses after R-induction and at the end of treatment were assessed using CT scans.

Nowadays, 18F-Fluorodeoxyglucose positron emission tomography/ computed tomography (^{18}F-FDG PET/CT) is recognized as the gold standard for the initial workup of diffuse large-cell B-cell lymphoma (DLBCL).[7] This examination allows the detection of some lymphomatous lesions not recognized by a CT scan. It also plays an essential role in the assessment of response at the end of treatment with the use of the Deauville visual scale. Several studies have reported the prognostic value of the total metabolic tumor volume (TMTV) calculated on the initial PET/CT on progression-free survival (PFS) and OS in DLBCL.[8,9] There are fewer data on the contribution of ^{18}F-FDG PET in PTLD. A recent meta-analysis reports the high sensitivity and specificity of PET in the detection of PTLD.[10] PET detects additional lesions compared to conventional imaging in 28% of cases, mainly extranodal lesions.[11] Its contribution has also been studied in the evaluation of the response to treatment, to guide monitoring or change of treatment.[12,13] Only 1 recent study on 88 patients explored the value of TMTV or other parameters such as total lesion glycolysis (TTLG) in PTLD and did not find a prognostic value of these parameters on OS.[14] However, the population of this study was heterogeneous in terms of histology and treatment (58/88 patients were treated with R-induction). Baseline high International Prognostic Index (IPI) remained predictive of worse OS as in the RSST PTLD-1 trial. The other strong independent prognostic factor for time to progression and OS in the RSST PTLD-1 trial was response to R-induction. However, the response to R-induction is, by definition, a post-treatment variable, highlighting the need to identify baseline predictive factors of this response.

This prompted us to analyze predictive factors of response to R-induction, including TMTV, and to investigate the role of PET in response assessment after R-induction, in a homogeneous cohort of PTLD patients treated with R-induction.

MATERIALS AND METHODS

Patients' selection

This retrospective, non-interventional, multicenter study is based on patients included in the K-VIROGREF cohort (epidemiological, clinical, and immunological study of a cohort of adult patients with viral-induced cancers, after solid organ and hematopoietic stem cell transplantation), across 15 French medical centers. Patients with PTLD were screened from July 2013 to October 2021. The inclusion criteria were as follows: (1) histologically proven polymorphic PTLD or monomorphic DLBCL PTLD; (2) initial treatment by rituximab alone; (3) available baseline ^{18}F-FDG PET/CT, performed within 30 days before treatment. The exclusion criteria were as follows: (1) age < 18 years; (2) indolent lymphomas; (3) previously treated PTLD; (4) central nervous system involvement; (5) noncompliance with fasting before PET; (6) incomplete DICOM data.

The diagnosis of PTLD was made in accordance with the WHO classification[3] of malignant lymphoma and confirmed by expert hematopathologists from the Lymphopath network, according to the standard French procedures.[15]

This study was conducted in accordance with the Declaration of Helsinki and was declared on the Health Data Hub (N°F20210407155710) in conformity with the reference methodology MR004 of the "Commission Nationale de l'Informatique et des Libertés," allowing the computerized management of medical data. The participants were informed of the possibility of using the information concerning them and had a right of opposition.

Data collection

For each patient, the following information were collected: sex, age at diagnosis of PTLD, transplanted organ, the time between transplantation and diagnosis of PTLD, histology, Epstein-Barr virus status of the tumor, Ann Arbor stage, lactate dehydrogenase (LDH) levels, extranodal involvement, Eastern Cooperative Oncology Group–Performance Status (ECOG PS), B symptoms, IPI, and National Comprehensive Cancer Network (NCCN) IPI scores. Treatment response, whether after R-induction or after the end of treatment, was based on ^{18}F-FDG PET/CT using Cheson criteria[16] (CR, partial response [PR], stable disease [SD], progressive disease [PD]). No centralized review was performed.

PFS was calculated from diagnosis until disease progression, relapse, or death from any cause or last follow-up. OS was defined from diagnosis to death or last follow-up. Disease-specific survival (DSS) was defined as the time from diagnosis until death from PTLD or TRM.

Regarding ^{18}F-FDG PET/CT: DICOM data, administered activity, weight, height, and capillary blood glucose were collected.

Baseline PET measurements

PET/CT were displayed on a dedicated interpretation console (AW server; General Electrics, Milwaukee, WI). TMTV and TTLG were measured. TMTV was obtained by summing the metabolic volumes of all nodal and extranodal lesions according to the method detailed by Meignan et al[17] (41% SUVmax threshold, inclusion of only focal bone marrow involvement, spleen considered involved in case of focal increased uptake or diffuse increased uptake of at least 1.5 times the liver uptake). TTLG was obtained by multiplying each metabolic volume composing the TMTV by their respective SUVmean (mean standard uptake value). These measurements were performed by an experienced nuclear medicine physician (DM) who was blinded to the clinical data of the patients.

Statistical analysis

For descriptive analysis, qualitative variables were described by their absolute and relative frequency (%). Quantitative variables were described by mean, standard deviation, median, interquartile range (IQR), and extreme values.

The main endpoint was the response to R-induction defined by patients in CR or PR after 4 weekly doses of rituximab. The optimal threshold of TMTV regarding rituximab response (CR and PR vs SD and PD) was determined using receiver operating characteristic (ROC) curves and was chosen to maximize specificity (maximal specificity with a sensitivity of at least 50%). The area under the curve (AUC) and corresponding 95% confidence intervals (95% CI) are reported.

Univariate analyses were conducted using the Chi-square or Fisher exact test when appropriate for binary and ordinal variables, and the Wilcoxon test for continuous variables. The odds

Table 1
Patients Characteristics

	Total (n = 67)	Responders to Rituximab Induction (n = 41)	Non-responders to Rituximab Induction (n = 26)
Clinical data			
Median age (range)	59 (20–80)	59 (20–80)	59 (28–73)
Sex			
Female	21 (31%)	14 (34%)	7 (27%)
Male	46 (69%)	27 (66%)	19 (73%)
PS ECOG ≥2	21 (31%)	10 (24%)	11 (42%)
B symptoms	33 (49%)	16 (39%)	17 (65%)
Lymphoma characteristics			
Histology			
Monomorphic (DLBCL)	56 (84%)	33 (81%)	23 (88%)
Polymorphic	11 (16%)	8 (19%)	3 (12%)
EBER (n = 66)			
Positive	20 (30%)	11 (27%)	9 (35%)
Negative	46 (70%)	29 (73%)	17 (65%)
Ann Arbor stage			
I (including 9-stage IE)	11 (16%)	6 (15%)	5 (19%)
II	6 (9%)	4 (10%)	2 (8%)
III	10 (15%)	6 (15%)	4 (15%)
IV	40 (60%)	25 (60%)	15 (58%)
Nodal involvement	41 (61%)	26 (63%)	15 (58%)
Extranodal involvement	54 (81%)	34 (83%)	20 (77%)
Extranodal organs involved ≥2	18 (27%)	8 (20%)	10 (38%)
Biological results			
Elevated LDH	32 (48%)	20 (49%)	12 (46%)
B2m (n = 37)			
Median (range)	4.51 (2–17.12)	4.46 (2–14)	4.98 (2.5–17.12)
Albumin (n = 62)			
Median (range)	35.1 (21–47)	35.7 (25.1–47)	33.6 (21–41.8)
Prognostic scores			
IPI			
0	9 (13%)	4 (10%)	5 (19%)
1–2	30 (45%)	22 (54%)	8 (31%)
3–5	28 (42%)	15 (36%)	13 (50%)
NCCN-IPI			
0–1	5 (7%)	2 (5%)	3 (12%)
2–3	29 (43%)	21 (51%)	8 (31%)
4–5	22 (33%)	12 (29%)	10 (38%)
>5	11 (16%)	6 (15%)	5 (19%)
Transplantation related data			
Time from transplantation to PTLD (y)			
Median (range)	8.3 (0.3–34)	9.9 (0.5–34)	8.1 (0.3–20.2)
Age at transplantation (y)			
Median (range)	46 (2–73)	39 (2–73)	51 (22–70)
Transplant type			
Kidney	34 (51%)	23 (56%)	11 (42%)
Liver	17 (25%)	12 (29%)	5 (19%)
Heart	3 (4%)	1 (2%)	2 (8%)
Lung	2 (3%)	1 (2%)	1 (4%)
Hematopoietic SCT	5 (7%)	2 (5%)	3 (12%)
Multiple	6 (9%)	2 (5%)	4 (15%)
Graft involvement	6 (9%)	3 (7%)	3 (12%)
Reduction of immunosuppression	60 (90%)	37 (90%)	23 (88%)
Baseline PET measurements			
TMTV (cm^3)			
Mean (standard deviation)	217.5 (476)	209.6 (579.8)	229.8 (245.1)
Median [1st quartile; 3rd quartile]	70 [26;222]	51 [23;112]	126.5 [56;431]
Minimum—Maximum	1–3603	1–3603	3.1–809
TTLG (cm^3)			
Mean (standard deviation)	2432.2 (4126.3)	2340.9 (4753.6)	2576.1 (2959.6)
Median [1st quartile; 3rd quartile]	721 [222–2512]	496.5 [178–2110]	1968.5 [539–3678]
Minimum—Maximum	9–23718	9–23718	17–12426

DLBCL = diffuse large-cell B-cell lymphoma; NCCN = National Comprehensive Cancer Network.

ratios (OR) were calculated for variables with a *P*-value of less than 0.1. A multivariable analysis using logistic regression was conducted using a manual backward selection procedure. All variables with a *P*-value less than 0.1 were retained in the final model. OR are presented along with their 95% CI. A *P*-value of <0.05 was considered significant.

As a prerequisite to validate our main endpoint, we checked if IPI and R-induction response were predictive of OS, as stated in previous studies, using Cox proportional hazards models. IPI was divided into two groups (0–2 versus 3–5) based on the RSST PTLD-1 study.[6] Results were presented as hazard ratios (HRs) and 95% CI. Survival data were estimated based on Kaplan-Meier curves.

RESULTS

Population

Among the 97 PTLD patients screened with available baseline ^{18}F-FDG PET/CT, 30 were not treated by R-induction and were excluded. The baseline characteristics of the remaining 67 patients are presented in Table 1. The median age at PTLD diagnosis was 59 years (range: 20–80 y), with a majority of male patients (69%). Half of the patients had undergone kidney transplantation (51%), followed by liver (25%). The median time from transplantation to PTLD was 8.3 years, with 10% of early PTLD (ie, PTLD occurred less than 1 y after transplantation). All cases were B-cell lymphomas with predominantly monomorphic DLBCL PTLD (86%). EBV-associated PTLD represented 20 (30%) of the cases. Fifty of 67 patients (75%) had stage III or IV disease and 32 of 67 (48%) had elevated LDH. Extranodal involvement assessed by PET/CT was seen in 81% of patients, especially gastro-intestinal, liver and bone localizations (48%, 21%, and 12%, respectively). No surgical resection was performed. Forty-two percent of patients had an IPI score ≥3 and 49% had an NCCN-IPI score ≥4. Median TMTV and TTLG were 70 cm^3 (IQR 26–222) and 721 cm^3 (IQR 222–2512), respectively.

Treatment and outcome

Immunosuppressive treatment was reduced for 90% of patients. The overall response rate (ORR) after R-induction was 61% (41/67 patients), including a 30% CR rate (20/67 patients)

(Figure 1). All patients in CR after R-induction received rituximab monotherapy consolidation. Of the 47 patients who were not in CR after R-induction, 44 received R-CHOP21, 2 received further rituximab monotherapy (1 in PR and 1 in SD) and 1 died of infectious complication after R-induction. No TOR inhibitors were used. The ORR at the end of treatment (R-induction and rituximab consolidation for patients in CR, and R-induction and R-CHOP for 4 cycles every 21 d for patients not in CR) was 82% (55/67 patients) and the CR rate was 78% (52 patients).

Median PFS was 4.2 years (95% CI, 1.2-not reached), with a 3-year estimate of 53% (42-67). Median OS and DSS were not reached. The 3-year estimates were 66% (95% CI, 55-79) and 76% (95% CI, 66-87) for OS and DSS, respectively (Suppl. Figure 2). After a median follow-up of 3.6 years (95% CI, 3.1-5.1), 22 patients (33%) died. Only 3 of 67 patients (4%) experienced TRM. One patient developed rejection. Thirteen deaths were related to lymphoma: 11 patients died from refractory/relapsing PTLD and 2 from infection (with PTLD on salvage therapy). Six deaths were unrelated to PTLD and due to infection (n = 4), hepatic failure (n = 1), and cardiac cause (n = 1).

Response to R-induction and IPI ≥ 3 were significant predictors of OS: HR = 0.26 (0.11-0.62) (P = 0.001) and HR = 2.77 (1.17-6.56) (P = 0.02), respectively (Suppl. Figure 3).

Prognostic factors

Univariate analysis was conducted for R-induction response prediction (Table 2): B symptoms and TMTV were significant (P = 0.036 and P = 0.031, respectively). The presence of B symptoms resulted in an OR of 2.95 (1.06-8.21). The optimal threshold for TMTV derived from ROC curve analysis was 135 cm^3. Sensitivity, specificity, positive, and negative predictive values were 0.50, 0.80, 0.62, and 0.72, respectively. The AUC was 0.66 (95% CI, 0.52-0.80).

TMTV ≥ 135 cm^3 was highly significant at univariate analysis (P = 0.009). The response rate to R-induction was 38% in the 21 patients with TMTV ≥ 135 cm^3 compared to 72% in the 46 patients with TMTV < 135 cm^3. In a multivariate model including B symptoms and TMTV ≥ 135 cm^3 (Table 2), only TMTV ≥ 135 cm^3 remained significant regarding response to R-induction (P = 0.022, OR = 3.71, 95% CI, 1.21-11.36).

DISCUSSION

The introduction of R-induction instead of upfront chemotherapy has profoundly changed the management of PTLD, with the promise of reduced side effects without altering treatment efficacy. Treatment after R-induction is guided by the early response: continuation of rituximab alone in case of CR, the addition of chemotherapy in other cases.

In this article, we present a large real-life cohort of patients treated homogeneously according to the RSST PTLD-1 protocol. The outcome of patients is similar to the few data available in the literature with CR rates of 30% after R-induction, 78% after treatment, and 66% of 3-year OS. Indeed, since the RSST PTLD-1 trial[6] included 148 patients, survival data related to this strategy in PTLD remain scarce and heterogeneous. In this study, a CR rate of 25% and 70% after R-induction and at the end of treatment respectively were reported, with a 3-year OS of 70%. Boyle et al[18] conducted a study on a subgroup of 24 patients treated by R-induction, with R-induction CR of 45% and 3-year OS of 70%. A study performed by Montes de Jesus et al included 58 patients treated with R-induction[14] but did not report survival data restricted to this group. Two other studies included patients treated by R-induction, but with a slightly different treatment strategy. González-Barca et al.[19] presented two cohorts of 38 and 22 patients with R-induction CR of 61% and 38%, respectively. Patients with PR were not treated upfront by R-CHOP but with additional rituximab and then R-CHOP if needed. End of treatment CR were 76.3% (29/38) and 81.8% (18/22), respectively. Jain et al[20] used a similar protocol on 109 patients (25% of PR patients treated by chemotherapy) and reported an R-induction CR rate of 43%.

As in the RSST PTLD-1 study,[6] TRM remains low in our population (4% versus 8% in the RSST PTLD-1 study).

IPI ≥ 3 and response to R-induction are confirmed as prognostic factors of OS with an HR of 2.77 (pejorative factor, P =

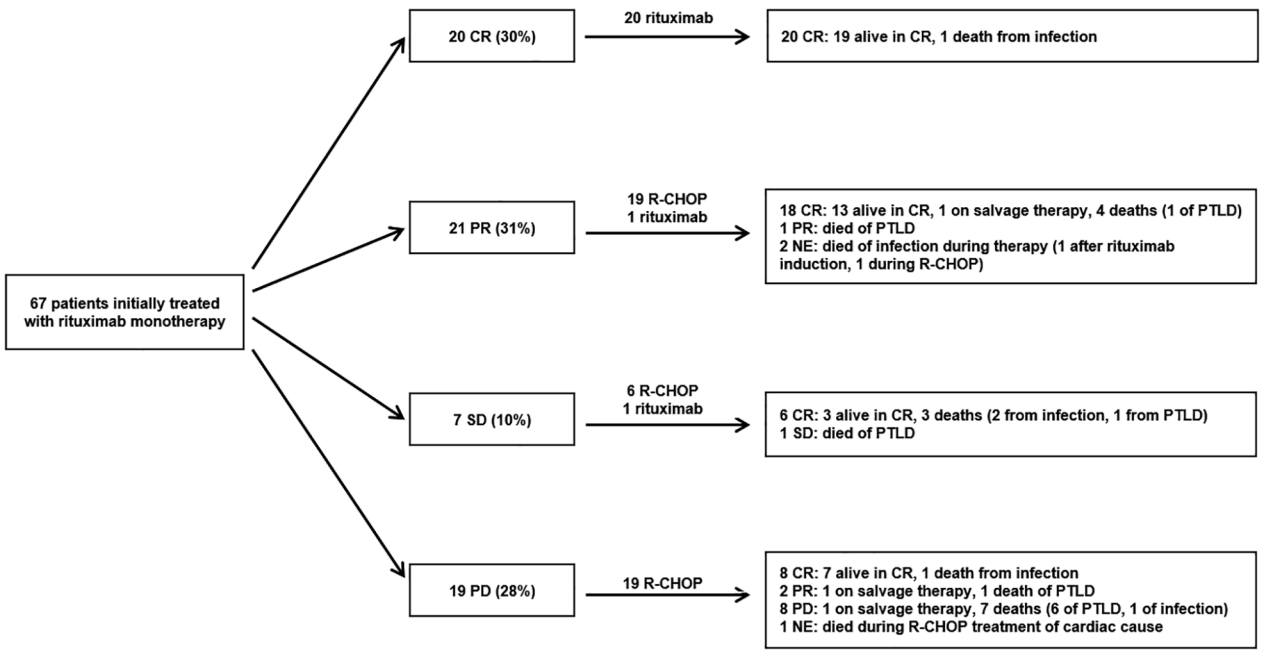

Figure 1. Diagram of patients treated with rituximab induction (4 weekly doses). CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; PTLD = post-transplant lymphoproliferative disorder; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SD = stable disease.

Table 2

Univariate and Multivariate Analysis—Prediction of Rituximab Response

	Univariate Analysis		Multivariate Analysis	
	P	Odd Ratio	*P*	Odd Ratio
Clinical data				
Age	0.954			
Sex	0.535			
PS ECOG ≥2	0.123			
B symptoms	0.036*	2.95 (1.06–8.21)	0.08	2.60 (0.89–7.56)
Lymphoma characteristics				
Histology	0.508			
EBER	0.539			
Stage	0.976			
Extranodal organs involved ≥2	0.088	2.58 (0.85–7.78)		
Biological results				
LDH > N	0.834			
B2m	0.693			
Albumin	0.142			
Prognostic scores				
IPI ≥3	0.278			
NCCN-IPI ≥4	0.271			
Transplantation related data				
Time between transplantation and PTLD	0.298			
Age at transplantation	0.287			
Multiple transplantation	0.197			
Graft involvement	0.670			
Reduction of immunosuppression	1.000			
PET measurements				
TMTV	0.031*	1.00 (1.00–1.00)		
TMTV > 135 ml	0.009*	4.13 (1.39–12.27)	0.022*	3.71 (1.21–11.36)
TTLG	0.070	1.00 (1.00–1.00)		

Odds ratios are calculated for variables with $P < 0.10$.
*$P < 0.05$.
TTLG = total lesion glycolysis.

0.02) and 0.26 (protective factor, $P = 0.001$) in our study, as previously described in prospective and retrospective studies.[6,14,20] Patients who were failing R-induction in the study by Jain et al[20] had a particular poor outcome (2-year OS between 32% and 45%). The prediction of the response to R-induction, which by definition is not an accessible factor at baseline, is in this context a major shortfall.

TMTV, using an optimal threshold of 135 mL, is a predictive factor of the response to R-induction in our study, with an OR of 3.7 (1.2-11.4). TMTV has only been studied so far for the prediction of OS in PTLD, with negative results.[14] These findings are not incompatible insofar as the response to R-induction (and thus the TMTV that predicts it) influences the subsequent therapeutic management.

Median TMTV in our cohort is low compared with that reported in Montes et al's study (70 versus 272). Several hypotheses can be advanced to explain this difference. The method of calculating the MTV is different: we used Meignan's method[17] based on ROI thresholds of 41%, whereas Montes' study[14] used a threshold derived from hepatic uptake. A second hypothesis could be that of an earlier detection due to a more regular monitoring of these patients and the use of more sensitive imaging techniques such as ^{18}F-FDG PET/CT. Finally, the inclusion in the Montes study of patients treated with upfront chemotherapy may have introduced a high MTV population, but there are insufficient data to confirm this hypothesis. The rest of the characteristics are comparable, with notably a similar proportion of stage IV (60% in our study, 64.8%), IPI (42% with IPI ≥ 3 in our study vs 47.7%), and extranodal involvement (81% in our study vs 70.5%).

The multiplicity of segmentation methods and the lack of consensus may be limiting factors to the use of TMTV and call for special attention. However, the method used in this study remains simple in its implementation.[17]

A normal level of LDH was previously reported as predictive of R-response,[21] however only on univariate analysis. Those results were not confirmed with our cohort ($P = 0.83$).

IPI ≥ 3 was not found to be predictive of the R-response despite being predictive of the OS. This factor was not investigated in the only previous study focusing on R-response.[21] In the RSST PTLD-1 study,[6] IPI and R-response were independent predictors of OS, which may support the fact that IPI does not predict response to rituximab.

Regardless of prediction, the imaging technique for R-induction response assessment is heterogeneous and alternates between CT and ^{18}F-FDG PET/CT, ranging from 100% of CT evaluation (RSST PTLD-1 study[6] and study of González-Barca et al[19]), to less than 20%.[18] Our cohort is systematically evaluated by ^{18}F-FDG PET-CT. The comparability of survival data and outcome shows that this second strategy is also valid.

The retrospective nature of this study and the lack of validation cohort is an inherent limitation to this study. However, we must underline the rarity of PTLD and stress the very homogeneous characteristics of our patient cohort. Compared to the study by Jain et al,[20] where 75% of patients in PR after R-induction were not treated with R-CHOP, patients in our cohort were more closely treated according to the RSST PTLD-1 trial (94% of patients not in CR were managed with further R-CHOP). Including only patients staged with PET/CT could have introduced a selection bias: some patients with high-tumor burden and/or compressive symptoms may have been referred to CT evaluation due to the need for urgent treatment. Nevertheless, the baseline characteristics of our patients are comparable to those of other retrospective and prospective studies and this uniform baseline staging allowed us to describe the response to R-induction in a homogeneous way and, thus, analyzed predictive factors of response.

The RSST PTLD-1 trial included only patients with solid organ transplant. However, we chose not to exclude hematopoietic SCT from our study considering they are treated in the same way and that the number of patients was low (5/67). Finally, a central review of images was not performed. The interobserver reproducibility of the Deauville Score assessment is however good (up to 0.86[22]) so that the uncertainties related to the assessment are probably low.

PTLD patients in CR after R-induction are a group of patients with an excellent long-term outcome. On the contrary, patients not responding to R-induction represent an unmet medical need. The good performance of TMTV in predicting response to R-induction may help refine the clinician's assessment, although additional prospective data will be needed to consider a change in therapeutic management.

Our findings may also allow us to discuss the treatment to be offered to patients with PR. The management of these patients is heterogeneous among studies: R-CHOP according to the RSST approach[6] or treatment with 4 additional rituximab in the article by González-Barca et al.[19] A better risk stratification of these patients by TMTV could allow the second option to be favored, or even to treat these patients like those in CR. Zimmermann[23] suggests this

approach for patients with an IPI of less than 3. However, further studies, particularly prospective ones, are needed.

In conclusion, early assessment of patient response and treatment stratification is feasible with ^{18}F-FDG PET/CT and leads to response, toxicity, and survival rates similar to those described in the literature. This study is the first to link baseline ^{18}F-FDG TMTV and response to R-induction in PTLD and opens the door to a better assessment of these patients.

AUTHOR CONTRIBUTIONS

Conceptualization, D.M., E.D.; methodology, D.M., L.K., E.D.; software, D.M., L.K.; validation, D.M., E.D., L.K.; formal analysis, L.K.; investigation, all authors; data curation, all authors; writing—original draft preparation, D.M.; writing—review and editing: all authors. All authors have read and agreed to the published version of the manuscript.

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