WILEY | Hindawi

Research Article

Prognostic Impact of Prephase Treatment Prior to First-Line Treatment in DLBCL: A Population-Based Registry Study

Anthony Levy,[1,2] Gautier Defossez,[3,4] Vincent Delwail,[1,4] Stéphanie Guidez,[1,4] Sammara Chaubard,[5] Christopher Nunes Gomes,[6] Laura Cailly,[1] Valentin Letailleur,[7] Antoine Machet,[8] Xavier Leleu,[1,4] Pierre Ingrand,[3,4] and Thomas Systchenko [1,3,4]

[1]*Haematology Department, CHU de Poitiers, Poitiers, France*
[2]*Haematology Department, CHU de Clermont-Ferrand, Clermont-Ferrand, France*
[3]*Poitou-Charentes General Cancer Registry, Université de Poitiers, Poitiers, France*
[4]*INSERM CIC 1402, CHU de Poitiers, Poitiers, France*
[5]*Haematology Department, CHU de Limoges, Limoges, France*
[6]*Haematology Department, CHU d'Angers, Angers, France*
[7]*Haematology Department, CHU de Nantes, Nantes, France*
[8]*Haematology Department, CHU de Tours, Tours, France*

Correspondence should be addressed to Thomas Systchenko; thomas.systchenko@chu-poitiers.fr

Introduction. Prephase treatment (PP) is recommended in diffuse large B-cell lymphomas (DLBCL) to decrease therapy-related toxicities and to avoid tumour lysis syndrome. Data in the real world are limited, and no study has evaluated the impact on overall survival. We aimed to evaluate overall survival (OS), progression-free survival (PFS), and grade III-IV toxicities during the first cycle according to PP. *Methods and Materials*. All DLBCL diagnosed between 2014 and 2017 and aged between 18 and 80 years were identified by the Poitou-Charentes General Cancer Registry (France). PP was defined as any treatment prior to first-line, excluding anthracycline and/or Rituximab. We performed propensity score matching (PSM) to control characteristics at diagnosis, reduce bias, and approximate a randomized trial. *Results*. Three hundred and forty patients received first-line treatment in 17 hospital centers: 126 (37%) with prephase and 214 (63%) without prephase (NPP). After PSM, 97 patients remained in each group without significant difference in characteristics at diagnosis; matched PP patients had a 2-year OS of 71% (vs. 77%, $P = 0.32$), a 2-year PFS of 61% (vs. 74%, $P = 0.12$), and 26% grade III-IV toxicities (vs. 27%, $P = 0.75$). No tumour lysis syndrome was reported. PP nonsignificantly decreases grade III-IV toxicities for patients with high tumour load ($P = 0.82$) or elderly patients ($P = 0.81$). *Conclusion*. PP treatment does not affect survival nor does it reduce therapy-related toxicities even for patients with high tumour load or elderly patients. Further studies are needed to evaluate the efficacy and safety of PP.

1. Introduction

In the early 2000s, R-CHOP significantly improved the outcome of diffuse large B-cell lymphomas (DLBCL), and a majority of patients were cured [1, 2]. Significant early morbi-mortality has been reported in the first cycle [3, 4], and prephase treatment (PP) is used to decrease therapy-related toxicities [4, 5]. PP has been included in many studies (MinT [6], RICOVER-60 [7], and LNH09-7B [8]) as an essential component of therapy and is recommended (grade Ia) by the latest ESMO guidelines to avoid tumour lysis syndrome [9].

However, data in the real-world clinical practice are limited [10, 11], and no study to our knowledge has evaluated the patient-level response of prephase treatment on overall survival (OS). Given the negative prognostic impact of decreasing the immunochemotherapy (ICT) intensity dose [12–15], it seemed important to evaluate the prognostic

impact of PP and thereby justify consideration of prephase treatment prior to first-line treatment in DLBCL.

Our main objective was to compare OS with PP prior to first-line treatment. The secondary outcomes were PFS and prevention of grade III-IV toxicities during the first cycle.

2. Methods

2.1. Study Design and Patients. Our study was a retrospective population-based and multicenter study. This study was conducted in accordance with "good clinical practice" and all applicable regulatory requirements, including the 2008 version of the Declaration of Helsinki. In compliance with French law, the collection and analysis of medical data by the General Cancer Registry of Poitou-Charentes received the approval of the French regulatory authorities. Patients were informed of their data registration and given the right to deny access or to rectify their personal data.

All newly diagnosed DLBCL cases in the Poitou-Charentes area (Western France, 1.8 million inhabitants) between January 1, 2014, and December 31, 2017, were exhaustively collected in the population-based Poitou-Charentes General Cancer Registry. Cases were classified according to the International Classification of Diseases for Oncology 3rd edition [16] and the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph) [17]: primary effusion lymphoma (9678/3), mediastinal large B-cell lymphoma (9679/3), diffuse large B-cell lymphoma (9680/3), and immunoblastic large B-cell lymphoma (9684/3). All diagnoses of DLBCL had to be proven histologically. Patients with primary central nervous system lymphoma were excluded, as were patients under 18 and over 80 years old, because standard first-line treatment is undefined and/or different from standard R-CHOP [18, 19]. A medical source file review was systematically performed to provide supplementary data, especially for grade III-IV toxicities.

As bulky mass was not standardized in the latest DLBCL guidelines, we empirically took into consideration any tumour mass greater than or equal to 7 cm, as previously published [20]. The age-adjusted international prognostic index (aaIPI), which includes LDH, Ann Arbor stage, and performance status (PS) [21, 22], was used to compare patients' baseline characteristics.

2.2. Treatment. Patients who had at least one cycle of first-line immunochemotherapy, with or without prephase treatment, were included in the final analysis.

Originally, prephase treatment consisted of a single injection of 1 mg vincristine and 7 days of oral prednisone [4]. However, several hospital centers used COP/CVP regimens (cyclophosphamide, vinca alkaloids, and prednisone) for PP in analogy to Burkitt lymphoma. For this study, we defined prephase as any treatment prior to first-line treatment, excluding anthracycline and/or immunotherapy (rituximab). Two groups were defined according to the initial decision to use or not to use prephase treatment: the PP group and the nonprephase (NPP) group.

2.3. Outcomes. OS was defined as the time from the histological diagnosis of DLBCL until death from any cause. Progression-free survival (PFS) was defined as time until first evidence of tumour progression according to the RECIL 2017 criteria [23] or until death from any cause. Vital status was obtained from the French National Directory of Identification of Physical Persons. The follow-up of living patients was censored as of December 31, 2020. We compared the occurrence of grade III-IV toxicities after the first cycle of ICT, based on Common Terminology Criteria for Adverse Events (CTCAE) v5.

2.4. Propensity Score Matching. Prephase treatment is recommended for patients with high tumour load [9]. To avoid reporting biased outcomes related to different characteristics at diagnosis of PP and NPP patients, we performed propensity score matching (PSM) aimed at determining real treatment effect. The propensity score is used to match patients with a similar distribution of baseline characteristics (confounders) so that the difference in outcomes (OS, PFS, and grade II-IV toxicities) can provide an unbiased estimate of treatment effect [24–26].

Our PSM included all patient and tumour characteristics at diagnosis usually used in randomized studies (age, sex, Ann Arbor stage, stage B, Bulky, LDH, and PS) and place of care.

A greedy algorithm was used to match cases to controls, also known as nearest neighbor matching. The cases were ordered and sequentially matched to the nearest unmatched control. A pair was closely matched if the distance between the case and the control was small, with a fixed caliper width of 0.25. Once a match was made, it was not reconsidered. If more than one unmatched control matched to a case, the control was selected at random. Patients were matched 1 : 1.

In sensitivity analysis, we performed two complementary analyses: a second PSM limited to variables identified as significant for PP use by multivariable stepwise logistic regression and different propensity score method, carried out by inverse probability of treatment weighting, which included all patients and not only matched samples.

2.5. Statistical Analyses. Patient characteristics before and after propensity score matching were compared with the McNemar Chi^2 or exact test for nominal variables and the Wilcoxon signed-rank test for quantitative variables. Survival rates were estimated by the Kaplan–Meier method and compared between groups by the log-rank test. Hazard ratios (HRs) were compared by univariate Cox proportional hazards models.

The main results are given with their 95% confidence interval (95% CI). The significance level $p = 0.05$ was used for the final comparative analyses. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and the package used to create matched samples was Proc PSMATCH.

3. Results

3.1. Patient Characteristics.
Between 2014 and 2017, 416 DLBCLs were diagnosed in 17 hospital centers. Seventy-six patients were excluded: 42 central nervous system (CNS) lymphomas, 22 without first-line immunochemotherapy, and 12 unexplored. The analysis population was composed of 340 patients (82%) treated with first-line treatment: 126 (37%) with prephase treatment prior to first-line (PP) and 214 (63%) without prephase (NPP).

The median age at diagnosis was 65 years (range 18–80), and the male/female sex ratio was 1.5 (204/136). Patient characteristics are summarized in Table 1.

3.2. Treatments and Outcomes of All Patients.
Prephase drugs were corticosteroids (98%), cyclophosphamide (72%), and vinca alkaloids (56%, especially vincristine and vindesine). Prephase treatment was mostly a combination of 3 drugs (72%). A median time from PP until first-line regimens was 9 days (min 1–max 72) for single/double drugs prephase and 14 days (min 5–max 73) for triple drugs prephase, respectively. Nine patients (25%) treated with single/double drugs prephase and 31 patients (34%) treated with triple drugs prephase had grade III-IV toxicities without significant difference ($P = 0.30$). The 2-year PFS was 57% (95% CI 39%–72%) for single/double drugs prephase and 62% (95% CI 50%–71%) for triple drugs prephase, respectively ($P = 0.49$).

First-line regimens were mostly "RCHOP-like" (85%). Thirty-eight patients (11%) were treated with "reduced dose RCHOP" (RD-RCHOP): 28 with doxorubicin $<50 \, mg/m^2$ per cycle, 9 without doxorubicin, and 1 without vincristine. Nine patients (3%) were treated with "intensive chemotherapy:" 4 with R-DHAC, 3 with R-ACVBP, 1 with R-CHOEP, and 1 treated as a Burkitt lymphoma (LMBA02 protocol). Two patients with other regimens received CHOP without Rituximab: one with CD20 and one with uncontrolled viral hepatitis.

The overall response rate was 84% including 75% complete responses and 9% partial responses. One hundred and twelve patients (33%) had relapse/refractory DLBCL, 103 patients had a salvage regimen, and 29 (9%) received an autologous stem cell transplantation.

With a median follow-up of 4.71 years (min 0.05–max 6.94), 102 patients (30%) died. Among these deaths, 77 (75%) were attributed to DLBCL, 21 to another cause, and 4 to an unknown cause. The 2-year OS and 2-year PFS were 79% (95% CI 74%–83%) and 71% (95% CI 66%–76%), respectively.

Ninety-two patients (27%) had grade III-IV toxicities after the first cycle of ICT. The 3 most frequent toxicities were neutropenia (22%), infection (8%), and febrile neutropenia (7%). No tumour lysis syndrome was reported.

3.3. Results according to Prephase Treatment before PSM

3.3.1. Patient Characteristics.
Patients with prephase treatment (PP) more frequently had stage III-IV (84% vs. 67%, $P = 0.0005$), elevated LDH (75% vs. 52%, $P < 0.0001$), PS > 1 (48% vs. 14%, $P < 0.0001$), and bulky mass (53% vs. 33%, $P = 0.0003$). PP patients had a DLBCL of worse prognosis with aaIPI ≥2 at 76% vs. 46% in the NPP group ($P < 0.0001$) (Table 1). Seventy-four PP patients (59%) had an improvement in PS, and 103 (82%) attained PS 0-1 before the first cycle of ICT (vs. 52% at diagnosis).

3.3.2. First-Line Regimens.
The distribution of first-line regimens was similar between the two groups ($P = 0.81$). PP patients less frequently achieved complete response (64% vs. 81%, $P = 0.002$), and more frequently had relapse/refractory DLBCL (42% vs. 28%, $P = 0.006$) without significant difference in salvage regimen eligibility (39% vs. 25%, $P = 0.008$) and autologous stem cell transplantation (8% vs. 9%, $P = 0.76$).

3.3.3. Overall and Progression-Free Survival.
Two-year OS was 67% (95% CI 59%–75%) for PP patients and 85% (95% CI 80%–89%) for NPP patients, respectively ($P = 0.0018$) (Figure 1(a)). Two-year PFS was 61% (95% CI 51%–69%) for PP patients and 77% (95% CI 71%–83%) for NPP patients, respectively ($P = 0.0011$) (Figure 1(b)).

3.3.4. Grade III-IV Toxicities after the First Cycle of ICT.
Forty PP patients (32%) and 52 NPP patients (24%) had grade III-IV toxicities without significant difference ($P = 0.14$). PP patients had more frequently febrile neutropenia (12% vs. 4% ($P = 0.004$)) and severe infection (15% vs. 4% ($P = 0.0004$)) (Table 2).

3.4. Results according to Prephase Treatment after PSM

3.4.1. Patient Characteristics.
After PSM, 97/126 (77%) patients remained in the PP group and 97/214 (45%) patients in the NPP group, without significant difference in patient and tumour characteristics (Table 1).

3.4.2. First-Line Regimens.
First-line regimens were not significantly different between the 2 groups ($P = 0.14$). The overall response rate (67% vs. 76%, $P = 0.16$), salvage regimen eligibility (39% vs. 29%, $P = 0.13$), and autologous stem cell transplantation (9% vs. 8%, $P = 0.80$) were not significantly different between PP and NPP patients, respectively.
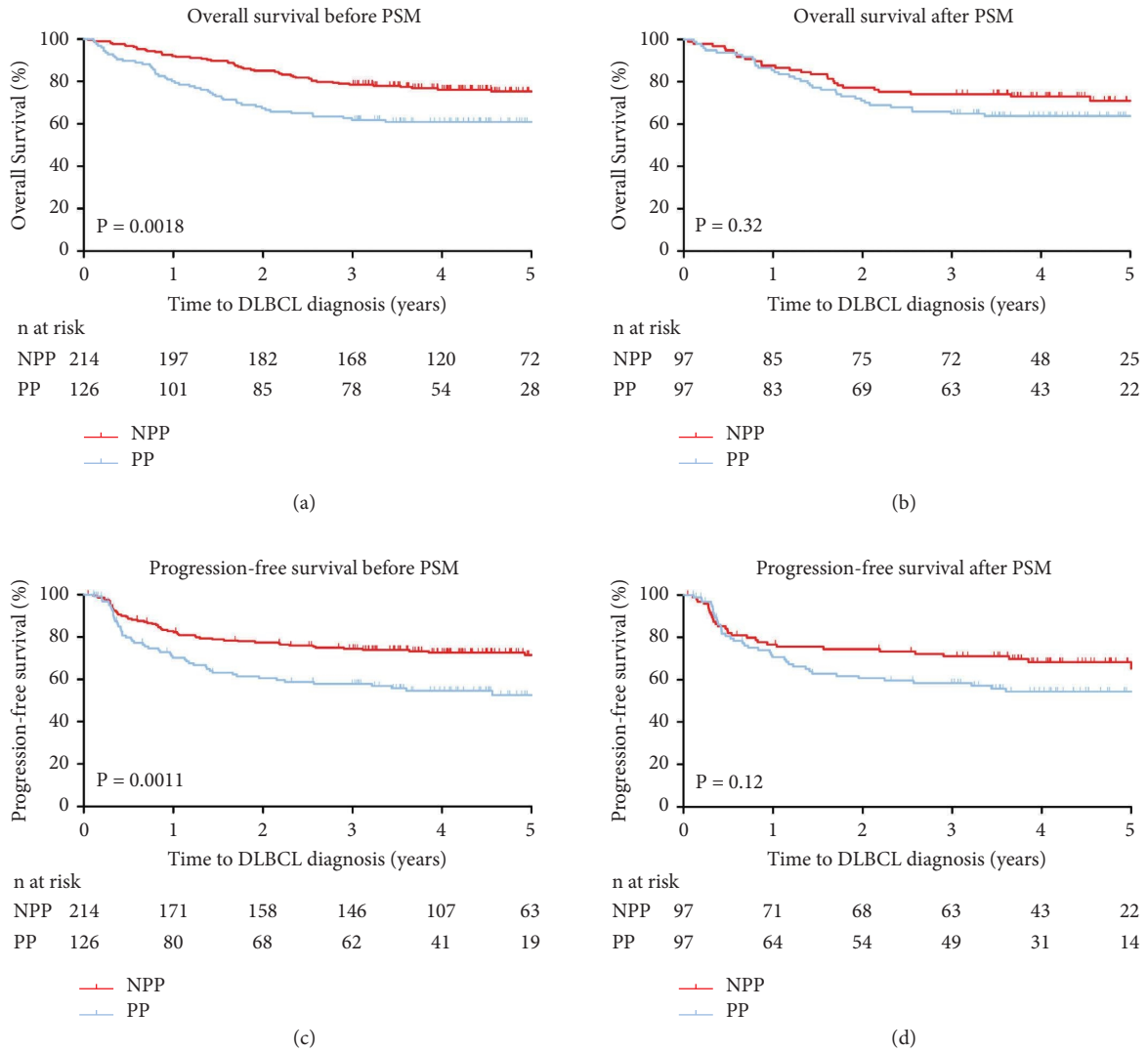
3.4.3. Overall and Progression-Free Survival.
Two-year OS was 71% (95% CI 61%–79%) for PP patients and 77% (95% CI 68%–84%) for NPP patients, respectively ($P = 0.32$) (Figure 1(c)). Two-year PFS was 61% (95% CI 50%–70%) for PP patients and 74% (95% CI 64%–82%) for NPP patients, respectively ($P = 0.12$) (Figure 1(d)).

3.4.4. Grade III-IV Toxicities after the First Cycle of ICT.
Twenty-five PP patients (26%) and 27 NPP patients (28%) had grade III-IV toxicities without significant difference

TABLE 1: Patient and tumour characteristics at diagnosis of diffuse large B-cell lymphoma.

	All patients (N = 340)	Before propensity score matching			After propensity score matching		
		With prephase (N = 126)	Without prephase (N = 214)	P	With prephase (N = 97)	Without prephase (N = 97)	P
Age (median (min-max)), years	65 [18–80]	67 [20–80]	65 [18–80]	0.06	67 [20–80]	67 [19–80]	1.00
Sex ratio (male/female)	1.5 (204/136)	1.7 (80/46)	1.4 (124/90)	0.31	1.7 (61/36)	1.7 (61/36)	1.00
Stage				0.0005			0.86
I-II	91 (27%)	20 (16%)	71 (33%)		19 (20%)	20 (21%)	
III-IV	249 (73%)	106 (84%)	143 (67%)		78 (80%)	77 (79%)	
Stage B	127 (37%)	65 (52%)	62 (29%)	<0.0001	44 (45%)	41 (42%)	0.66
Bulky (X)	138 (40%)	67 (53%)	71 (33%)	0.0003	50 (52%)	50 (52%)	1.00
Serum LDH > normal	200 (60%)	92 (75%)	108 (52%)	<0.0001	68 (70%)	65 (67%)	0.64
PS				<0.0001			0.44
0-1	251 (74%)	66 (52%)	185 (86%)		64 (66%)	69 (71%)	
>1	89 (26%)	60 (48%)	29 (14%)		33 (34%)	28 (29%)	
aaIPI score				<0.0001			0.53
0	60 (18%)	10 (8%)	50 (24%)		10 (10%)	10 (10%)	
1	82 (25%)	19 (16%)	63 (30%)		19 (20%)	25 (26%)	
2	123 (37%)	48 (39%)	75 (36%)		44 (45%)	41 (42%)	
3	67 (20%)	46 (37%)	21 (10%)		24 (25%)	21 (22%)	
Place of care				0.048			0.64
University hospitals	223 (66%)	91 (72%)	132 (62%)		66 (68%)	69 (71%)	
Hospital centers	117 (34%)	35 (28%)	82 (38%)		31 (32%)	28 (29%)	

LDH, lactate dehydrogenase; PS, performance status; aaIPI, age-adjusted International Prognostic Index.

PSM: propensity score matching, NPP: without prephase treatment, PP: with prephase treatment

FIGURE 1: Overall survival (a) before PSM and (b) after PSM and progression-free survival (c) before PSM and (d) after PSM after diagnosis of diffuse large B-cell lymphoma (DLBCL) according to prephase treatment.

TABLE 2: Grade III-IV toxicities after the first-line regimens of diffuse large B-cell lymphoma.

	All patients $(N = 340)$	Before propensity score matching			After propensity score matching		
		With prephase $(N = 126)$	Without prephase $(N = 214)$	P	With prephase $(N = 97)$	Without prephase $(N = 97)$	P
All toxicities	92 (27%)	40 (32%)	52 (24%)	0.14	25 (26%)	27 (28%)	0.75
Febrile neutropenia	23 (7%)	15 (12%)	8 (4%)	0.004	9 (9%)	5 (5%)	0.27
Neutropenia	74 (22%)	34 (27%)	40 (19%)	0.07	22 (23%)	20 (21%)	0.73
Anemia	13 (4%)	8 (6%)	5 (2%)	0.08	1 (1%)	1 (1%)	1.00
Thrombocytopenia	10 (3%)	5 (4%)	5 (2%)	0.51	4 (4%)	2 (2%)	0.68
Infection	28 (8%)	19 (15%)	9 (4%)	0.0004	11 (11%)	6 (6%)	0.20
Cardiac toxicity	4 (1%)	2 (2%)	2 (1%)	0.63	2 (2%)	2 (2%)	1.00
Neurologic toxicity	2 (1%)	1 (1%)	1 (1%)	1.00	1 (1%)	0	1.00

$(P = 0.75)$. Febrile neutropenia and severe infection were not significantly different between PP patients and NPP patients $(P = 0.27$ and $P = 0.20$, respectively) (Table 2).

3.4.5. *Subgroups Analysis among Matched Patients.* Prephase treatment is recommended for patients with high tumour load or elderly patients. No significant difference

between PP patients and NPP patients was observed in patients with bulky mass ($N = 100$) for grade III-IV toxicities (24% vs. 26%, $P = 0.82$), OS (HR 1.33 [0.63–2.81], $P = 0.46$), and PFS (HR 1.30 [0.65–2.81], $P = 2.62$); in elderly patients (>65 years, $N = 117$) for grade III-IV toxicities (26% vs. 28%, $P = 0.81$), OS (HR 1.36 [0.75–2.46], $P = 0.31$), and PFS (HR 1.51 [0.83–2.76], $P = 0.18$); and in patients with PS > 1 ($N = 61$) for grade III-IV toxicities (39% vs. 21%, $P = 0.13$), OS (HR 1.24 [0.61–2.53], $P = 0.55$), and PFS (HR 1.10 [0.48–2.52], $P = 0.82$). Originally, prephase treatment consisted of a single injection of 1 mg vincristine and 7 days of oral prednisone. No significant difference between patients with single/double drugs prephase ($N = 31$), triple drugs prephase ($N = 66$), and without prephase was observed for grade III-IV toxicities (19% vs. 29% vs. 28%, $P = 0.32$), OS ($P = 0.19$), and PFS ($P = 0.15$) (Supplementary Figure 1).

3.5. Sensitivity Analysis. Variables identified for the second PSM were bulky mass, PS, and LDH level. After second PSM, no significant difference between PP patients (94/126) and NPP patients (94/126) was observed in patients for grade III-IV toxicities ($P = 0.33$), OS ($P = 0.14$), and PFS ($P = 0.06$).

After propensity score weighting, NPP patients had a risk of death and progression reduced by 12% (HR 0.88 [0.58–1.32]) and 30% (HR 70 [0.48–1.02]) as compared to PP patients.

4. Discussion

Our study is to our knowledge the first to show that PP nonsignificantly decreases OS and PFS in real-world clinical practice. In addition, PP does not decrease therapy-related toxicities during the first cycle even for patients with high tumour load or elderly patients. To control indication bias, the major bias in our study, we performed PSM. The benefit of PSM is to approximate a randomized trial so that differences in outcomes (OS, PFS, or grade III-IV toxicities) are unbiased estimates of PP effect [24–26].

PP nonsignificantly decreases OS and PFS, a finding suggesting that PP may have a prognostic impact. If propensity score methods try to control the worse characteristics at diagnosis of PP patients compared to NPP patients, the risk remains that a part of the residual numerical differences in outcomes may be explained by these characteristics. External validity of our survival results could not be assessed because no data are available for comparison. To improve the internal validity of our study, we performed two complementary analyses: a second PSM and another propensity score method by weighting. For the second PSM, only variables using PP in our study identified by logistic regression were retained: bulky mass, PS, and LDH level. The first PSM included these three variables in addition to five others (age, sex, Ann Arbor stage, stage B, and place of care). Differences in OS and PFS were smaller with the first PSM compared to the second. The more confounders were taken into account, the smaller the difference in survival results. Propensity score weighting included all patients, and no significant difference between PP and NPP patients was

observed for OS and PFS. The reproducibility of our results with the same trends for the PP effect was reassuring for internal validity.

Grade III-IV toxicities after the first cycle of ICT were not significantly decreased by PP. Our results differ from those of other studies. Pfreundschuh et al. introduced prephase treatment in the non-Hodgkin lymphoma (NHL)–B2 trial [4] to prevent the "first-cycle effect" (described as the deepest ANC nadir, longest duration of neutropenia, and highest rate of therapy-associated deaths) [3, 4]. But this clinical trial included elderly patients aged between 61 and 75 years, whereas in our study, 35% of patients were younger than 61 years. However, we did not show more grade III-IV toxicities ($P = 0.81$) for elderly patients (>65 years, $N = 117$). In a recent prospective and randomized study, Lakshmaiah et al. [5] showed that prephase treatment reduced febrile neutropenia and grade III-IV neutropenia. Prophylactic growth factor was given to 22 patients (22%) whereas in our study, it was systematic. Only 23/341 patients (7%) had febrile neutropenia, versus 25/100 patients in the Lakshmaiah study. The significance of their results can be explained by the difference in population size, and we believe that the systemic use of G-CSF in the first cycle of ICT is more likely to limit the occurrence of febrile neutropenia. No tumour lysis syndrome was reported for PP and NPP patients in our study, even though prephase treatment is recommended (grade Ia) in the latest ESMO guidelines to avoid the pathology [9]. Rasburicase for high tumour load is systematically used in our center and can explain the absence of lysis syndrome. Recently, a retrospective study on PP prior to definitive multiagent chemotherapy in aggressive lymphomas did not report any significant difference in the episodes of febrile neutropenia, tumour lysis syndrome, hospitalization, emergency visits, or 30-day mortality [10]. In our study, PP was primarily a tritherapy (72%) and most often combined with corticosteroids, a vinca alkaloid (vincristine or vindesine), and cyclophosphamide. In subgroups analysis, the addition of cyclophosphamide and a triple therapy did not appear to increase grade III-IV toxicities for patients with PP and therefore could not help to explain the lack of benefit of prephase treatment.

If the propensity score in cancer studies has recently been much more frequently used as a means of controlling indication bias [27], some limitations must be analyzed.

First, our results after PSM must be interpreted for a matched sample ($N = 194$) and not for all patients ($N = 340$). When choosing the best matching algorithm, there usually exists a trade-off between bias from a sizable sample loss and residual confounding from the inclusion of poorly matched subjects [28]. This trade-off was highlighted, not only because our study had a population-based design, allowing a high degree of completeness of case collection before PSM, but also due to the representativeness of our population. PSM is not all-inclusive and excludes extreme patients [29]. After PSM, although the matched sample was less representative, it was not limited to patients for whom PP is recommended. Indeed, the matched sample included 94 patients without a high tumour load (48%) and 77 young patients ≤65 years (40%).

Second, propensity score analysis is limited by its inability to control for unmeasured confounders. If all DLBCL prognostic factors are not known, the best prognostic assessment is aaIPI (including level of LDH, Ann Arbor stage, and PS) [21, 22]. The choice of our PSM with all of the diagnostic characteristics generally used in randomized studies appeared to us to be the best method to control the known confounding factors in DLBCL. While the Poitou-Charentes General Cancer Registry database mainly contains diagnostic data, patient care pathways are also particularly clearly identified. We were consequently able to reach a high degree of completeness of prognostic factors at diagnosis with a systematic medical source file review.

Third, the quality of reporting is essential for study interpretation and reproducibility. We used guidelines from the Journal of the National Cancer Institute for reporting propensity score analysis, modified from the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Statement [27, 30].

The recommended prephase treatment is corticosteroids ± vincristine for patients with high tumour load or elderly patients. However, prephase treatment in our real-world clinical practice study is often a COP/CVP regimen (72%) and 29% of patients without high tumour load and 33% of nonelderly patients received prephase treatment, respectively. Our results highlight that prephase treatment does not have any impact, favorable or unfavorable, on survival or safety outcomes for all DLBCL patients. The frequent use of prephase treatment outside the recommendations should be confirmed by further real-world clinical practice studies. Results for patients with a high tumour load or elderly patients should be analyzed with caution due to analyzes in subgroups with a small sample size. Our results and the lack of randomized data to support the recommendation of prephase treatment suggest that a prospective randomized, controlled study may be beneficial.

Data Availability

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

Disclosure

This manuscript was presented for the thesis paper work of medicine of Anthony LEVY intituled "Prognostic impact of prephase treatment prior to first line in diffuse large B-cell lymphomas: a cancer registry study" [31].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

AL, TS, GD, PI, and VD conceptualized and designed the study. AL, TS, SC, CNG, LC, VL, and AM collected and assembled the data. AL, TS, GD, and PI interpreted and analyzed the data. AL, TS, GD, VD, SG, XL, and PI wrote the manuscript.

Supplementary Materials

Supplementary Figure 1: overall survival and progression-free survival according to prephase treatment. (*Supplementary Materials*)

References

[1] J. O. Armitage, "My treatment approach to patients with diffuse large B-cell lymphoma," *Mayo Clinic Proceedings*, vol. 87, no. 2, pp. 161–171, 2012.

[2] B. Coiffier, E. Lepage, J. Briere et al., "CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma," *New England Journal of Medicine*, vol. 24, no. 4, pp. 235–242, 2002.

[3] M. Pfreundschuh, "How I treat elderly patients with diffuse large B-cell lymphoma," *Blood*, vol. 116, no. 24, pp. 5103–5110, 2010.

[4] M. Pfreundschuh, L. Trümper, M. Kloess et al., "Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL," *Blood*, vol. 104, no. 3, pp. 634–641, 2004.

[5] K. C. Lakshmaiah, V. Asati, G. Babu K et al., "Role of prephase treatment prior to definitive chemotherapy in patients with diffuse large B-cell lymphoma," *European Journal of Haematology*, vol. 100, no. 6, pp. 644–648, 2018.

[6] M. Pfreundschuh, L. Trümper, A. Osterborg et al., "CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group," *The Lancet Oncology*, vol. 7, no. 5, pp. 379–391, 2006.

[7] M. Pfreundschuh, J. Schubert, M. Ziepert et al., "Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60)," *The Lancet Oncology*, vol. 9, no. 2, pp. 105–116, 2008.

[8] F. Peyrade, S. Bologna, V. Delwail et al., "Combination of ofatumumab and reduced-dose CHOP for diffuse large B-cell lymphomas in patients aged 80 years or older: an open-label, multicentre, single-arm, phase 2 trial from the LYSA group," *The Lancet Haematology*, vol. 4, no. 1, pp. e46–e55, 2017.

[9] H. Tilly, M. Gomes da Silva, U. Vitolo et al., "Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up," *Annals of Oncology*, vol. 26, no. 5, pp. v116–v125, 2015.

[10] L. Malpica, B. Mufuka, J. Galeotti et al., "A retrospective study on prephase therapy prior to definitive multiagent chemotherapy in aggressive lymphomas," *Leukemia and Lymphoma*, vol. 61, no. 6, pp. 1508–1511, 2020.

[11] Y. Cui, X. Li, Z. Sun et al., "Safety and efficacy of low-dose prephase before conventional-dose chemotherapy for ulcerative

gastric diffuse large B-cell lymphoma," *Leukemia and Lymphoma*, vol. 56, no. 9, pp. 2613–2618, 2015.

[12] Y. Terada, H. Nakamae, R. Aimoto et al., "Impact of relative dose intensity (RDI) in CHOP combined with rituximab (R-CHOP) on survival in diffuse large B-cell lymphoma," *Journal of Experimental & Clinical Cancer Research*, vol. 28, no. 1, p. 116, 2009.

[13] T. Hirakawa, H. Yamaguchi, N. Yokose, S. Gomi, K. Inokuchi, and K. Dan, "Importance of maintaining the relative dose intensity of CHOP-like regimens combined with rituximab in patients with diffuse large B-cell lymphoma," *Annals of Hematology*, vol. 89, no. 9, pp. 897–904, 2010.

[14] M. Długosz-Danecka, S. Szmit, T. Ogórka, A. B. Skotnicki, and W. Jurczak, "The average relative dose intensity of R-CHOP is an independent factor determining favorable overall survival in diffuse large B-cell lymphoma patients," *Cancer Medicine*, vol. 8, no. 3, pp. 1103–1109, 2019.

[15] T. A. Eyre, R. Salisbury, D. W. Eyre, C. Watson, G. P. Collins, and C. S. Hatton, "Results of a large retrospective analysis of the effect of intended dose intensity of R-CHOP on outcome in a cohort of consecutive, unselected elderly patients with de novo diffuse large B cell lymphoma," *British Journal of Haematology*, vol. 173, no. 3, pp. 487–491, 2016.

[16] S. H. Swerdlow, E. Campo, N. L. Harris et al., *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, IARC Press, Lyon, France, 4th edition, 2008.

[17] L. M. Morton, J. J. Turner, J. R. Cerhan et al., "Proposed classification of lymphoid neoplasms for epidemiologic research from the pathology working group of the international lymphoma Epidemiology Consortium (InterLymph)," *Blood*, vol. 110, no. 2, pp. 695–708, 2007.

[18] U. Vitolo, J. F. Seymour, M. Martelli et al., "Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up," *Annals of Oncology*, vol. 27, no. 5, pp. 91–102, 2016.

[19] C. Buske, M. Hutchings, M. Ladetto et al., "ESMO Consensus Conference on malignant lymphoma: general perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma," *Annals of Oncology*, vol. 29, no. 3, pp. 544–562, 2018.

[20] T. Lamy, G. Damaj, P. Soubeyran et al., "R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma," *Blood*, vol. 131, no. 2, pp. 174–181, 2018.

[21] International Non-Hodgkin's Lymphoma Prognostic Factors Project, "A predictive model for aggressive non-Hodgkin's lymphoma," *New England Journal of Medicine*, vol. 329, no. 14, pp. 987–994, 1993.

[22] L. H. Sehn, B. Berry, M. Chhanabhai et al., "The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP," *Blood*, vol. 109, no. 5, pp. 1857–1861, 2007.

[23] A. Younes, P. Hilden, B. Coiffier et al., "International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017)," *Annals of Oncology*, vol. 28, no. 7, pp. 1436–1447, 2017.

[24] P. R. Rosenbaum and D. B. Rubin, "The central role of the propensity score in observational studies for causal effects," *Biometrika*, vol. 70, no. 1, pp. 41–55, 1983.

[25] P. C. Austin, "An introduction to propensity score methods for reducing the effects of confounding in observational studies," *Multivariate Behavioral Research*, vol. 46, no. 3, pp. 399–424, 2011.

[26] U. Benedetto, S. J. Head, G. D. Angelini, and E. H. Blackstone, "Statistical primer: propensity score matching and its alternatives," *European Journal of Cardio-Thoracic Surgery*, vol. 53, no. 6, pp. 1112–1117, 2018.

[27] X. I. Yao, X. Wang, P. J. Speicher et al., "Reporting and guidelines in propensity score analysis: a systematic review of cancer and cancer surgical studies," *Journal of the National Cancer Institute*, vol. 109, no. 8, p. 323, 2017.

[28] M. Caliendo and S. Kopeinig, "Some practical guidance for the implementation of propensity score matching," *Journal of Economic Surveys*, vol. 22, no. 1, pp. 31–72, 2008.

[29] J. A. Reiffel, "Propensity-score matching: optimal, adequate, or incomplete?" *Journal of Atrial Fibrillation*, vol. 11, no. 4, p. 2130, 2018.

[30] E. von Elm, D. G. Altman, M. Egger et al., "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies," *Journal of Clinical Epidemiology*, vol. 61, no. 4, pp. 344–349, 2008.

[31] A. Levy, "Prognostic Impact of Prephase Treatment Prior to First Line in Diffuse Large B Cell Lymphomas: A Cancer Registry Study," MD Thesis, Université de Poitiers, Poitiers, France, 2021.