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 Systchenko1,3,4

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

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

Received 19 May 2023; Revised 11 August 2023; Accepted 8 September 2023; Published 25 September 2023

Academic Editor: Liren Qian

Copyright © 2023 Anthony Levy et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 Chi² or exact test for nominal variables and the Wilcoxon signed-rank test for quantitative variables. Survival rates were estimated by the Kaplan–Meier 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 vincar alkaldoids (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 5–max 73) for triple drugs prephase, respectively. Twenty-five PP patients (26%) and 27 NPP patients (28%) were treated 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 10.16), 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 71% (95% CI 61%–79%) and 77% (95% CI 71%–83%) for NPP patients, respectively (P = 0.0011) (Figure 1(b)).

3.3. Results according to Prephase Treatment after PSM

3.3.1. 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).

3.3.2. 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. 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).
Table 1: Patient and tumour characteristics at diagnosis of diffuse large B-cell lymphoma.

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>All patients ($N = 340$)</th>
<th>Before propensity score matching</th>
<th>After propensity score matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With prephase ($N = 126$)</td>
<td>Without prephase ($N = 214$)</td>
<td>With prephase ($N = 97$)</td>
</tr>
<tr>
<td>All toxicities</td>
<td>40 (32%)</td>
<td>52 (24%)</td>
<td>25 (26%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15 (12%)</td>
<td>8 (4%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34 (27%)</td>
<td>40 (19%)</td>
<td>22 (23%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (6%)</td>
<td>5 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (4%)</td>
<td>5 (2%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (15%)</td>
<td>9 (4%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>2 (2%)</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Neurologic toxicity</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

($P = 0.75$). 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 0.70 [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]. Rusburicase 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 aALPI (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.

Acknowledgments

The authors would like to thank the entire team of Poitou-Charentes General Cancer Registry, the Clinical Investigation Center of Poitiers University Hospital, the University of Poitiers, the Regional Health Agency of Nouvelle Aquitaine, and all hospital centers that treated patients. The authors would also like to thank Jeffrey Arsham for transcription help.

Supplementary Materials

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

References