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Real-world Outcomes of Relapsed/Refractory Diffuse Large B-cell Lymphoma Treated With Polatuzumab Vedotin-based Therapy

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ABSTRACT

After FDA and EMA approval of the regimen containing polatuzumab vedotin plus rituximab and bendamustine (PolaBR), eligible relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients in Italy were granted early access through a Named Patient Program. A multicentric observational retrospective study was conducted focusing on the effectiveness and safety of PolaBR in everyday clinical practice. Fifty-five patients were enrolled. There were 26 females (47.3%), 32 patients were primary refractory and 45 (81.8%) resulted refractory to their last therapy. The decision to add or not bendamustine was at physician's discretion. Thirty-six patients underwent PolaBR, and 19 PolaR. The 2 groups did not differ in most of baseline characteristics. The final overall response rate was 32.7% (18.2% complete response rate), with a best response rate of 49.1%. Median disease-free survival was reached at 12 months, median progression-free survival at 4.9 months and median overall survival at 9 months, respectively. Overall, 88 adverse events (AEs) were registered during treatment in 31 patients, 22 of grade ≥3. Eight cases of neuropathy occurred, all of grades 1–2 and all related to polatuzumab. The two groups of treatment did not differ for effectiveness endpoints but presented statistically significant difference in AEs occurrence, especially in hematological AEs, in AEs of grade equal or greater than 3 and in incidence of neuropathy. Our data add useful information on the effectiveness of Pola(B)R in the setting of heavily pretreated DLBCL and may also suggest a better tolerability in absence of bendamustine without compromise of efficacy.

INTRODUCTION

Recently, the treatment landscape for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) has been definitely enriched, but there is no defined standard of care for second-line setting and beyond, especially for transplant ineligible patients. Treatments recently approved by both FDA and EMA include the antibody–drug conjugate polatuzumab vedotin in combination with bendamustine and rituximab (PolaBR), the anti-CD19 monoclonal antibody tafasitamab in combination with lenalidomide, the CD19-directed chimeric antigen receptor (CAR) T-cell therapies axicabtagene ciloleucel,

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tisagenlecleucel, and lisocabtagene maraleucel for the third-line setting, as well as selinexor, a selective inhibitor of nuclear export and loncastuximab tesirine (only FDA approval). All these treatments are characterized by peculiar response rates and toxicities.[1] Pola, an anti-CD79b antibody–drug conjugate, in which the monoclonal antibody is linked to the microtubule poison monomethyl auristatin E, has shown efficacy as monotherapy and in combination with rituximab in R/R DLBCL and was subsequently evaluated in combination with BR with a complete response (CR) rate of 40.0% and a median progression-free survival (PFS) of 9.5 months.[2–4] Based on these findings, FDA has granted commercial approval to PolaBR for DLBCL patients after ≥2 prior treatment lines.[5] In Europe, the PolaBR regimen was approved for R/R DLBCL who are not candidates for hematopoietic stem cell transplant.[6,7] After the approval by FDA, eligible R/R DLBCL patients in Italy were granted early access to PolaBR through a Named Patient Program (NPP) between June 2019 and February 2020. At that time, CAR-T cells therapy was just approved for this indication as the first product was approved in August 2019 and many centers were not yet accredited for the procedure. To date, real-world data on the use of PolaBR are still scarce in the literature,[8–11] especially as for as potential additional uses of this drug are concerned (eg, bridging to CAR-T or salvage therapy after CAR-T).[12,13] Data from patients treated with PolaBR outside a controlled clinical trial could give additional information about the clinical use, treatment duration, effectiveness, and toxicity of this regimen in R/R DLBCL patients. It is worth to be noted, in fact, that tafasitamab, loncastuximab tesirine and selinexor are not currently available in Italy for R/R DLBCL, reducing the available treatment options in this critical setting.

Furthermore, the decision to add or not bendamustine was at physician discretion and this could give additional useful information about the use of the regimen and its best location in patients cancer journey.

MATERIALS AND METHODS

We have conducted an observational retrospective, multicenter Italian study focusing on the effectiveness and safety of PolaR (± B) in adult patients with R/R DLBCL who received at least one dose of PolaR (± B) under the NPP in the period between June 2019 and February 2020.

The study was approved by our institutional board (Ethical Committee AVEC of Bologna, approval id 185/2021/Oss/AOUBO). All participants gave written informed consent (when applicable) in accordance with the Declaration of Helsinki to retrospectively collect their data. As for the retrospective design of the study, we received an authorization to analyze data also of patients who were deceased or lost to follow up at the time of data collection. L.A. performed all the analysis and all authors had access to primary clinical study data.

The primary endpoint of the study was the overall response rate (ORR), defined as the sum of partial response (PR) and CR rates at the end of treatment. Secondary study endpoints were the best ORR (defined as the best response achieved at any timepoint after start of PolaR [± B]), overall survival (OS), disease-free survival (DFS) and PFS, as well as the type, incidence, severity of any adverse events (AEs) occurred from the start of treatment to 30 days after the last infusion and their possible relationship with study drugs. Explorative endpoints were the differences in outcomes and safety between the two groups of treatment, that is, PolaR and PolaBR. OS was calculated from the date of infusion until death from any cause or last available follow-up. DFS was estimated from the date of first documented CR to the last follow-up or to the date of disease recurrence or death as a result of lymphoma or acute toxicity of study treatment; PFS was defined as the time from infusion for all treated patients to the first observation of progressive

disease or death as a result of any cause.[14] Positron emission tomography (PET) response assessment was done according to Lugano 2014 criteria, with Deauville score 1–3 defined as PET-CR.[15] Safety and tolerability were assessed through the evaluation of AEs and serious AE with the National Cancer Institute Common Terminology Criteria of AEs v5.0. To minimize compilation bias, a data dictionary was provided to all the participating Centers.

Demographics and patients' characteristics were summarized by descriptive statistics. Comparison between groups were performed—for categorical variables—using the contingency table analysis with the chi-squared or Fisher's exact test, as appropriate, whereas continuous data were analyzed using a Student's t test, after checking whether data are normally distributed (based on the Shapiro–Wilk statistic), or a Wilcoxon rank-sum test otherwise. Comparison of survival across subgroups were performed using Kaplan–Meier product-limit survival curve estimates and log-rank tests. All tests were two-sided and a P-value of less than 0.05 was considered statistically significant. Statistical analyses were performed with Stata 17 (StataCorp LP, TX).

RESULTS

Patients' characteristics

Fifty-five patients with first diagnosis of DLBCL between 2009 and 2019 were enrolled. There were 26 females (47.3%) and 29 males. All patients underwent R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or a CHOP-like regimen as first line. Thirty-two were primary refractory and 45 (81.8%) proved to be refractory to the last therapy prior to Pola. Median number of treatments received before Pola was 3 (range, 1–6). At baseline, that is, just before Pola therapy, the majority of patients were in stage III/IV (80.0%) with an ECOG (Eastern Cooperative Oncology Group) performance status (PS) score of 0–1 (78.2%). Thirty-six patients received PolaBR, whereas 19 ones underwent PolaR. The two groups did not differ for baseline characteristics, except for bone marrow involvement (Table 1).

Effectiveness and outcomes

After a median of 4 cycles (range 1–6), the final ORR was 32.7% (18.2% CR rate), with a best response rate of 49.1% (Table 2). Best CR rate for PolaBR was 27.8% (achieved after median of 4 cycles) and 26.3% for PolaR (after a median of 6 cycles), respectively. Twenty-one patients treated with PolaBR had an early treatment discontinuation: besides PD (N = 18), 2 patients were addressed to transplantation and 1 patient refused to continue due to poor drug tolerance. In the PolaR group 9 early discontinuation occurred: 7 for PD and 2 due to AEs (pneumonia and drug-related toxidermia).

Median DFS was reached at 12.0 months, median PFS at 4.9 months (26.4% at 1 year) and median OS at 9.0 months (48.7% at 1 year), respectively (Figure 1).

After a median follow-up of 11 months, 35 deaths occurred, all but 5 caused by lymphoma (1 due to gastrointestinal hemorrhage, 2 due to COVID-19 infection, 1 due to unspecified infection and 1 due to other cause; all not related to study drugs). Thirty-three patients received further treatment(s) after Pola. In particular, in 4 of them Pola was used as bridge to stem cell infusion (namely, 2 patients underwent autologous and 1 patient allogeneic transplantation) or CAR-T therapy (1 patient). At the time of the analysis, 4 patients were in continuous response, 2 of them in continuous CR without any consolidation at 19.5 and 16.2 months after the end of Pola, respectively.

Regarding the comparison between the two treatment groups, median PFS for PolaBR was reached at 5.5 months with an estimated 29.4% of patients relapse-free at 12 months, while for PolaR it was reached at 5.1 months with an estimated 21.1%

Table 1

Baseline Characteristics and Comparison Between the 2 Treatment Groups

	Total (n = 55)	PolaBR (n = 36)	PolaR (n = 19)	P
Sex, female/male, n(%)	26/29 (47.3/52.7)	17/19 (47.2/52.8)	9/10 (47.4/52.6)	ns
Age at diagnosis, y, median (range)	63.6 (29.2-84.2)	61.5 (29.2-84.2)	67.6 (30.4-81.8)	ns
Pathology classification at diagnosis, n (%)				ns
GCB	22 (40.0)	15 (41.7)	7 (36.7)	
ABC	6 (10.9)	5 (13.9)	1 (5.3)	
Non-GCB	17 (30.9)	11 (30.6)	4 (21.5)	
DLBCL-nos	10 (18.2)	8 (22.2)	2 (10.5)	
DLBCL subtypes, n (%)				ns
Double-hit	3 (5.5)	2 (5.6)	1 (5.3)	
Triple-hit	1 (1.8)	1 (2.8)	0 (0.0)	
Double expressor	3 (5.5)	2 (5.6)	1 (5.3)	
Ann Arbor stage, n (%)				ns
I	0	0	0	
II	11 (20.0)	6 (16.7)	5 (26.3)	
III	14 (25.5)	11 (30.6)	6 (31.6)	
IV	30 (54.5)	19 (52.8)	8 (42.1)	
Bone marrow involvement, n (%)	10 (18.2)	9 (25.0)	1 (5.2)	0.021
B symptoms, n (%)	11 (20.0)	7 (19.4)	4 (21.1)	ns
Outcome first line, n (%)				ns
Relapsed	23 (41.8)	16 (44.4)	7 (36.8)	
Refractory	32 (58.2)	20 (55.6)	12 (63.2)	
Outcome last line, n (%)				ns
Relapsed	10 (18.2)	6 (16.7)	4 (21.1)	
Refractory	45 (81.8)	30 (83.3)	15 (78.9)	
Previous therapies, median (range)	3 (1–6)	3 (1–6)	3 (2–5)	ns
ECOG score at Pola, n (%)				ns
0	22 (40.0)	13 (36.1)	8 (42.1)	
1	21 (38.2)	15 (41.7)	7 (36.8)	
2	9 (16.4)	6 (16.7)	3 (15.8)	
3	3 (5.4)	2 (5.5)	1 (5.3)	
Age at Pola, y median (range)	67.0 (29.9–85.1)	63.8 (29.9–85.1)	72.3 (32.1–83.4)	ns

ABC = activated B cell subtype; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B cell subtype; nos = not otherwise specified; ns = not significant; PolaBR = polatuzumab, bendamustine, and rituximab; PolaR = polatuzumab and rituximab.

Table 2

Response Rates and Comparison Between the 2 Treatment Groups

	Total (n = 55)	PolaBR (n = 36)	PolaR (n = 19)	P
ORR, %	32.7	30.6	36.9	ns
CR, n (%)	10 (18.2)	7 (19.4)	3 (15.8)	
PR, n	8	4	4	
Best response rate, %	49.1	47.2	52.6	ns
CR, n (%)	15 (27.3)	10 (27.8)	5 (26.3)	
PR, n	12	7	5	

CR = complete response; ns = not significant; ORR = overall response rate; PolaBR = polatuzumab, bendamustine and rituximab; PolaR = polatuzumab and rituximab; PR = partial response.

of patients relapse-free at 1 year (hazard ratio [HR] 0.8826, P = 0.7452). Median DFS for PolaBR was reached at 12.7 months, at 9.6 months for PolaR, respectively (HR = 0.9142, P = 0.7940).

The 2 groups of treatment did not differ in terms of both response rates and survivals.

Safety

Overall, 88 AEs were registered during treatment in 31 patients, 22 of grade ≥3. A total of 20 hematological events occurred, 16 of grade ≥ 3. In detail: 1 leukopenia, 11 neutropenia, 3 thrombocytopenia, and 1 anemia. The remaining 4 events were 2 grade 2 thrombocytopenia and 2 grade 2 anemia. Only one febrile neutropenia of grade 3 was registered in the PolaBR group and jit was urged as related to study drug. Five

serious AEs were registered, namely 1 pneumonia (not related to study drugs), 1 Stevens-Johnson syndrome (judged as related to polatuzumab), 2 hospitalizations due to treatment-related hematological AEs, and 1 death caused by gastrointestinal hemorrhage (not related). Eight episodes of neuropathy occurred, all of grades 1–2 and related to polatuzumab and, overall, 4 infections were registered, all in the PolaBR group.

In the PolaBR group, 20 patients had at least one toxicity for a total of 18 hematological events (N = 13 of grade ≥ 3) and 20 extrahematological ones (N = 5 of grade ≥ 3). In the PolaR group, 11 patients had at least 1 AE: 2 hematological toxicities in the same patient (grade 4, leucopenia and neutropenia both resolved after with granulocyte colony-stimulating factor support), and 25 extrahematological AEs (N = 2 of grade ≥ 3). The two groups presented a statistically significant difference in terms of AEs occurrence: hematological AEs and AEs of grade equal or greater than 3 were more frequently observed in the PolaBR group whereas neuropathy was more likely to occur in the PolaR group (Table 3).

DISCUSSION

Our study confirms the feasibility and safety of the Pola(B) R regimen for R/R DLBCL also in the real-life. We found an ORR of 32.7% with a best ORR of 49.1% (CR rate 27.3%) in a setting of heavily pretreated patients with a high percentage of subjects refractory to the last prior therapy (81.8%). Some studies have been already published on the same issue, but with several differences. Anyway, efficacy results did not differ
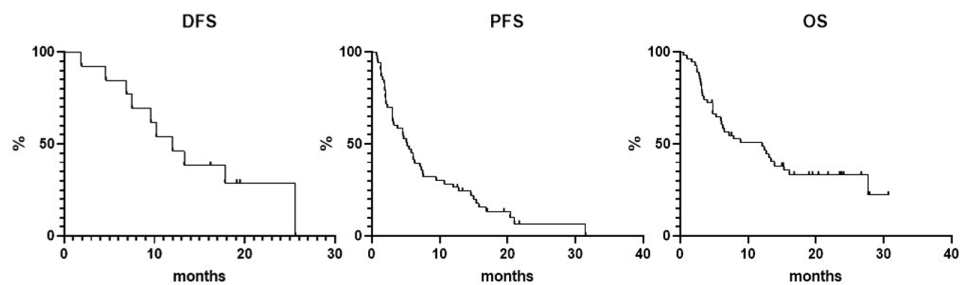
Figure 1. DFS, PFS, and OS curves for the whole study population. DFS = disease-free survival; OS = overall survival; PFS = progression-free survival.

Table 3

Adverse Events Occurrence in Study Population and Comparison Between the 2 Treatment Groups

Number of Episodes	All	PolaBR (n = 36)		PolaR (n = 19)		P^a
Any grade	66	38		27		ns
≥3	22	18		4		0.034
Serious adverse events	5	3		2		Ns
Adverse events	**All**	**All grades**	**Grades 3–4**	**All grades**	**Grades 3–4**	
Blood and lymphatic system disorders	21	19	13	2	2	<0.01
Anemia	3	3	1	0	0	
Neutropenia	11	10	9	1	1	
Thrombocytopenia	5	5	3	0	0	
Leukopenia	1	0	0	1	1	
Febrile neutropenia	1	1	1	0	0	
Extrahematological	45	20	5	25		ns
Gastrointestinal disorders	15	10	3			
Diarrhea	9	6	3	3	0	
Nausea	4	3	0	1	0	
Constipation	2	1	0	1	0	
General disorders	13	5	0	13	0	
Fatigue	3	1	0	7	0	
Pyrexia	10	4	0	6	0	
Neuropathy	8	3	0	5	0	<0.01
Infections	4	2	2	0	0	
Other	5	0	0	2	2	

^{a}Comparisons were performed on the total of the type of adverse events of each treatment group (all grades).

ns = not significant; PolaBR = polatuzumab, bendamustine and rituximab; PolaR = polatuzumab and rituximab.

Table 4

Real-life Studies Comparison

	n	Refractory to Last Prior Therapy	mOS, mo	mPFS, mo	CR Rate	ORR	mFUP, mo
Vodicka et al[8]	21	76.2	8.7	3.8	23.8	33.3	6.8
Dimou et al[9]	49[a]	78.0	8.5	4.0	20.0	35.0	10.8
Segman et al[10]	47	23.0	8.3	5.6	40.0	61.0	6.8
Northend et al[11]	133	68.4	8.2	4.8	31.6 (best)	57.0 (best)	7.7
Present study	55	81.8	9.0	4.9	18.2	32.7	11
					27.3 (best)	49.1 (best)	

^{a}Efficacy analysis on 49 patients treated with PolaBR.

CR = complete response; mFUP = median follow-up; mOS = median overall survival; mPFS = median progression-free survival; ORR = overall response rate.

among these studies (Table 4).[8–11] In particular, median PFS and median OS as well as ORR and CR rates were similar. Higher response rates reported by Segman et al could be ascribed to a lower percentage of patients refractory to the last prior therapy, which constitutes a negative prognostic factor,[10,11] whereas Northend et al reported only best response rates.[11]

Comparing our patients' characteristics with the ones of the phase II study,[4] we found that real-world patients in present study had a higher median of previous therapy (3 versus 2), higher rates of ECOG PS score equal or grater than 2 (21.8% versus 15.0%) and of subjects refractory to the last prior therapy (81.8% versus 75.0%). These findings in part may explain the differences in efficacy endpoints, that is, the higher ORR and PFS obtained in the clinical trial. An update of the GO29365 study—which led to regulatory approvals— reported similar ORR but longer PFS and OS,[16] but these results were almost foreseeable as real-life patients are not selected with stringent criteria as happens in a trial. On the other hand, this strengthens the value of the response rates reported in our study.

In addition, we have also analyzed the differences between patients who received bendamustine and patients who did not. The other real-life study did not address this subject, besides Segman and colleagues who reported differences in AEs occurrence similar to the ones occurred in our study (but did not analyze difference in effectiveness endpoints).[10] In particular, we did not detect differences in the 2 treatment groups in terms of response rates or survivals, but differences were seen in AEs occurrence, especially for hematological toxicities and for AEs equal or greater than grade 3 to the detriment of the PolaBR group. This indicates that, with equal effectiveness, the PolaR regimen could be preferred at least for 3 reasons: patients have less toxicities, there is a cost saving by removing a drug from the combination and physicians may use bendamustine in later lines as rescue due to a further relapse. These results, however, should be checked through a randomized controlled trial.

On the other hand, in the PolaR group, a significantly higher incidence of neuropathy was noticed, probably due to the fact that these patients received more cycles (median of 6 cycles versus 4). Nevertheless, a very low percentage of patients discontinued treatment due to an AE (3.6%) in both groups, confirming the manageable safety profile of the regimen.

The median DFS of 12 months is a good achievement for such a critical patient setting, although it refers to only ten patients: in particular, 4 subjects are in continuous CR at the latest available follow-up.

Polatuzumab may also be an effective bridging therapy toward CAR-T-cell therapy or transplant or may be considered as salvage therapy after CAR-T-cell failure.[12,13,17] However, this issue could not be addressed by our study as the NPP was active when CAR-T-cell therapy was just approved in Italy (with the majority of hematological centers not yet accredited for these products) and in only 3 patients polatuzumab was used as bridge to transplant.

The major limitation of this study, besides its retrospective nature, was the lack of a centrally reviewed response assessment, although PET/CT scan was used by all the investigators. In addition, sample size has to be considered small for a retrospective study but comparable with the one of the phase II study.[4]

DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 31% of NHL cases.[18] Among patients receiving second- or third-line treatment for DLBCL, a significant proportion are transplant ineligible due to their advanced age, lack of adequate response or being unfit for the procedure.[19] Taken together, these data point to a significant unmet clinical need of safe and effective treatment options for transplant ineligible R/R DLBCL.

For transplant ineligible R/R DLBCL patients, current second- and third-line therapeutic options include Pola(B)R, BR, gemcitabine with oxaliplatin ± rituximab (R-GEMOX), rituximab ± lenalidomide, pixantrone monotherapy, CAR-T-cell therapies, loncastuximab tesirine, and tafasitamab plus lenalidomide, but direct comparisons between these agents are lacking.

Matching-adjusted indirect comparisons of tafasitamab plus lenalidomide were performed using data from the L-MIND study and comparator studies assessing rituximab-based combination therapies, including PolaBR, showing longer duration of response and higher median OS but not differences in response rates or PFS were found.[20] Recognizing that response rates and PFS are not dissimilar to the ones obtained with other drugs, it is, however, important to underline for this reason that PolaBR has to find its place in the therapeutic algorithm of DLBCL. The challenge is to understand the right sequence of the available options, or rather if the same drugs sequence can be identified for all DLBCL patients or each patient can benefit from a personalized sequence.

CONCLUSIONS

As there is no one-size-fits-all approach or indication about a patient-tailored approach, guidance regarding optimal algorithm of subsequent therapies is claimed. Thus, one of the principal goals of present and future research is to establish the optimal sequencing of therapeutic approaches for R/R or transplant ineligible DLBCL patients.

The present study confirms that real-world data augment and improve evidence from trials, providing hematologists useful information to apply in everyday practice and to make the more suitable choice for patients.

AUTHOR CONTRIBUTIONS

LA and PLZ conceived the study; LA, AB, and PLZ wrote the manuscript; AB, CP, AF, BP, RB, MCT, FM, LF, MEN, MM, MS, PRS, DD, IF, EP, EL, FGR, CM, FG, PM, CP, VS, and PLZ provided study data; LA conducted all data analyses; all authors read and approved the final version of the manuscript after revising it critically. All authors have access to the final database.

DISCLOSURES

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