Research Article

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Second-line rituximab–bendamustine versus rituximab–gemcitabine–oxaliplatin in diffuse large B-cell lymphoma in the real world

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Aim: Despite long-term responses to first-line immunochemotherapy, many patients with diffuse large B-cell lymphoma (DLBCL) have relapsed/refractory disease. Second-line treatment options are available. However, a large proportion of patients are ineligible for transplantation/intensive therapy. **Patients & methods:** This observational study of 702 patients in the USA, who used second-line therapies for relapsed/refractory DLBCL, evaluated treatment patterns and overall survival (OS). The study focused on the OS outcome of patients receiving second-line rituximab–bendamustine or rituximab–gemcitabine–oxaliplatin. **Results & conclusion:** Rituximab–bendamustine and rituximab–gemcitabine–oxaliplatin were received by 4.6 and 1.4% of patients, respectively (N = 42/702). Median and 1-year OS rates were similar between regimens. Many of the 200 different treatment regimens observed in second line were modified versions of National Comprehensive Cancer Network regimens.

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Keywords: bendamustine • diffuse large B-cell lymphoma • gemcitabine • oxaliplatin • real-world study • rituximab

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), representing 30−58% of all cases [1,2]. DLBCL is an aggressive form of NHL. Patients have a poor prognosis, and without treatment will typically die within weeks or months of diagnosis [3]. Rituximab, an anti-CD20 monoclonal antibody, has proven efficacy and a tolerable safety profile in CD20-positive DLBCL [4]. In combination with other drugs, rituximab has been approved as first-line standard of care for several types of NHL [5,6]. In particular, R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) is the current standard of care for previously untreated DLBCL, both in Europe [5] and in the USA [6]. Although 60% of patients treated with R-CHOP achieve long-term responses, approximately 20–25% of patients will eventually relapse or 10–15% will exhibit refractory disease within the first 2–3 years following immunochemotherapy [7]. Life expectancy is reduced in patients with previously treated relapsed/refractory DLBCL, and most patients die within 2 years [7].

Current treatment options for relapsed/refractory DLBCL are limited and present a therapeutic challenge, as tumors can exploit multiple escape mechanisms to evade the immune system [8,9]; a more personalized treatment strategy is thus required. Although high-dose chemotherapy followed by autologous stem-cell transplantation

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(ASCT) is the standard of care for chemosensitive patients aged <70 years with relapsed/refractory DLBCL [5], only around half of patients are eligible for this treatment approach [10]. Currently, there is no standard of care for patients with relapsed/refractory DLBCL who are ineligible for ASCT; however, a broad spectrum of therapeutic options are available [5,6]. There are few data on the patterns of second-line therapies currently used in routine clinical practice in patients with relapsed/refractory DLBCL. The real-world outcomes associated with these second-line treatments are also not clear, particularly for patients not suitable for ASCT and intensive therapy.

Rituximab–bendamustine (R–benda) and rituximab–gemcitabine–oxaliplatin (R–GemOx) are two regimens with proven efficacy and safety for patients not eligible for ASCT [11,12]. R–benda and R–GemOx can usually be administered easily as an outpatient [13,14]; data regarding real-world outcomes using these regimens are limited.

This retrospective, real-world observational study, set in the USA, aimed to evaluate treatment patterns, as well as overall survival (OS), in patients with DLBCL who received second-line R–benda or second-line R–GemOx.

Patients & methods

Data source & study sample

Electronic medical records and the raw oncology domain dataset were extracted from the US Veterans Health Administration database.

Inclusion criteria

Patients (veterans) with a diagnosis of NHL were initially identified from the database. This group was further screened to include only those with an indicator for complete chart extraction in the raw oncology domain and with at least 1 month of follow-up time. The final sample included patients diagnosed with DLBCL between 2004 and 2016 who received both first- and second-line therapy. Patients who initiated second-line therapy were assumed to have relapsed/refractory DLBCL (i.e., either progressed following first-line therapy [relapsed] or did not respond to first-line therapy [refractory]). Of this sample, survival outcomes were analyzed in patients receiving R–benda or R–GemOx.

Exclusion criteria

Patients with T-cell/histiocyte-rich large B-cell lymphoma, plasmablastic lymphoma, large B-cell (plasmablastic) lymphoma arising from human herpesvirus 8-associated multicentric Castleman disease or primary effusion lymphoma were excluded. Patients with other malignancies prior to first DLBCL diagnosis were also excluded.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and all applicable local laws and regulations. The study protocol and its amendments, and other study-related materials, were approved by institutional review boards/ethics committees. The institutional review board granted a waiver of informed consent for this database study.

Measurement of second-line therapy

Lines of therapy were identified from the start/end dates of agents, based on an algorithm adapted from previously published algorithms [15,16]. Lines of therapy were measured from the initial DLBCL diagnosis and not from the diagnosis of relapsed/refractory disease. Initiation of second-line therapy corresponded to the initiation date of a drug not included in first-line, or reinitiation of first-line agent(s) after a gap of >120 days. The second-line regimen was defined as those agents used in the 42 days after second-line therapy was initiated.

Data analysis

Patient characteristics, median OS and 1-year OS, were compared between patients with DLBCL who received second-line R–benda or second-line R–GemOx. The OS from the initiation of second-line therapy was calculated using Kaplan–Meier methodology and univariate/multivariate Cox regression. Surviving patients were censored at the data cut-off date (31 December 2017). A multivariate Cox regression model was adjusted for risk factors that were selected based on results of univariate models and clinical significance, including patient age, cancer stage, first-line regimen, abnormal LDH or hemoglobin 6 months before second-line treatment initiation.

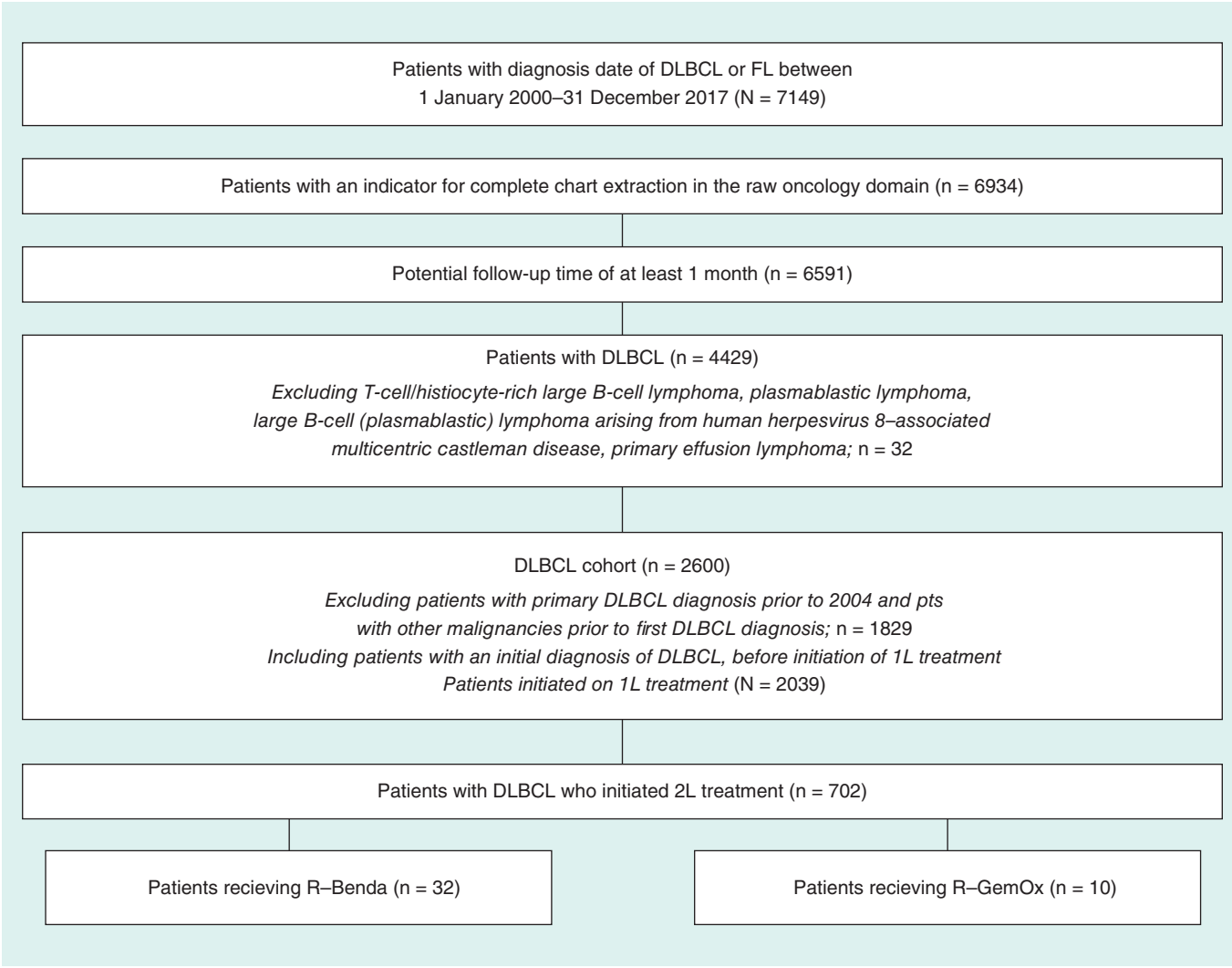

Figure 1. Patient flow.
2L: Second line; DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma.

Results

Overall study sample characteristics

Of 2600 patients with DLBCL identified that satisfied the study inclusion criteria, 702 received second-line therapy and were included in the final analysis (Figure 1). A total of 12 regimens were used by ≥10 patients per regimen, which included 345/702 (49%) of the patient population (Table 1). The remaining 188 regimens were used by <10 patients/regimen (357/702 [51%]; Table 1). All National Comprehensive Cancer Network (NCCN)-recommended regimens [6] were among the 12 commonly used (≥10 patients/regimen) regimens. Of these 12 regimens, rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) (77/702 [11.0%]) and R-CHOP (75/702 [10.7%]) were the most commonly used. Many of the less common regimens were modified versions of the recommended regimens.

Patients receiving second-line R–benda or R–GemOx

A total of 32/702 patients (4.6%) received R–benda and 10/702 patients (1.4%) received R–GemOx. Analysis of baseline characteristics identified numerical imbalances between R–benda and R–GemOx cohorts in terms of race, number of involved lymph nodes, B symptoms, Charlson Comorbidity Index score and abnormal lactate dehydrogenase results (Table 2). Median follow-up time after second-line treatment initiation was 11.3 months in the R–benda cohort and 11.7 months in the R–GemOx cohort, with median OS durations of 11 and 13 months,

Table 1. Second-line treatment regimens received by patients with diffuse large B-cell lymphoma.

	Total N = 702
Treatment regimens used in ≥10 patients (± maintenance)	n (%)
– R-ICE	77 (11.0)
– R-CHOP	75 (10.7)
– Rituximab	34 (4.8)
– R–benda	32 (4.6)
– Methotrexate	24 (3.4)
– R-ESHAP	23 (3.3)
– R-DHAP/R-EPOCH/R-GDP	18 (2.6)
– Cyclophosphamide + doxorubicin + rituximab + vinblastine + vincristine	15 (2.1)
– R-CVP	14 (2.0)
– Cyclophosphamide + etoposide + rituximab + vincristine	13 (1.9)
– R–GemOx	10 (1.4)
– Carmustine + cyclophosphamide + etoposide	10 (1.4)
Other treatment regimens (<10 patients/regimen)	n (%)
– All NCCN guideline-recommended agents	262 (37.3)
– Not all NCCN guideline-recommended agents	95 (13.5)

NCCN: National Comprehensive Cancer Network; R–benda: Rituximab + bendamustine; R-CHOP: Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP: Rituximab + cyclophosphamide + vincristine + prednisone; R-DHAP: Rituximab + dexamethasone + high-dose cytarabine + cisplatin; R-EPOCH: Rituximab + etoposide phosphate + prednisone + vincristine + cyclophosphamide + doxorubicin; R-ESHAP: Rituximab + etoposide + cytarabine + cisplatin + methylprednisolone; R-GDP: Rituximab + gemcitabine + dexamethasone + cisplatin; R–GemOx: Rituximab + gemcitabine + oxaliplatin; R-ICE: Rituximab + ifosfamide + carboplatin + etoposide.

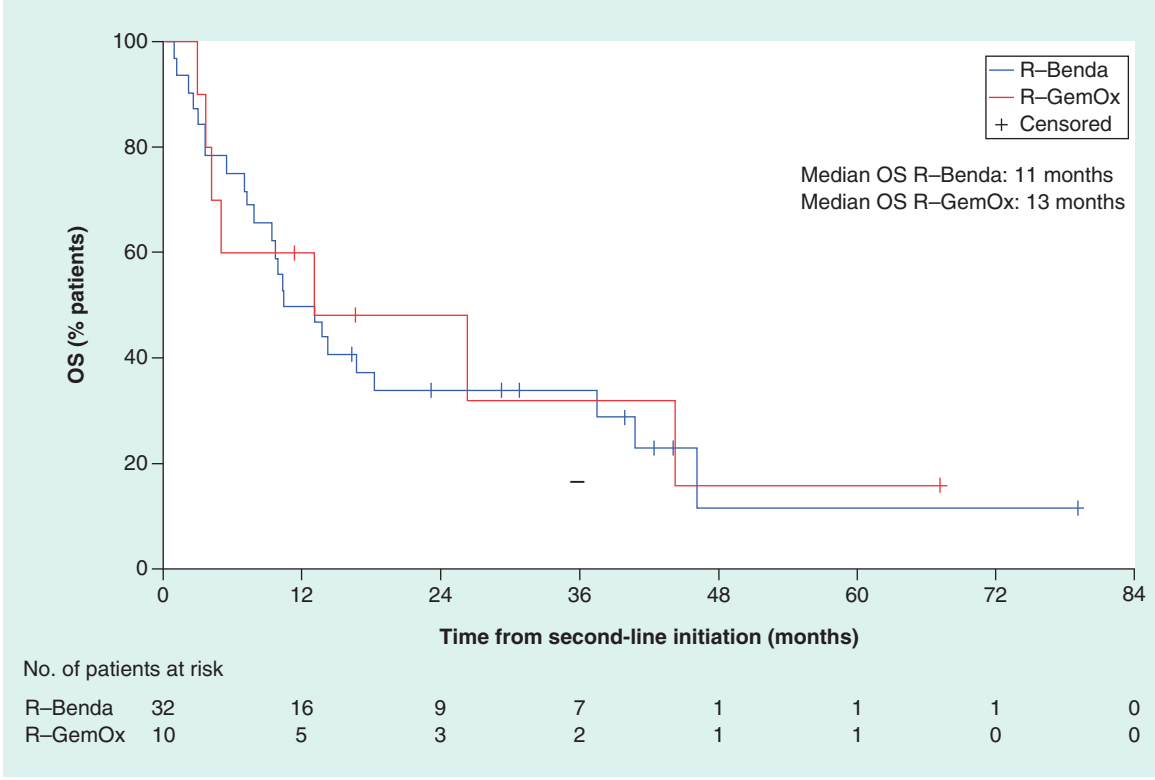

Figure 2. Overall survival from initiation of second-line therapy with rituximab–bendamustine or rituximab–gemcitabine–oxaliplatin in patients with diffuse large B-cell lymphoma.
OS: Overall survival; R–benda: Rituximab–bendamustine; R–GemOx: Rituximab–gemcitabine–oxaliplatin.

respectively (Figure 2). One-year OS rates were 50.0% (95% CI: 31.9–65.7%) with R–benda and 60.0% (95%

Table 2. Baseline characteristics in patients with diffuse large B-cell lymphoma who received rituximab–bendamustine or rituximab-gemcitabine-oxaliplatin as second-line therapy.

Characteristic	Second-line R–benda (n = 32)	Second-line R–GemOx (n = 10)	p-value[†]
Age, years:			
– Mean ± SD	65 ± 10	66 ± 6	0.59
– Median (IQR)	63 (60–69)	64 (62–70)	–
Male, n (%)	31 (96.9)	10 (100.0)	1.00
Caucasian/White, n (%)	25 (78.1)	6 (60.0)	0.41
Refractory DLBCL[‡], n (%)	13 (40.6)	4 (40.0)	1.00
Number of lymph nodes involved, n (%):			
– 0	21 (65.6)	5 (50.0)	0.47
– ≥1	10 (31.3)	2 (20.0)	0.70
– Unknown/missing	1 (3.1)	3 (30.0)	0.04
Stage, n (%):			
– I	1 (3.1)	1 (10.0)	0.42
– II	5 (15.6)	1 (10.0)	1.00
– III	8 (25.0)	2 (20.0)	1.00
– IV	14 (43.8)	4 (40.0)	1.00
– Unknown/missing	4 (12.5)	2 (20.0)	0.62
B symptoms, n (%):			
– No	19 (59.4)	4 (40.0)	0.47
– Yes	12 (37.5)	3 (30.0)	1.00
– Unknown/missing	1 (3.1)	3 (30.0)	0.04
Charlson comorbidity index score:			
– Mean ± SD	3.9 ± 2.2	3.2 ± 1.9	0.37
– Median (IQR)	3 (2–6)	2 (2–4)	
Patients with LDH test[§], n (%):	19 (59.4)	4 (40.0)	0.47
– ≥1 abnormal result	15 (46.9)	3 (30.0)	0.47
Patients with hemoglobin test[§], n (%):	32 (100.0)	8 (80.0)	0.05
– ≥1 abnormal result	26 (81.3)	5 (50.0)	0.09
First-line regimen R-CHOP, n (%)	18 (56.3)	6 (60.0)	1.00

[†]Statistical comparisons were conducted with Wilcoxon rank-sum tests for the continuous variables and Chi-square tests for the categorical variables.
[‡]Refractory DLBCL was defined as <180 days between first-line end and second-line start.
[§]In the baseline period.
DLBCL: Diffuse large B-cell lymphoma; IQR: Interquartile range; R–benda: Rituximab–bendamustine; R–GemOx: Rituximab–gemcitabine–oxaliplatin; SD: Standard deviation.

CI: 25.3–82.7%) with R–GemOx. In univariate and multivariate analyses, administration of R-CHOP as first-line therapy versus other regimens was the only covariate with a significant effect on OS (Table 3). Treatment with R–GemOx or R–benda did not significantly affect OS (hazard ratio [HR]: 0.89; 95% CI: 0.38–2.08; p = 0.79; and HR: 0.68; 95% CI: 0.27–1.73; p = 0.42, respectively).

Discussion

Currently, there is no standard of care for patients with relapsed/refractory DLBCL who are ineligible for transplant. This study examined the use of second-line therapies for relapsed/refractory DLBCL in real-world clinical practice in the USA. A wide range of treatment (200 distinct therapy regimens) had been used in the 702 patients included in the analysis. Of the 12 regimens used in ≥10 patients, 11 were recommended by NCCN guidelines [6]. Second-line R-CHOP is not recommended in the NCCN guidelines. Despite this, we observed a high number of patients who were treated with second-line R-CHOP and modified regimens of R-CHOP that are outside of NCCN guidelines in the second-line setting. Alternatively, in the cases where first-line R-CHOP was not used, these patients may have received second-line R-CHOP. Many patients did not receive first-line R-CHOP; however, a small number of patients were rechallenged with second-line R-CHOP after progressing on first-line R-CHOP. Furthermore, these analyses include patients dating back to the year 2004, when fewer agents were available. In many cases, if

Table 3. Univariate and multivariate estimates of the effect of rituximab–gemcitabine–oxaliplatin versus rituximab–bendamustine and other factors on overall survival in second-line diffuse large B-cell lymphoma.

	Univariate Cox regression models		Multivariate Cox regression model†	
	HR (95% CI)	p-value	HR (95% CI)	p-value
R–GemOx vs R–benda	0.89 (0.38–2.08)	0.79	0.68 (0.27–1.73)	0.42
Age (per year increase)	1.04 (0.99–1.09)	0.09	1.03 (0.98–1.08)	0.28
Refractory DLBCL (vs relapsed DLBCL)‡	1.02 (0.50–2.10)	0.95	–	–
With ≥1 lymph nodes involved (vs 0 nodes)	0.85 (0.37–1.94)	0.70	–	–
Cancer stage IV (vs stage I–III)	0.66 (0.31–1.39)	0.27	0.65 (0.26–1.65)	0.37
Charlson comorbidity index (per point increase)	1.01 (0.86–1.19)	0.90	–	–
Abnormal LDH§ (vs normal LDH)	1.51 (0.74–3.09)	0.26	1.74 (0.80–3.77)	0.16
Abnormal hemoglobin§ (vs normal hemoglobin)	1.82 (0.76–4.36)	0.18	1.73 (0.68–4.41)	0.25
First-line regimen R-CHOP (vs others)	2.20 (1.00–4.84)	0.05¶	2.49 (1.11–5.62)	0.03¶

†Model included all shown covariates (selected based on results of univariate models and clinical significance). Sex was not included among the potential predictors because 41/42 patients were male.
‡Refractory DLBCL was defined as <180 days between first-line end and second-line start, and relapsed DLBCL was defined as ≥180 days between first-line end and second-line start.
§Patients for whom a test was not ordered were assumed to have normal test results.
¶Significant p-value.
DLBCL: Diffuse large B-cell lymphoma; HR: Hazard ratio; R–benda: Rituximab–bendamustine; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R–GemOx: Rituximab–gemcitabine–oxaliplatin.

patients experienced a good response to first-line R-CHOP, with a long duration of remission, they may have been challenged a second time with R-CHOP.

From the broad range of treatment regimens used in this patient cohort, we chose to focus on R–benda and R–GemOx as they are typically used in patients ineligible for ASCT, there have been no previous randomized, controlled trials of patients with relapsed/refractory DLBCL comparing these two regimens [11,12], and they can be administered in an outpatient setting [13,14]. R–benda has been studied previously in a prospective Phase II trial in patients with relapsed/refractory DLBCL who were considered ineligible for intensive salvage therapies [11,17]. While R–benda was an active combination in this setting, median OS was not reached because of the high number of censored data due to withdrawals from the study [17]. In a similar study [11], comparable efficacy with R–benda was demonstrated; however, OS was not reported. In the current analysis, median OS was 11 months with R–benda. A previous study of R–GemOx in patients with relapsed/refractory DLBCL showed a 5-year OS of 14% and a median OS of 11 months [12], which is comparable with the median OS of 13 months in the current analysis. Also in the current study, no statistical difference was found in 1-year OS or median OS between patients treated with second-line R–benda and second-line R–GemOx. Median OS was reached approximately 1 year after initiation of second-line therapy with both regimens.

Patients, who are either refractory or have received multiple lines of therapy, typically have a very poor prognosis. In this study, the proportion of patients with refractory disease was 40% for both treatment cohorts, which is consistent with that expected in the general DLBCL population that relapses after front-line therapy [7]. When comparing these real-world outcomes with interventional studies in this setting, it is important to note that the proportion of patients with refractory disease and the lines of therapy have a significant impact on expected outcomes. The current study specifically examined patients who received second-line therapy in the first relapse or refractory setting. Other clinical studies in this area typically have broader entry criteria; multiple prior lines of therapy are permitted and studies include variable proportions of primary, refractory patients. Therefore, outcomes may not be directly comparable. For example, response to therapies may differ depending on the proportion of primary refractory patients studied. Our data illustrate the vast range of second-line regimens currently used when patients relapse. Of the two regimens of interest, R–benda and R–GemOx, there appear to be no differences in OS. Together, these data highlight that there is still more to be done in this setting to achieve long-term remission for those patients ineligible for transplant in the first relapse setting.

The Scholar-1 study of pooled data, from two large randomized trials and two academic databases, provided seminal data on outcomes for patients with refractory DLBCL [18]. A median OS of 6.3 months was reported and outcomes were poor across patient subgroups and study cohorts. However, these data are not directly comparable with the current study as the populations examined and the eligibility criteria were different. Scholar-1 included patients who were refractory to second-line or later-line therapy or relapsed ≤12 months after ASCT, while the current study examined patients in the real-world setting who received second-line therapies.

The current study has several limitations. For example, of the 702 patients eligible for inclusion, only 32 were treated with R–benda and 10 with R–GemOx; the study may, therefore, be underpowered to detect small differences between the cohorts. There is also potential for overfitting the multivariate regression model. However, the multivariate analysis does provide insight into the potential modifying factors. An electronic medical record-based algorithm was used to identify lines of therapy and regimens; consequently, these data may not be as accurate as data collected from a clinical trial. Prognostic factors were selected *a priori* and were restricted to the variables available in the US Veterans Affairs database. International Prognostic Index, Follicular Lymphoma International Prognostic Index and International Prognostic Score were considered, but were not included due to high proportion of missing data (62.7, 96.0 and 95.6%, respectively). Eligibility criteria for ASCT are based on several clinical criteria and physician assessments that were not available in the Veterans Affairs database. Finally, the Veterans Affairs data includes mostly male veterans.

Overall the findings of this study reveal poor outcomes for patients with relapsed/refractory DLBCL treated with R–benda and R–GemOx. However, newer therapies such as chimeric antigen receptor T-cell therapies have shown promising outcomes in relapsed/refractory DLBCL as third-line or later therapies [19], providing hope for patients with this condition. The chimeric antigen receptor T-cell therapy, tisagenlecleucel, was approved for DLBCL in August 2017 and not available during the study period [20]. Polatuzumab vedotin in combination with bendamustine and a rituximab product is also now approved by the US FDA for adults with relapsed/refractory DLBCL after at least two prior therapies [21].

Conclusion

This real-world study showed heterogeneity in second-line therapy for DLBCL and highlights an unmet need for the treatment of relapsed/refractory DLBCL. Wide varieties of treatments are being administered as second-line treatment regimens in DLBCL, some of which are not recommended by NCCN. In this real-world analysis, a similar OS was observed in the two second-line treatment regimens studied, R–benda and R–GemOx. Further research using alternative sources of real-world data is warranted to determine whether these findings are reflected more widely.

Summary points

- There are few data on second treatment patterns for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) currently used in routine clinical practice.
- We carried out a retrospective, real-world observational study, set in the USA, evaluating treatment patterns and overall survival (OS) in patients diagnosed with DLBCL between 2004 and 2016 who received second-line rituximab–bendamustine (R–benda) or second-line Rituximab–gemcitabine–oxaliplatin (R–GemOx).
- A wide range of second-line treatment regimens (200 distinct therapy regimens) had been used in the 702 anonymized patients included in the analysis: 11 of the 12 regimens used by ≥10 patients/regimen were recommended by National Comprehensive Cancer Network guidelines (345/702 [49%]).
- R-ICE (rituximab plus ifosfamide, carboplatin and etoposide; 77 [11.0%]) and R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; 75 [10.7%]) were the most commonly used regimens; 4.6% of patients received R–benda; 1.4% of patients received R–GemOx.
- There was no statistical difference in 1-year OS rates (R–benda: 50.0% [95% CI: 31.9–65.7%]; R–GemOx: 60.0% [95% CI: 25.3–82.7%]) or median OS (R–benda: 11 months; R–GemOx: 13 months) between patients treated with second-line R–benda and second-line R–GemOx.
- No statistical difference was found in OS with second-line R–GemOx compared with second-line R–benda in the univariate analysis (hazard ratio: 0.89; 95% CI: 0.38–2.08; $p = 0.785$) nor the multivariate analysis (hazard ratio: 0.68; 95% CI: 0.27–1.73; $p = 0.424$).
- This real-world study highlights that a wide variety of treatments are being administered as second-line treatment regimens in DLBCL, some of which may not be recommended by National Comprehensive Cancer Network.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. The institutional review board granted a waiver of informed consent for this database study.

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