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Real World Outcomes in Patients with Relapsed/Refractory Diffuse Large B-cell Lymphoma Receiving Palliative Intent Therapies

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Abstract

Background—Outcomes in patients with relapsed/refractory (R/R) diffuse large b-cell lymphoma (DLBCL) who are ineligible for and/or fail high dose chemotherapy and autologous stem cell transplantation (ASCT) in the 2nd line are poor. There is no preferred palliative-intent treatment for patients in this setting.

Methods—A retrospective cohort study was performed using the nationwide de-identified electronic health record-derived Flatiron Health database. Event-free survival (EFS) and overall survival (OS) was evaluated for patients with R/R DLBCL who were ineligible for and/or failed ASCT in the 2nd line and received bendamustine, gemcitabine, or lenalidomide.

Results—Three hundred eighty-three patients were included. Therapy received was bendamustine in 158 patients, gemcitabine in 142 patients, and lenalidomide in 83 patients. Median EFS and OS for all patients was 4.1 months and 8.7 months, respectively. Compared to patients receiving bendamustine or gemcitabine, those receiving lenalidomide demonstrated significantly longer median EFS (6.8 months vs 3.8 months, $p=0.006$) and median OS (15.4 months vs 7.7 months, $p=0.045$). Survival outcomes were also improved for lenalidomide-treated patients specifically in the 2nd as well as 3rd or 4th line settings.

Conclusion—Use of lenalidomide resulted in prolonged EFS and OS as compared to bendamustine or gemcitabine in this cohort of R/R DLBCL patients receiving palliative therapy. This first large-scale analysis of real-world outcomes for this patient population may guide current clinical management as well as serve as a benchmark for survival outcomes in the standard of care setting which may aid in the design of future clinical trials..

Microabstract

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The nationwide de-identified Flatiron Health database was analyzed for survival of patients with relapsed/refractory diffuse large B-cell lymphoma who are ineligible for and/or fail autologous stem cell transplantation and are treated with subsequent palliative-intent therapy. Compared to patients receiving bendamustine or gemcitabine, those receiving lenalidomide demonstrated improved survival outcomes. Use of lenalidomide may benefit patients in this clinical setting.

Keywords

Non-Hodgkin lymphoma; relapsed; chemotherapy; lenalidomide

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and comprises roughly one quarter of all malignant lymphoproliferative disorders. While 60–70% of patients can achieve long-term remission following receipt of first line therapy, the remaining 30–40% of patients will ultimately develop relapsed/refractory (R/R) disease and require further systemic therapy¹. High-dose chemotherapy and autologous stem cell transplantation (ASCT) can lead to long-term remission in roughly 50% of eligible patients with R/R DLBCL and chemosensitive disease following receipt of salvage immunochemotherapy, although most patients with R/R DLBCL do not ultimately receive ASCT^{2,3}. The standard approach to patients with R/R DLBCL who are not candidates for and/or whose disease persisted or recurred following ASCT is less well defined, and data demonstrate that these patients have a poor prognosis^{4–6}.

In addition, outcomes among patients with R/R DLBCL who receive therapy in the third-line setting and beyond are dismal, with a median overall survival of 10 months^{7,8}. While chimeric antigen receptor T cell (CAR-T) therapy has been approved by the United States Food and Drug Administration (US FDA) in this setting, this treatment is not yet widely available to all eligible patients, and many patients may not be fit to receive it^{9,10}. Additionally, while polatuzumab-based therapy was recently approved by the US FDA, the current experience in the standard of care setting is limited. As a result, there remains equipoise in recommending alternative treatment options for R/R DLBCL patients in this clinical setting.

Current guidelines recommend enrollment in clinical trial, palliative immunochemotherapy, or best supportive care for this patient population¹¹. Endorsed regimens include bendamustine-based immunochemotherapy (bendamustine-rituximab) and gemcitabine-based immunochemotherapy (gemcitabine-oxaliplatin and gemcitabine/cisplatin/dexamethasone with rituximab)^{12–14}. These regimens have both been studied in phase I/II studies but have not been prospectively compared with one another. Additional therapy considerations in the salvage setting include ibrutinib, an oral Bruton's tyrosine kinase inhibitor, and lenalidomide, an immunomodulatory agent, although these two novel agents do not currently have US FDA approval for use in this patient population^{15–19}.

The lack of consensus regarding an optimal therapy for patients with R/R DLBCL who are not candidates for and/or whose disease has not responded to ASCT has led to the use of

multiple treatment regimens in this clinical setting. This study aims to use real-world data to investigate outcomes of this patient population in the current era of novel therapeutics, which has not been previously performed.

Methods

Study design and patient population

Patient data were sourced from the nationwide Flatiron Health electronic health record-derived de-identified database. Eligible patients were aged 18–90 years with a histologic diagnosis of DLBCL made from July 1, 2011 to December 31, 2018 with R/R disease after frontline immunochemotherapy, who were treated with bendamustine-based immunochemotherapy, gemcitabine-based immunochemotherapy, or lenalidomide without receipt of subsequent ASCT. Follow-up was censored on December 31, 2018. Patients who received standard salvage immunochemotherapy given in preparation for high-dose chemotherapy and ASCT (R-ICE, R-DHAP) were excluded for analysis in the 2nd line setting, as were patients who received chemotherapy indicated for other non-hematologic malignancies. The study protocol was approved by the University of Pennsylvania Institutional Review Board (IRB) and the Copernicus Group IRB prior to study conduct, with waived informed consent.

Outcomes

The primary objective for this analysis was event free survival (EFS), which was defined as the interval between the start of current therapy and the start of the next line of therapy, last follow-up while on current therapy, or death. The secondary objective of interest was overall survival (OS), defined as the interval between the start of current therapy and last follow-up while alive or death.

Statistical Methods

Categorical data were analyzed by the Pearson's χ^2 test. EFS and OS curves were constructed using Kaplan-Meier estimates. Median follow up time was calculated using the reverse Kaplan-Meier method. The impact of categorical variables on both EFS and OS was analyzed using Cox proportional-hazard regression. Comparison of survival functions was performed with the log-rank test. Statistical significance was defined as a two-tailed p-value of 0.05 for all analyses. STATA version 15.1 (StataCorp, College Station, TX) was used for analysis.

Results

Patients

A total of 383 patients from 35 different states were included in the final analysis (Figure 1). As listed in Table 1, 158 patients received bendamustine-based therapies, 142 received gemcitabine-based therapies, and 83 received lenalidomide, with 220 patients receiving one of these therapies in the 2nd line, 114 in the 3rd line, and 49 in the 4th line. Overall, median age was 73 years with 70% older than age 60 years, 56% were male, 52% had ECOG

performance status > 1, 86% had stage III–IV disease, and 82% had an International Prognostic Index (IPI) score > 2. Eighty-six percent of patients received care at community treatment centers, and 21 patients (5.5%) had received ASCT in the 2nd line. Compared to patients receiving lenalidomide or bendamustine, those receiving gemcitabine were younger ($p<0.001$). Patients receiving lenalidomide were more likely to be under treatment at an academic center ($p<0.001$) and were more likely to have received ASCT in the 2nd line ($p=0.01$) as compared to those receiving bendamustine or gemcitabine. There were no other statistically significant differences in other baseline clinicopathologic characteristics between the different treatment groups.

Of patients receiving bendamustine-based therapies, 141 received bendamustine and rituximab, 9 received bendamustine and obinutuzumab, and 8 received bendamustine monotherapy. Among the 142 patients treated with gemcitabine-based therapies, 112 received rituximab/gemcitabine/oxaliplatin, 17 received rituximab/gemcitabine/cisplatin, 5 received rituximab/gemcitabine/carboplatin, 7 received rituximab/gemcitabine, and 1 received rituximab/gemcitabine/cyclophosphamide. Fifty-one percent of patients treated with lenalidomide received concurrent rituximab.

Outcomes

The median length of follow-up was 22.7 months. Median survival times by treatment group and line of therapy are listed in Table 2. For all patients included in the analysis, median EFS was 4.1 months (95% CI: 3.6 – 5.1 months, Figure 2A). Stratified by line of therapy, EFS was 5.1 months (95% CI: 3.7 – 6.6 months) in the 2nd line and 3.6 months (95% CI: 2.6 – 4.6 months) in the 3rd and 4th lines. We observed statistically significant difference in EFS between all three therapy groups in all lines of therapy ($p = 0.009$), in the 2nd line ($p = 0.01$), and in the 3rd and 4th lines ($p = 0.007$). There was no statistically significant difference in EFS between patients receiving bendamustine and patients receiving gemcitabine overall ($p=0.19$), in the 2nd line ($p=0.08$), or in the 3rd and 4th lines ($p=0.09$). Compared to patients receiving bendamustine or gemcitabine-based regimens, patients receiving lenalidomide experienced significantly longer median EFS in all lines ($p = 0.006$, Figure 2B), as well as specifically in the 2nd line ($p=0.01$, Figure 3A) and in the 3rd and 4th lines ($p=0.01$, Figure 3B). One year EFS for patients receiving lenalidomide was 48.4% in the 2nd line and 29.8% in the 3rd and 4th lines. One year EFS for patients receiving bendamustine or gemcitabine was 24.1% in the 2nd line and 7.9% in the 3rd and 4th lines.

For all patients, median OS was 8.7 months (95% CI: 6.9 – 11.1 months, Figure 2C). Stratified by line of therapy, median OS was 13.6 months (95% CI: 8.8 – 16.1 months) in the 2nd line and 6.8 months (95% CI: 5.2 – 8.3 months) in the 3rd and 4th lines. We observed statistically significant difference in OS between all three therapy groups in all lines of therapy ($p = 0.03$) and in the 3rd and 4th lines ($p = 0.02$), but not in the 2nd line ($p = 0.18$). There was no statistically significant difference in OS between patients receiving bendamustine and gemcitabine overall ($p=0.10$), in the 2nd line ($p=0.20$), or in the 3rd and 4th lines ($p=0.53$). Patients receiving lenalidomide experienced significantly longer median OS compared to patients receiving bendamustine or gemcitabine-based therapies for all lines ($p = 0.05$, Figure 2D) and in the 3rd and 4th lines, ($p = 0.006$, Figure 3D) but not in the 2nd

line ($p=0.2$, Figure 3C). One year OS for patients receiving lenalidomide was 58.9% in the 2nd line and 47.1% in the 3rd and 4th lines. One year OS for patients receiving bendamustine or gemcitabine was 48.6% in the 2nd line and 25.4% in the 3rd and 4th lines.

Univariate cox regression was performed using clinicopathologic risk factors at the time of diagnosis and therapy received. Multivariate cox regression analyses incorporating baseline characteristics which were significant by univariate analysis also suggested an EFS benefit associated with lenalidomide compared to bendamustine or gemcitabine. The hazard ratio for lenalidomide patients compared to those patients receiving bendamustine or gemcitabine was 0.70 (95% CI: 0.53 – 0.92, $p = 0.01$) in all lines of therapy, 0.58 (95% CI: 0.37 – 0.92, $p = 0.02$) in the 2nd line setting, and 0.62 (95% CI: 0.42 – 0.91, $p = 0.01$) in the 3rd and 4th line settings. The OS HR for lenalidomide patients compared to those patients receiving bendamustine or gemcitabine was 0.76 (95% CI: 0.55 – 1.05, $p = 0.10$) in all lines, 0.74 (95% CI: 0.44 – 1.25, $p = 0.26$) in the 2nd line, and 0.58 (95% CI: 0.38 – 0.89, $p = 0.01$) in the 3rd and 4th lines. ECOG performance status >1 was significantly associated with EFS with a HR of 1.52 (95% CI: 1.21 – 1.92, $p < 0.001$) in all lines, 1.82 (95% CI: 1.33 – 2.49, $p < 0.001$) in the 2nd line, and 1.23 (95% CI: 0.88 – 1.74, $p = 0.23$) in the 3rd and 4th line settings. Similarly, ECOG performance status > 1 was significantly associated with OS with a HR of 1.77 (95% CI: 1.36 – 2.29, $p < 0.001$) in all lines, 2.16 (95% CI: 1.50 – 3.12, $p < 0.001$) in the 2nd line, and 1.47 (95% CI: 1.01 – 2.15, $p = 0.05$) in the 3rd and 4th line settings.

There was no difference in EFS among patients treated with lenalidomide according to cell of origin, with median EFS of 7.9 months (95% CI 2.4 – 20.9 months) in patients with GCB DLBCL as compared to 4.9 months (95% CI 1.8 – 7.0 months) in patients with non-GCB for all lines of therapy ($p = 0.22$). Similarly, there was no difference in OS between GCB and non-GCB patients treated with lenalidomide in all lines of therapy, with median OS of 9.9 months (95% CI 4.3 – 32.0 months) in GCB patients compared to 13.9 months (95% CI 4.1 – 20.8 months) in non-GCB patients ($p = 0.44$).

Discussion

To the best of our knowledge, this is the first use of this novel real world database to perform a comparative effectiveness analysis of both immunochemotherapy and targeted therapy in patients with R/R DLBCL who are not candidates for and/or whose disease persisted or recurred following ASCT. Our results suggest lenalidomide may have more favorable outcomes as compared to cytotoxic chemotherapy in the treatment of patients with R/R DLBCL in this clinical setting. Patients treated with lenalidomide experienced a statistically significant longer median EFS overall, in the 2nd line, and in the 3rd and 4th line as well as median OS overall and in the 3rd and 4th line setting compared to patients treated with bendamustine or gemcitabine-based immunochemotherapy. While patients receiving lenalidomide were more likely to be treated at an academic medical center and have received ASCT in the 2nd line setting as compared to those receiving bendamustine- or gemcitabine-based therapies, neither of these characteristics were predictive of EFS or OS on multivariate analysis. It is interesting to note that patients with R/R DLBCL receiving lenalidomide

monotherapy are being studied in an observational manner to serve as a comparator arm to those receiving tafasitamab, an antiCD19 anti-body ([NCT04150328](#)).

Of note, the data used in this analysis were censored in December 2018 and therefore preceded the US FDA approval of polatuzumab-based therapy. In addition, the data did not include patients receiving CAR-T therapy given the timeframe of the study, although many patients in this clinical setting may not have access to nor be fit to proceed with CAR-T therapy²¹.

As this is a retrospective study, it is potentially subject to selection bias. While we excluded patients who received standard pre-ASCT salvage immunochemotherapy regimens, it is possible some patients in this cohort receiving gemcitabine-based regimens were initially intended for ASCT. We were also unable to determine the number of treatment cycles given due to the structure of the database used. Additionally, in some cases, survival outcomes in our cohort differed as compared to those previously published for these regimens in smaller prospective and retrospective studies^{12,13,20,22}. However, we feel that both the size of our patient population and the generalizability of the source database validate our findings. Finally, while the US FDA has recognized EFS as a surrogate endpoint both to support drug approval and to represent direct clinical benefit for the patient, our definition here is time to next treatment as opposed to time to progression due to limitations of our dataset²³. However, R/R DLBCL is an aggressive B-cell lymphoma which requires prompt treatment and, as such, time to next treatment is likely a reasonable proxy for time to progression in these patients and has been used in prior studies²⁴.

In conclusion, this analysis of survival outcomes for patients with R/R DLBCL who are not candidates for and/or whose disease persists or recurs following ASCT provides useful data both for treating clinicians and for the future design of prospective clinical trials. The use of this novel real-world database makes these results broadly applicable to patients with R/R DLBCL receiving palliative therapy in the 2nd line setting and beyond in both community and academic treatment centers, which is a scenario frequently faced in clinical practice. Our results suggest that lenalidomide should be considered a reasonable treatment option in this clinical setting. Additionally, these data derived from the standard of care setting may aid in the design of future clinical trials for this patient population.

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Figure 1.
CONSORT (Consolidated Standards of Reporting Trials) Diagram of Distribution of Patients and Reasons for Exclusion

Figure 2.

(A) EFS for all Patients in all Lines of Therapy. (B) EFS for Patients Receiving Lenalidomide Compared with Patients Receiving Bendamustine or Gemcitabine-Based Immunochemotherapy in all Lines of Therapy. (C) OS for all Patients in all Lines of Therapy. (D) OS for Patients Receiving Lenalidomide Compared with Patients Receiving Bendamustine or Gemcitabine-Based Immunochemotherapy in all Lines of Therapy

Abbreviations: EFS = event-free survival; OS = overall survival.

Figure 3.

EFS for Patients Receiving Lenalidomide Compared with Patients receiving Bendamustine or Gemcitabine-Based Immunochemotherapy in the Second line (A) and in the Third and Fourth Line (B). OS for Patients Receiving Lenalidomide Compared to Patients Receiving Bendamustine or Gemcitabine-Based Immunochemotherapy in the Second Line (C) and in the Third and Fourth Line (D)

Abbreviations: EFS = event-free survival; OS = overall survival.

Table 1:

Clinicopathologic Characteristics at Time of Diagnosis

Factor	All Patients	Bendamustine	Gemcitabine	Lenalidomide	p-value
N	383	158	142	83	
Age at diagnosis, median (IQR)	73.1 (62.3, 78.8)	74.9 (65.9, 80.3)	68.9 (57.5, 76.3)	73.6 (66.2, 79.8)	<0.001
Age >60		34 (21.5%)			
No	115 (30.0%)	124 (78.5%)	62 (43.7%)	19 (22.9%)	
Yes	268 (70.0%)		80 (56.3%)	64 (77.1%)	<0.001
Sex	168 (43.9%)	77 (48.7%)			
Female	215 (56.1%)	81 (51.3%)	54 (38.0%)	37 (44.6%)	
Male			88 (62.0%)	46 (55.4%)	0.17
Practice Type					
Academic	54 (14.1%)	12 (7.6%)	21 (14.8%)	21 (25.3%)	
Community	329 (85.9%)	146 (92.4%)	121 (85.2%)	62 (74.7%)	<0.001
ECOG PS					
0–1	185 (48.3%)	75 (47.5%)	66 (46.5%)	44 (53.0%)	
2–5	198 (51.7%)	83 (52.5%)	76 (53.5%)	39 (47.0%)	0.62
Stage					
I-II	55 (14.4%)	22 (13.9%)	18 (12.7%)	15 (18.1%)	
III-IV	328 (85.6%)	136 (86.1%)	124 (87.3%)	68 (81.9%)	0.53
Extranodal disease >1 site					
No	213 (55.6%)	85 (53.8%)	75 (52.8%)	53 (63.9%)	
Yes	170 (44.4%)	73 (46.2%)	67 (47.2%)	30 (36.1%)	0.23
IPI	69 (18.0%)				
0–2	314 (82.0%)	25 (15.8%)	26 (18.3%)	18 (21.7%)	
>2		133 (84.2%)	116 (81.7%)	65 (78.3%)	0.53
LDH > ULN					
No	101 (26.4%)	43 (27.2%)	35 (24.6%)	23 (27.7%)	
Yes	133 (34.7%)	(36.1%)	50 (35.2%)	26 (31.3%)	
Unknown	149 (38.9%)	(36.7%)	57 (40.1%)	34 (41.0%)	0.81
Cell of origin					
Non-GCB	78 (20.4%)				
GCB	98 (25.6%)	26 (16.5%)	26 (18.3%)	26 (31.3%)	
Unknown	207 (54.0%)	33 (20.9%)	44 (31.0%)	21 (25.3%)	
		99 (62.7%)	72 (50.7%)	36 (43.4%)	0.15
MYC FISH positive					
No	182 (47.5%)	61 (38.6%)	73 (51.4%)	48 (57.8%)	

Factor	All Patients	Bendamustine	Gemcitabine	Lenalidomide	p-value
N	383	158	142	83	
Yes	24 (6.3%)	9 (5.7%)	12 (8.5%)	3 (3.6%)	0.32
Unknown	177 (46.2%)	88 (55.7%)	57 (40.1%)	32 (38.6%)	
ASCT in 2nd Line					
No/Unknown	362 (94.5%)	155 (98.1%)	133 (93.7%)	74 (89.2%)	0.013
Yes	21 (5.5%)	3 (1.9%)	9 (6.3%)	9 (10.8%)	
Transformed disease					
No	306 (79.9%)	124 (78.5%)	110 (77.5%)	72 (86.7%)	0.21
Yes	77 (20.1%)	34 (21.5%)	32 (22.5%)	11 (13.3%)	
Line of Therapy					
2nd	220 (57.4%)	114 (72.2%)	73 (51.4%)	33 (39.8%)	<0.001
3rd	114 (29.8%)	29 (18.4%)	54 (38.0%)	31 (37.3%)	
4th	49 (12.8%)	15 (9.5%)	15 (10.6%)	19 (22.9%)	
Time to 1st Line Treatment (months), median (IQR)	0.67 (0.30, 1.13)	0.70 (0.37, 1.12)	0.60 (0.30, 1.1)	0.73 (0.30, 1.13)	0.35
Time to 2nd Line Treatment					
<6 months	64 (16.7%)	33 (20.9%)	19 (13.4%)	12 (14.5%)	0.16
6–12 months	114 (29.8%)	43 (27.2%)	49 (34.5%)	22 (26.5%)	
12–24 months	117 (30.5%)	41 (25.9%)	49 (34.5%)	27 (32.5%)	
>24 months	88 (23.0%)	41 (25.9%)	25 (17.6%)	22 (26.5%)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IPI international prognostic index; LDH, lactate dehydrogenase; ULN, upper limit of normal; GCB, germinal center B-cell like; FISH, fluorescence in situ hybridization; ASCT, autologous stem cell transplantation.

* Pearson's χ^2 test

Table 2:

Median Event Free and Overall Survival by Therapy Type and Line of Treatment

Median Event Free Survival, months (95% Confidence Interval)			
Therapy	All Lines	2 nd Line	3 rd and 4 th Lines
All Patients	4.1 (3.6 – 5.1)	5.1 (3.7 – 6.6)	3.6 (2.6 – 4.6)
Bendamustine	4.6 (3.7 – 6.4)	6.1 (4.2 – 7.6)	2.4 (1.3 – 4.1)
Gemcitabine	3.2 (2.4 – 3.8)	2.8 (2.2 – 3.8)	3.5 (2.4 – 4.8)
Lenalidomide	6.8 (3.8 – 11.9)	6.9 (3.9 – 34.3)	5.8 (3.1 – 7.9)
Overall Survival, months (95% Confidence Interval)			
All Patients	8.7 (6.9 – 11.1)	13.6 (8.8 – 16.1)	6.8 (5.2 – 8.3)
Bendamustine	8.6 (6.5 – 15.1)	14.8 (8.5 – 19.0)	5.0 (2.7 – 7.5)
Gemcitabine	6.5 (5.5 – 8.8)	8.7 (5.5 – 14.8)	6.4 (4.8 – 7.5)
Lenalidomide	15.4 (9.3 – 24.2)	24.2 (5.2 – NYR)	10.7 (7.8 – 20.8)

Abbreviations: NYR, not yet reached.