11-29-2021

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Leukemia Research Reports 16 (2021) 100284

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Outcomes of patients with double/triple expressor diffuse large B-cell lymphoma (DLBCL) treated with R-DA-EPOCH/R-CHOP: A single-center experience.

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ARTICLE INFO

Keywords:
Diffuse large B-cell lymphoma
Non-hodgkin lymphoma
R-DA-EPOCH
R-CHOP
Survival

ABSTRACT

In Pakistan 76.4% of all NHLs to be diagnosed as DLBCLs. The survival of R-CHOP is better compared to the DA-REPOCH treatment regimen. A prospective follow-up study was conducted with 113 patients to study the outcomes of treatment. Multivariable cox-proportional hazard model was used to estimate the hazard ratios in patients receiving these treatment regimens considering p-value ≤ 0.05 significant. The survival rate among double/triple expressor lymphoma patients received R-DA-EPOCH was 82.8%, and 83.3% received R-CHOP. For double/triple expressor lymphoma patients received R-DA-EPOCH. The findings of our study demonstrated that the survival rate in both R-CHOP and R-DA-EPOCH is mostly similar.

1. Introduction

Diffuse Large B-cell lymphomas (DLBCLs) are by far the most common non-Hodgkin's lymphomas (NHLs) [1]. DLBCL is a heterogeneous [2], highly aggressive [3], clonal neoplasm of large B-lymphoid cells originating from germinal centers. The disease is characterized by massive lymphadenopathy and constitutional symptoms [4] and constitutes 40% of all NHLs globally, with a higher prevalence in developing countries [5]. Indeed, a study from Pakistan found 76.4% of all NHLs to be diagnosed as DLBCLs [6].

In keeping with this, the treatment of DLBCLs is under extensive research. Half a century ago, the standard of treatment regimen was a combination of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [7]. This regimen resulted in response rates of 45–55%, with 30–40% of patients achieving cure [7, 8]. Despite the advent of newer regimens, CHOP remained the mainstay of therapy for decades because of superior cure rates and lesser toxicity [8]. Recently, a new regimen, with the addition of rituximab to the previous combination chemotherapy (R-CHOP) showed promise with better cure rates (of 50–60%) [4] without increased toxicity [9]. Despite the success of R-CHOP, there are important shortcomings to this combination chemotherapy. Liu et al. reported that, of the 40% of patients who have refractory disease or those who relapse, most patients will not respond to this chemotherapy [4]. Considering this, newer regimens are being investigated to improve survival. One such combination is dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-REPOCH) [7]. However, studies comparing the effectiveness of R-CHOP with that of DA-REPOCH have been inconclusive. Bartlett et al. found no difference between the two treatments [10]. Yet, Knouse et al. reported that while there was no improvement in survival between the two treatments, fewer patients in the DA-REPOCH arm relapsed or progressed after treatment [7], suggesting that the benefits of this new treatment must be re-evaluated.

With results of prior studies inconclusive, it is necessary to assess the effectiveness of R-DA-EPOCH combination therapy to assess any advantages of this treatment. Thus, this study aims to compare the survival rates of the DA-REPOCH regimen with the R-CHOP chemotherapy regimen.

; COO, Cell of Origin; DLBCL, Diffuse large B-cell Lymphoma; OS, Overall Survival; PFS, Progression Free Survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; WHO, World Health Organization.

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https://doi.org/10.1016/j.lrr.2021.100284
Received 24 August 2021; Received in revised form 3 November 2021; Accepted 27 November 2021
Available online 29 November 2021

2. Methods

A retrospective study design was used to investigate the treatment outcomes of patients previously diagnosed with the either DE or TE subtype of DLBCL compared with non-expressor DLBCL. A sample of 113 patients who presented to the tertiary care hospital at Karachi, Pakistan was selected. All consenting patients aged 18 and above, with a diagnosis of DE or TE subtype of DLBCL as per World Health Organization (WHO) classification, who were treated between January 1, 2019, to December 31, 2020, with either DA-REPOCH or R-CHOP, were included in the study. Patients with a history of prior treatment for aggressive or indolent lymphoma were not included. All toxicities that were reported were graded using the common terminology criteria for adverse events, version 5.0 [11]. Participants' demographic characteristics, such as age, sex, and co-morbidities; disease characteristics, such as disease stage, cell of origin, expressors, and International Prognostic Index (IPI) scores; and treatment variables, such as the type of treatment given, and the number of chemotherapy cycles were recorded in the study. The data were analyzed using STATA version 16.0. All independent and outcome variables were analyzed descriptively. Normally distributed continuous variables were represented as means and standard deviations while categorical variables were presented as frequency counts and percentages. Progression-free survival (PFS) and overall survival (OS) were calculated in months using the Kaplan-Meier survival function. In addition, the log-rank test was conducted to compare survival distributions. Cox proportional hazard regression model was used to analyze the results [12]. Univariate analysis was conducted to assess the significance of variables. Then the inter-variable multicollinearity was also assessed. All variables with a significance of $\leq$0.25 were admissible in the multivariable model and significant variables without multicollinearity were analyzed at p-value $\leq$0.05 on multivariable analysis.

3. Results

A total of 113 patients were treated for DLBCL from January 1, 2019, to December 31, 2020. The total follow-up was of two years duration (24 months). Out of the 113 patients, 44 (39%) were non-expressors and 69 (61%) had double/triple expressor lymphomas. R-CHOP was given as standard therapy to 44 (39%) of the DLBCL patients. Of the 69 (61%) patients with double/triple expressor lymphoma, R-DA-EPOCH was administered to 18 (26.1%), R-CHOP was administered to 38 (55.1%), and 13 (18.8%) received other treatment regimens i.e., R-Benda and R-CVP.

4. Baseline demographic and clinical characteristics of participants

The baseline characteristics of the patients with non-expressor (NE) and double/triple expressor lymphoma diagnosed basis of IHC receiving different treatment regimens (R-DA-EPOCH, R-CHOP, and Others) are displayed in Table 1. The mean (±SD) age of non-expressor DLBCL patients was 52.5 (±15.5) years, while the mean age of participants with double/triple expressor lymphoma receiving R-DA-EPOCH was 50 (±14.7) years, R-CHOP was 56.6 (±11.1) years, and those receiving other treatments was 63.8 (±9.0) years. Out of the 44 non-expressor DLBCL patients, 30 (68.2%) were male and 14 (31.8%) were female. Among the 69 patients with double/triple expressor lymphoma, there were 9 (13%) males and 9 (13%) females in the R-DA-EPOCH arm, and 22 (31.9%) males and 16 (23.3%) females in the R-CHOP arm, and 9 (13%) males and 4 (5.8%) females in the other treatment arm. DLBCL subtypes were described based on the cell of origin. Among the 44 non-expressor DLBCL cases, 28 (63.6%) cases had the germinal center B-cell (GCB) subtype, while among those with double/triple expressor lymphoma, 36 (52.2%) cases had the subtype with germinal center B-cells (GCB). They latter received either R-DA-EPOCH, R-CHOP, or other treatment regimens. Most patients had stage IV disease by Lugano staging system, with 31 (70.5%) patients from the non-expressor DLBCL group and 55 (79.7%) patients from the double/triple expressor lymphoma group. The two main comorbidities were hypertension and diabetes mellitus, found in 15.9% of NE DLBCL patients and 63.8% of double/triple expressor lymphoma patients. The median Eastern Cooperative Oncology Group (ECOG) score in patients with both NE DLBCL and double/tripe expressor lymphoma was [1]. The median IPI score for patients with NE DLBCL was 3, while the group with double/triple expressor lymphoma receiving DA-EPOCH had a score of 5, and the group with double/triple expressor lymphoma receiving R-CHOP and other treatment regimens had a score of 6. The median central nervous system IPI (CNS IPI) score was 3 for patients with NE DLBCL and 4 for patients with double/triple expressor lymphoma receiving any treatment. Among NE DLBCL patients, 23 (52.3%) received 6 cycles of R-CHOP, while out of the 69 patients with double/triple expressor lymphoma, 13 (18.8) received 6 cycles of R-DA-EPOCH, 25 (36.2) received 6 cycles of R-CHOP, and 10 (14.5%) received 6 cycles of other treatment regimens.

The survival rate in NE DLBCL patients receiving R-CHOP as the standard treatment was 81.8%, while the survival rate was 82.8% among double/triple expressor lymphoma patients receiving R-DA-EPOCH, and 83.3% among double/triple expressor lymphoma patients receiving R-CHOP. For those who received treatment other than these two treatment regimens, i.e., R-Benda and R-CVP, the survival rate was 62.5% (Table 2).

Table 1
Baseline clinical characteristics of patients with diffuse large B-cell lymphoma.

Variables	Expressors n = 113 (n%)			
	Non-Expressor (n = 44)	Double/Triple expressor (n = 69)		
	R-CHOP	R-DA-EPOCH	R-CHOP	Others
Age (Mean ±SD)	52.5 (±15.5)	50 (±14.7)	56.6 (±11.1)	63.8 (±9.0)
Sex				
Male	30 (68.2)	9 (13.0)	22 (31.9)	9 (13.0)
Female	14 (31.8)	9 (13.0)	16 (23.2)	4 (5.8)
COO subtype				
Non-GCB	16 (36.4)	8 (11.6)	19 (27.5)	6 (8.7)
GCB	28 (63.6)	10 (14.5)	19 (27.5)	7 (10.2)
Disease Stage				
1	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
2	6 (13.6)	0 (0.0)	3 (4.3)	0 (0.0)
3	6 (13.6)	2 (2.9)	8 (11.6)	1 (1.4)
4	31 (70.5)	16 (23.2)	27 (39.1)	12 (17.4)
Co-morbidities				
No-any	34 (77.3)	5 (7.2)	15 (21.7)	5 (7.2)
Hypertension	3 (6.8)	3 (4.3)	9 (13.0)	4 (5.8)
Diabetes Mellitus	4 (9.1)	3 (4.3)	10 (14.5)	1 (1.4)
Others	3 (6.8)	7 (10.1)	4 (5.8)	3 (4.3)
ECOG (median)	1	1	1	1
IPI Score (median)	3	5	6	6
CNS IPI Score (median)	3	4	4	4
IT Chemotherapy				
No	17 (38.6)	3 (4.3)	4 (5.8)	1 (1.4)
Yes	27 (61.4)	15 (21.7)	34 (49.3)	12 (17.4)
No. of Chemotherapy Cycles				
≤5	21 (47.7)	5 (7.2)	13 (18.8)	3 (4.3)
6	23 (52.3)	13 (18.8)	25 (36.2)	10 (14.5)

Abbreviations: COO subtype, cell of origin subtype; ECOG PS, eastern cooperative oncology group performance status; GCB, germinal center; IPI, international prognostic index; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

Table 2
The overall survival rate in patients receiving different chemotherapy regimens for DLBCL after a two-year follow-up.

Survival rate	Expressors $n = 113$ (Number of patients%)			
	Non-Expressor($n = 44$)	Double/Triple expressor ($n = 69$)		
	R-CHOP	R-DA-EPOCH	R-CHOP	Others
%	81.8	82.8	83.3	62.5

5. Progression-free survival (PFS) and overall survival (OS)

At 2 years, the median PFS for the entire cohort was 19.6 months (range 2.3- 21.6 months). Median 2-year OS ($n = 85$) was 16.8 months (3.3–24 months) while OS till the last follow-up was 22.5 months (1.5–24 months). Among the NE DLBCL patients, the median progression-free survival was 10.3 months while the overall survival was 13.6 months. For double/triple expressor lymphoma patients, in those receiving R-DA-EPOCH, the PFS was 10.5 months and OS was 13.8 months, in those receiving R-CHOP, the PFS was 10.6 months and OS was 14.2 months and in those receiving other treatment regimens, the PFS was 6.6 months and OS 10.6 months (Table 3, Fig. 1, 2& 3).

6. Description of toxicity by treatment

A description of the toxicity by grade with each treatment regimen is displayed in Table 4. Adverse events are divided into two broad categories: hematologic and non-hematologic. Most patients had hematologic adverse events i.e., neutropenia, pancytopenia, or anemia, and most had a severity of grade 3 or 4. When excluding hematologic events, gastrointestinal events were the most common adverse events, with severity of grade 3 or 4.

7. Univariate and multivariable analysis

The Univariate and Multivariable regression model was applied, assessing the association between treatment regimen received by the patient and the outcome, which is given in Table 5. Both univariate and multivariable analysis showed that the treatment regimen, disease expressors, and toxicity are significant prognostic factors for overall survival in DLBCL. The hazard ratio for survival in patients who received R-CHOP was 1.9 times (95% CI 1.1–6.8) compared to those who received R-DA-EPOCH or other treatments. The hazard ratio of survival in patients who received other treatments was 4.3 times (95% CI 1.2–6.5) compared to those who received R-DA-EPOCH or R-CHOP. Additionally, the hazard ratio of survival in NE DLBCL patients was 2.6 times (95% CI 1.1–6.4) compared to double/triple expressor lymphoma. Moreover, the hazard ratio of survival in patients who have pancytopenia was 3.1 times (95% CI 1.6–5.5) compared to neutropenia and other adverse events, while the hazard ratio of survival in patients who had other adverse events was 5.6 times (95% CI 1.2–7.7) compared to neutropenia and pancytopenia.

8. Discussion

The treatment of double/triple expressor DLBCL remains a

Table 3
Progression-free survival and overall survival at 2 years of the follow-up.

Survival rate	Median PFS and OS (in months)			
	Non-Expressor($n = 44$)	Double/Triple expressor ($n = 69$)		
	R-CHOP	R-DA-EPOCH	RCHOP	Others
Progression Free Survival (months)	10.3	10.5	10.6	6.6
Overall Survival (months)	13.6	13.8	14.2	10.6

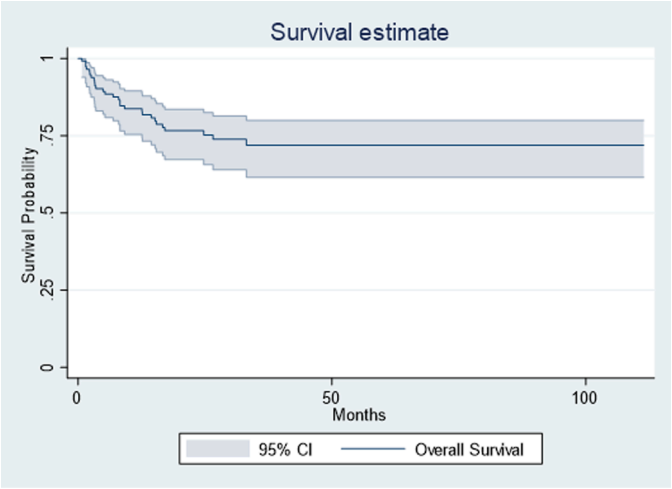

Fig. 1. Kaplan Meir plot for overall survival (in months) for NE DCBCL and double/triple expressor lymphoma combined.

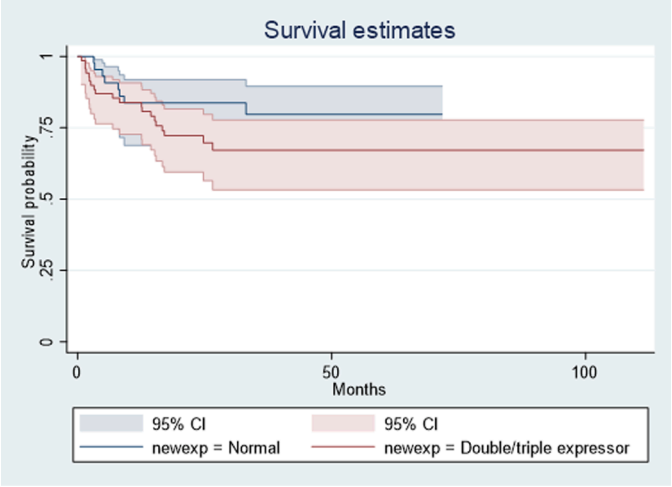

Fig. 2. Kaplan Meir plot for overall survival (in months) in NE and double/triple expressor lymphoma.

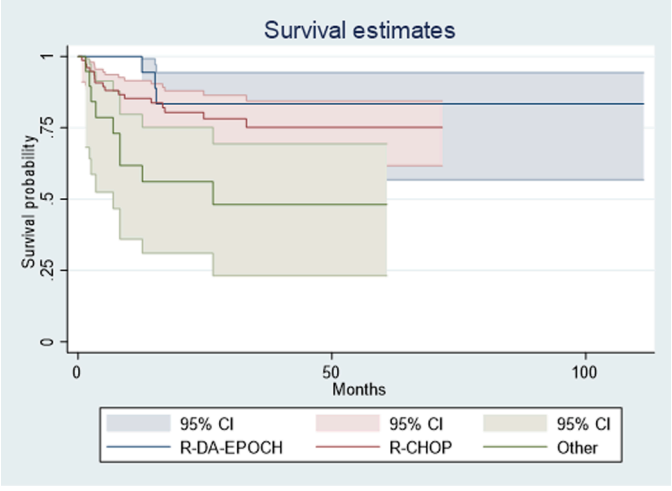

Fig. 3. Kaplan Meir plot for overall survival (in months) in double/triple expressor lymphoma receiving each of the three treatment regimens.

Table 4
Description of the toxicity with grade by treatment received (R-DA-EPOCH, R-CHOP, and Others).

Adverse Event	Grade 1/2, n (%)	Grade 3/4, n (%)				
	R-DA-EPOCH	R-CHOP	Others	R-DA-EPOCH	R-CHOP	Others
Hematologic						
Pancytopenia	04 (3.5)	14	02	07	19	01
Neutropenia	02 (1.8)	(12.4)	(1.8)	(6.2)	(16.8)	(0.9)
Anemia	00 (0.0)	09	03	01	01	02
Non-Hematologic	00 (0.0)	(8.0)	(2.7)	(0.9)	(0.9)	(1.8)
Infection	01 (0.9)	01	00	02	05	00
(other)	01 (0.9)	(0.9)	(0.0)	(1.8)	(4.4)	(0.0)
Gastrointestinal	00 (0.0)	03	01	02	01	01
Electrolyte		(2.7)	(0.9)	(1.8)	(0.9)	(0.9)
Imbalance		00	01	02	05	02
Sepsis		(0.0)	(0.9)	(1.8)	(4.4)	(1.8)
Tumor lysis		02	01	01	03	02
		(1.8)	(0.9)	(0.9)	(2.7)	(1.8)
		02	01	01	03	01
		(1.8)	(0.9)	(0.9)	(2.7)	(0.9)
		00	00	01	01	01
		(0.0)	(0.0)	(0.9)	(0.9)	(0.9)

challenge. Double/triple expressor lymphomas contain both MYC and BCL-2 and/or BCL-6 expression without translocation. There is a poor prognosis in patients with expression of both MYC and BCL2 [13]. Hence, studies have shown that double/triple expressor lymphomas have an invasive, aggressive clinical course and respond poorly to standard R-CHOP therapy, with an average OS of 5 months to 2 years [14–16]. In fact, 40% of patients relapse, and mortality rates are high, even after receiving R-CHOP [8]. Despite this poor course, few treatments have proven more effective than R-CHOP at improving survival.

R-DA-EPOCH is a newer regimen that holds promise for the treatment of double/triple expressor lymphoma [17]. This study shows that the survival rate of double/triple expressor lymphoma patients receiving R-DA-EPOCH is more or less similar to the survival rate of double/triple expressor lymphoma patients receiving R-CHOP (82.8% vs 83.3%). A possible reason for this may also be the dominant GCB subtype, with has present in roughly half of all types, as is also reported in literature [9, 10]. Petrich et al. reported that R-DA-EPOCH showed significant advantages over RCHOP for PFS and OS [17], suggesting that R-DA-EPOCH may demonstrate therapeutic advantages [18]. However, as some of these studies may be limited by small sample sizes. More recently, Dodero et al. found similar outcomes for both groups [19]. The authors also found that treatment in younger patients was more efficacious because they received a higher dose [19]. Magnusson et al. also reported no difference between the R-CHOP and R-EPOCH regimens [20]. The study further looked at the risks of poor outcomes and found LDH to be associated with poor prognosis. We studied the association of LDH via the IPI and found no association. While evidence may be varied, it seems to weight towards no difference between the two regimens.

As the R-DA-EPOCH regimen is administered as a continuous intravenous infusion, the incidence of adverse reactions is expected to be high [19]. However, our study also found fewer adverse events in the R-DA-EPOCH arm compared to the R-CHOP arm (Table 4). Hematological adverse events were the most common, mostly constituting pancytopenia, followed by neutropenia. Of those receiving R-DA-EPOCH, 9.7% of patients developed pancytopenia, compared to 29.2% of patients receiving R-CHOP. These adverse events were reversed shortly after symptomatic treatment. None of the patients developed chemotherapy-related deaths or secondary malignancy. Ma et al. reported no significant difference in adverse effects in patients with R-DA-EPOCH compared to R-CHOP [18]. However, Knouse et al. has also reported fewer adverse effects with R-DA-EPOCH [10]. The authors suggest this may be due to the different age ranges of patients treated

Table 5
Univariate and Multivariable Survival Analysis Reporting Crude and Adjusted Hazard Ratio with 95% Confidence Interval for overall survival in DLBCL.

Variables	CHR (95% CI)	p-value	AHR (95% CI)	p-value
Treatment				
REPOCH	1	0.03	1	<
RCHOP	1.5 (0.5–5.2)		1.9 (1.1–6.8)	0.001
Other	4.1		4.3 (1.2–6.5)	
	(1.1–15.3)			
Age (years)	1.01	0.22	–	–
	(1.0–1.4)			
Sex				
Male	1	0.32	-	-
Female	1.5 (0.7–3.1)			
COO subtype				
Non-GCB	1	0.67	-	-
GCB	1.2 (0.6–2.5)			
Expressors				
Double/Triple	1	0.08	1	<
Non-expressor	2.5 (1.1–5.9)		2.6 (1.1–6.4)	0.001
Disease Stage				
1–3	1	<	-	-
4	2.64	0.001		
	(1.5–4.2)			
Co-morbidities				
No-any	1	0.74	-	-
Hypertension	1.4 (0.5–3.9)			
Diabetes Mellitus	1.6 (0.6–4.4)			
Others	1.5 (0.5–4.2)			
ECOG	1.3 (0.8–2.3)	0.29	–	–
IPI Score	1.2 (0.9–1.6)	0.13	–	–
CNS IPI Score	1.0 (0.7–1.6)	0.9	–	–
IT Chemotherapy				
No	1	0.21	-	-
Yes	1.9 (0.6–5.4)			
No. of Chemotherapy				
Cycles	1	0.35	-	-
6	1.4 (0.7–3.0)			
≤5				
Toxicity				
Neutropenia	1	0.08	1	<
Pancytopenia	1.9 (0.4–8.8)		3.1 (1.6–5.5)	0.001
Others	3.6		5.6 (1.2–7.7)	
	(0.8–15.8)			

Abbreviations: COO subtype, cell of origin subtype; ECOG PS, eastern cooperative oncology group performance status; GCB, germinal center; IPI, international prognostic index; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; CHR: Crude Hazard Ratio; AHR: Adjusted Hazard Ratio.

with either regimen, as more patients in the R-CHOP arm were aged at least 70 years. However, the difference in age ranges in patients treated with R-DA-EPOCH and R-CHOP in our study was minimal (56.6 ± 11.1 vs 50 ± 14.7). However, there were some other differences in the number of patients with a higher stage of disease, comorbidities, and prognostic scores. Hence, we cannot conclude whether R-DA-EPOCH has fewer adverse events than R-CHOP. Further studies, with matched cohorts, may be required to study this.

There are some limitations to our study. It is a single-center study and has a small sample size of 113 patients due to the rare nature of the disease. It is also for this reason that we could not balance the baseline demographic and disease characteristics of patients who received each treatment. Despite these limitations, this is a prospective study design that has reported data on the PFS, OS, and adverse effects of treatments for high-risk DLBCL. It is also the first study of its kind from the local population.

This study shows similar efficacy of R-DA-EPOCH as compared to R-CHOP for the treatment of double/triple expressor lymphoma. We have also demonstrated fewer adverse effects with R-DA-EPOCH compared with R-CHOP, suggesting its value as a possible first-line treatment in

high-risk DLBCL. In the future, multicentered studies, with larger sample sizes, equal distribution of treatments, and matching, are required to better compare the efficacy and safety of R-DA-EPOCH with that of R-CHOP in the treatment of double/triple expressor lymphoma to improve progression-free survival and overall survival in this aggressive disease.

9. Conclusion

In conclusion, the findings of our study demonstrated that the survival rate in both R-CHOP and R-DA-EPOCH is mostly similar. A multicenter, large-scale study with equal distribution of treatment regimens is needed for comparison to establish the usefulness of the R-CHOP and R-DA-EPOCH regimen for double/triple expressor lymphoma.

Funding

Not Applicable

Ethics approval and consent to participate

Ethical Approval was taken from the Ethical Review Committee (ERC), Aga Khan University (AKU), Karachi Pakistan prior to the data collection [ERC Ref # 2020–3343–8894]. Informed written consent was taken from all the participants prior to the data collection. Participants who voluntarily participated in the study by giving consent were included in the study. Data collection process and methods followed ethical guidelines and participants privacy, anonymity and confidentiality were maintained at every stage.

Authors' contributions

K.D. and N.A. conceptualize the idea, K.D. and S.S contributed to the data collection. S.S. performed the analysis. K.D, S.S, M.A written the draft of manuscript U.S. and S.A. reviewed the manuscript and made the corrections. All authors reviewed final manuscript and approved for publication.

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Consent for publication

Not Applicable

Availability of data and materials

Data and materials are available to the corresponding author, which can be shared on a reasonable request.

Declaration of Competing Interests

The authors declare no competing interest

Acknowledgements

We would like to acknowledge and thank Department of Oncology, Aga Khan University Hospital for their logistic support and Department of Health Management and Information Systems (HIMS), Aga Khan University Hospital for their support in data processing.

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