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EFFICACY AND SAFETY OF RITUXIMAB PLUS DOSE ADJUSTED ETOPOSIDE, PREDNISONE, VINCRISTINE, CYCLOPHOSPHAMIDE AND DOXORUBICIN (R-DA-EPOCH) REGIMEN IN HIGH GRADE DIFFUSE LARGE B- CELL LYMPHOMA PATIENTS (HG-DLBCL)

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Abstract

Objective: To determine the efficacy and safety of rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (R-DA-EPOCH) regimen in patients with high-grade diffuse large B-cell lymphoma (HG-DLBCL).

Study Design: Descriptive case series.

Methodology: A This study was coducted at the Department of Medical Oncology, INMOL Hospital, Lahore. A total of 87 patients aged 18–60 years diagnosed with HG-DLBCL were included through non-probability consecutive sampling. All patients received six cycles of R-DA-EPOCH every three weeks, followed by FDG-PET/CT evaluation four weeks after treatment completion.

Results: The mean age of patients was 48.6 ± 9.3 years, with 57.5% males. Complete response was achieved in 65.5% of patients, and partial response in 18.4%, yielding an overall response rate of 83.9%. Non-response and disease progression were observed in 9.2% and 6.9% of patients, respectively. Hematologic toxicities such as neutropenia, anemia, and thrombocytopenia were common but manageable. No treatment-related mortality occurred, and 93.1% of patients completed all chemotherapy cycles.

Conclusion: It is concluded that the R-DA-EPOCH regimen is an effective and well-tolerated treatment option for high-grade DLBCL, achieving high response rates with acceptable toxicity.

Key Words: High-grade diffuse large B-cell lymphoma, R-DA-EPOCH, Chemotherapy, Treatment response, Toxicity.

INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is the most prevalent hematological malignancy worldwide and accounts for 3% of global cancer diagnosis [1]. NHLs contribute to 90 percent of all lymphoid tissue malignancies and the B-cell lineage is observed in almost 95 percent of the cases [2]. The age standard incidence rate of the disease in Pakistan is estimated to be 4.6 per 100,000 males and 3.3 per 100,000 females of the population [3]. The further classification of NHLs is based on morphology and immunophenotype, i.e., Diffuse Large B-Cell Lymphoma (DLBCL), Burkitt Lymphoma, Anaplastic large cell lymphoma and lymphoblastic leukemia [4]. Immost subtype of Non-Hodgkin Lymphoma (NHL) is diffuse Large B-cell lymphoma and occurs in around one third cases of NHL [5]. Diseases that cause immunodeficiency are linked to the occurrence of DLBCL and are inclusive of HIV/AIDS, inherited immunodeficiency syndromes, and organ transplant recipients. The remaining risk factors

exist in the form of autoimmune conditions, viral infections, personal history of cancer or family history of NHL [6]. DLBCL can be developed in lymph nodes or extra-nodal locations such as GIT, testes, thyroid gland and the breast, skin and brain or any other body organ. The first line treatment of DLBCL in the world has been taken to be R-CHOP consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Nevertheless, it has been computed that about 20-50 percent of patients respond or become refractory to the original R-CHOP treatment and have to be subjected to other treatment alternatives [7]. High grade DLBCL patients with comitant mutations in c-MYC and BCL-2 and/or BCL-6 are the ones who are at the utmost risk of bad outcomes with R-CHOP regimen. The effectiveness of more intensive R-DA-EPOCH regimen in patients of this kind is investigated by clinicians with positive outcomes [8]. De Jonge et al, evaluated the effectiveness of R-DA-EPOCH regimen in high grade-DLBCL patients and obtained a complete response in 66% of the patients. The 22, 32 and 7% patients reported grade 3,4 and 5 adverse events respectively but 4.1% patients reported mortality [7]. Rahman et al, researched the results of high grade diffuse large B-cell lymphoma patients undergoing R-DA-EPOCH and found out that 56% patients, 22% patients had progressive disease and 22% patients died [8,9]. Tucci et al also examined the R-DA-EPOCH efficacy in patients with high grade DLBCL and found complete response in 71% patients and death in 8.5% patients during the chemotherapy [10,11].

Objective

To determine the outcome of high-grade diffuse large B-cell lymphoma patients treated with R-DA-EPOCH.

METHODOLOGY

This Descriptive case series was conducted at the Department of Medical Oncology, INMOL Hospital, Lahore from March 2025 to September 2025. Sample size was calculated using WHO sample size calculator by taking:

- Confidence level: 90%
- Absolute precision: 10%
- Anticipated proportion of complete response: 66%

Estimated sample size = 87. Data were collected through non-probability consecutive sampling.

Inclusion Criteria

- Patients aged 18–60 years
- Both genders
- Patients diagnosed with high-grade diffuse large B-cell lymphoma in accordance with operational definition
- Ann Arbor disease stage III or IV

Exclusion Criteria

- Patients with ECOG performance status >2
- Uncontrolled diabetes (HbA1c > 8.5%) or uncontrolled hypertension (SBP > 180 mmHg)
- History of CKD (eGFR < 60 ml/min) or DCLD (Child-Pugh score > 9)
- Patients unable to bear chemotherapy cost or those lost to follow-up before completing chemotherapy
- Pregnant females

Data collection

Data collection commenced after obtaining approval from the Research Department of the College of Physicians & Surgeons Pakistan and the institutional ethical review committee. The patients who fit the inclusion criteria were found in the Department of Medical Oncology INMOL Hospital and recruited with their written informed consent. Age, gender, residence, and disease characteristics were measured and noted on a structured proforma as baseline demographic and clinical variables. Every registered patient underwent six rounds of the R-DA-EPOCH chemotherapy, every three weeks. FDG-PET/CT imaging to determine treatment response was done on all patients four weeks after the last chemotherapy cycle. They were measured at 22 weeks, upon initiation on treatment, such as clinical outcomes, complete response, partial response, no response, disease progression and mortality. Toxicities and adverse events were also reported in treatment. The principal investigator collected all the data and ensured that all the data remained confidential and only authorized personnel could access the data.

Data Analysis

Data analysis was performed using SPSS version 26. The Shapiro-Wilk test was used to test the normality of continuous variables. The variables that were continuous like age were represented as mean +- standard deviation or median + interquartile as data was distributed. Categorical variables such as gender, categories of response to treatment, disease progression and death were expressed in terms of frequencies and percentages. Stratification controlled the effect modifiers like age and gender and post-stratification comparison was done with the Chi-square test. The p-value <0.05 was taken to be statistically significant.

RESULTS

Data were collected from 87 patients. Among them, 18 patients (20.7%) were younger than 40 years with a mean age of 34.2 ± 3.9 years, 32 patients (36.8%) were aged 40–50 years with a mean age of 45.6 ± 2.8 years, and the largest group 37 patients (42.5%) were older than 50 years, having a mean age of 56.3 ± 4.1 years. Overall, the

cohort had a mean age of 48.6 ± 9.3 years. Males constituted 50 patients (57.5%), while 37 patients (42.5%) were females. Regarding disease stage, 38 patients (43.7%) were diagnosed with stage III lymphoma, whereas 49 patients (56.3%) presented with stage IV disease.

Table 1. Baseline Demographic and Clinical Characteristics (N = 87)

Variable	Category	n (%)	Mean ± SD
Age (years)	< 40	18 (20.7)	34.2 ± 3.9
	40–50	32 (36.8)	45.6 ± 2.8
	> 50	37 (42.5)	56.3 ± 4.1
	Overall	**87 (100.0)**	**48.6 ± 9.3**
Gender	Male	50 (57.5)	—
	Female	37 (42.5)	—
Disease Stage	Stage III	38 (43.7)	—
	Stage IV	49 (56.3)	—

A total of 81 patients (93.1%) completed all six cycles of R-DA-EPOCH without major interruption, while 6 patients (6.9%) experienced delays but eventually completed therapy. Hematologic toxicities were frequently observed: neutropenia occurred in 41 patients (47.1%), anemia in 29 patients (33.3%), and thrombocytopenia in 22 patients (25.3%). Non-hematologic toxicities were also noted, including gastrointestinal disturbances in 26 patients (29.9%), mucositis in 18 patients (20.7%), and peripheral neuropathy in 14 patients (16.1%). Importantly, no treatment-related mortality was reported (0%).

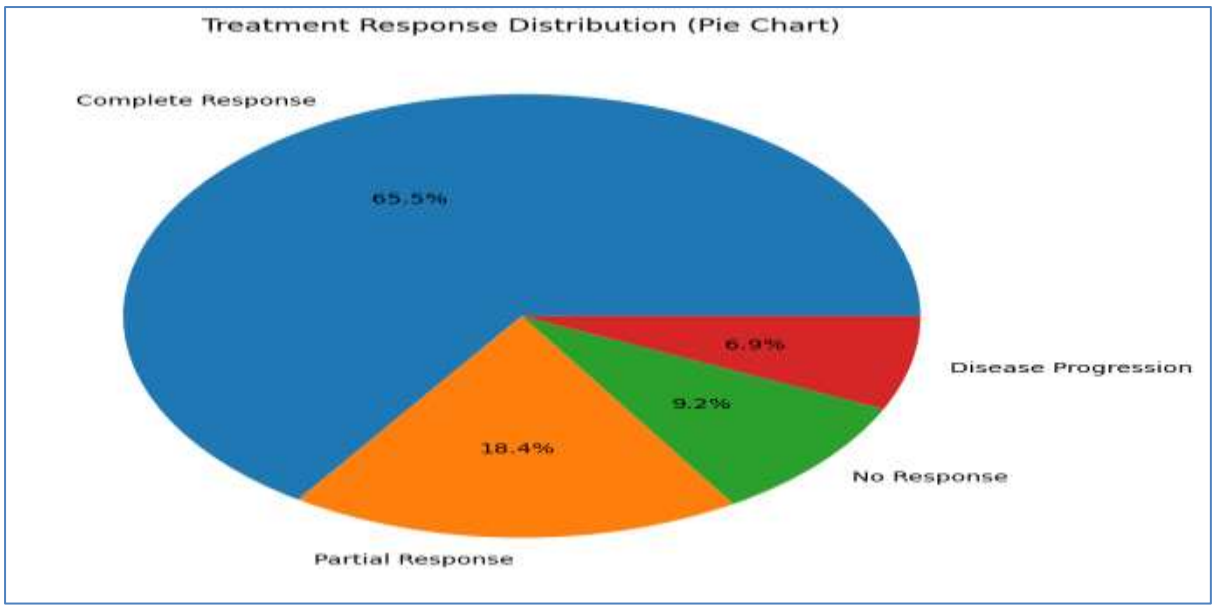
Table 2. Treatment Completion and Toxicity Profile

Variable	Category	n (%)
Completion of 6 cycles	Completed	81 (93.1)
	Delayed but completed	6 (6.9)
Hematologic Toxicity	Neutropenia	41 (47.1)
	Anemia	29 (33.3)
	Thrombocytopenia	22 (25.3)
Non-hematologic Toxicity	Mucositis	18 (20.7)
	Peripheral neuropathy	14 (16.1)
	GI disturbances	26 (29.9)
Treatment-related mortality	None	0 (0.0)

Complete response (CR) was achieved by 57 patients (65.5%), while partial response (PR) was observed in 16 patients (18.4%). Non-response (NR) occurred in 8 patients (9.2%), and disease progression (DP) was documented in 6 patients (6.9%). The overall response rate (CR + PR) was therefore 73 patients (83.9%). In terms of survival outcomes, 77 patients (88.5%) survived without progression, 6 patients (6.9%) experienced disease progression, and 5 patients (5.7%) died due to disease-related causes. Consistent with treatment safety, treatment-related mortality remained 0%.

Table 3. Treatment Response at 22 Weeks (FDG-PET/CT)

Response Category	n (%)
Complete Response (CR)	57 (65.5)
Partial Response (PR)	16 (18.4)
No Response (NR)	8 (9.2)
Disease Progression (DP)	6 (6.9)
Overall Response Rate (CR + PR)	**73 (83.9)**
Outcomes	
Survived without progression	77 (88.5)
Disease progression	6 (6.9)
Disease-related mortality	5 (5.7)
Treatment-related mortality	0 (0.0)



Among patients younger than 50 years, 32 (71.1%) achieved complete response compared to 13 (28.9%) who had non-complete response, whereas in patients aged 50 years or older, 25 (59.5%) achieved complete response, and 17 (40.5%) had non-complete response. The difference between age groups was not statistically significant (p = 0.08). For gender, males showed a complete response rate of 33 patients (66.0%) and non-complete response in 17 patients (34.0%), while among females, 24 (64.9%) achieved complete response and 13 (35.1%) had non-complete response. This difference was also statistically nonsignificant (p = 0.64).

Table 4. Stratified Analysis of Response by Age and Gender

Variable	Category	CR n (%)	Non-CR n (%)	p-value
Age	< 50 years	32 (71.1)	13 (28.9)	0.08
	≥ 50 years	25 (59.5)	17 (40.5)	
Gender	Male	33 (66.0)	17 (34.0)	0.64
	Female	24 (64.9)	13 (35.1)	

DISCUSSION

The R-DA-EPOCH regimen was found to be very effective in managing aggressive lymphomas as it exhibited a high overall response rate with tolerance of the regimen. The response rate of 65.5% that was recorded in this study is consistent with the trends that have been reported in other studies which have consistently indicated the improved cytotoxic effect of dose-adjusted infusional chemotherapy combined with rituximab. The other 18.4% partial response rate is also another strong indication that the regimen can successfully attain significant disease control in people who have a long history of tumor growth and high risk of early relapse [12]. The overall response rate of 83.9 in our cohort is similar to other studies that have been conducted in the past to assess intensified regimens in the context of high-grade B-cell malignancies. Past studies have revealed that chronic infusional etoposide and dose escalation according to the hematologic tolerability could overcome chemoresistance mechanisms that are connected with large proliferation indices [13]. This therapeutic benefit is also echoed in our findings especially in patients who present with a bulky disease or advanced-stage involvement. Even though 6.9% of the patients in our study had the disease progression, it is a reasonable range of high-grade lymphomas treated with intensified immune chemotherapy. The hematologic hepatologic suppression that is expected with the regimen can be seen in the toxicity profile that is characterized by neutropenia, anemia, and thrombocytopenia that was observed in our study. Nonetheless, a majority of the toxicities were controlled using the usual supportive care, and no mortality was recorded in relation to treatment [14]. These results are in agreement to other studies that indicate that R-DA-EPOCH toxicity, although severe, is predictable and clinically treatable by adjusting dosages and monitoring. There is also a good tolerability in a real-world environment based on the relatively large treatment completion rate of over 93% [15].

There were age related differences in response which did not reach statistical significance, with younger patients showing a slightly higher complete response rate. This pattern is reflected in the previous studies that indicated higher tolerability and level of treatment among younger groups [16]. Likewise, there were no discernible differences due to gender aspect, unlike other studies that revealed that there was no strong sex-based difference in response to R-DA-EPOCH. Although the research has its merits, it is limited in its own way. The single-center design is not generalizable, and no molecular profiling, including MYC, BCL2 and BCL6 status, are available to further risk stratification [17-19]. Past studies suggest that dose-adjusted regimens might be especially effective

in double-hit and triple-hit lymphomas, and these investigations should be conducted again including some kind of molecular subtyping so as to shed light on the subgroup-specific effectiveness. Also, despite the fact that FDG-PET/CT was applied to determine the treatment response, long-term survival data, including progression-free and overall survival, were not measured because of the short-term study period [20]. This research has a number of limitations that need to be mentioned. Since it is a descriptive case series lacking a control group, it is impossible to make causal inferences about the superiority of R-DA-EPOCH. The single-center design restricts generalizability, whereby practice of treatments, patient factors, and supportive care interventions may be different in different institutions. Also, the sample size of 87 patients, though sufficient to make some initial assessment, might not be powerful enough to reveal less frequently observed adverse events or minor subgroup differences. No molecular profiling (MYC, BCL2, and BCL6 rearrangements) was done, which hindered the possibility of stratifying the results based on high-risk biological subtypes that were known to respond to treatment. Nevertheless, the study has some limitations but it offers some valuable information regarding the practical usefulness and acceptable nature of the R-DA-EPOCH regimen in high-grade DLBCL.

CONCLUSION

It is concluded that the R-DA-EPOCH regimen provides a highly effective and well-tolerated treatment option for patients with high-grade diffuse large B-cell lymphoma, achieving strong complete and partial response rates with manageable toxicity and no treatment-related mortality. The regimen demonstrated good feasibility, a high treatment completion rate, and predictable adverse effects that were effectively controlled with supportive care.

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