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A STUDY TO EVALUATE THE ROLE OF FRACTIONATED CYCLOPHOSPHAMIDE WITH R-CHOP CHEMO-IMMUNOTHERAPY IN HIGH RISK DLBCL PATIENTS.

Oncology

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ABSTRACT

Background: DLBCL has a response rate of 60-65% with R-CHOP. No trial apart from the POLARIX has shown a better PFS. The limitation for the utilization of polatuzumab vedotin is the high cost. **Methods:** We conducted a Retro-Prospective single arm interventional study using historical control among patients of high risk DLBCL treated at our institute. In the experimental arm, patients were treated with the Fractionated cyclophosphamide in RCHOP regimen (RfCHOP). Historical patients treated with the standard RCHOP. High-risk defined by non-GCB, Stage 3/4 and IPI 2-5. The response was assessed using FDG-PET-CT done 4–6 weeks after completion of chemotherapy. **Results:** 54 patients were included in the study - 27 in RfCHOP arm (Arm A) and 27 in the RCHOP arm (Arm B). Median age - 56 and 58 years in arms A and B respectively. 80% and 84% had stage 3/4 disease in arms A and B respectively. Complete Response rates were 74% and 66% in arms A and B respectively (p value = 0.04). Number of grade 3/4 adverse events were 37% in arm A and 29% in arm B (p value = 0.07). There was 1 mortality in arm A due to Myocardial infarction and no mortality in arm B. **Conclusion:** Use of fractionated cyclophosphamide resulted in statistically significant improvement in CR rates in high risk DLBCL patients with a similar adverse event profile. Further studies can help in devising a cost-effective regimen for patients with high risk DLBCL.

KEYWORDS

Diffuse Large B Cell Lymphoma, High Risk IPI Score, Fractionated Cyclophosphamide, RCHOP Chemo-immunotherapy.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is currently recognized as the predominant form of non-Hodgkin lymphoma in India, accounting for approximately one-third to nearly half of cases in national studies, with its prevalence documented at 35–43% depending on the regional cohort analyzed. [1] The primary treatment protocol for advanced-stage DLBCL remains combination immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[2] However, patient outcomes have not matched those achieved in less aggressive disease subsets. Efforts to enhance treatment response have provided limited or no additional survival benefit in first-line management and can lead to increased toxicity [2] except substituting polatuzumab vedotin for vincristine in the R-CHOP regimen in the POLARIX study which improved progression-free survival in previously untreated patients with intermediate- or high-risk DLBCL, achieving CR rates close to 78% and higher five-year PFS compared to standard R-CHOP.[3] Deployment of polatuzumab vedotin, however, is challenged in many resource-limited settings by prohibitive costs and lack of access, limiting its real-world impact in low- and middle-income countries (LMICs).

Cyclophosphamide has shown pharmacokinetic evidence that suggests that its fractionation may enhance the exposure to active metabolites through increased hepatic auto-induction, with studies in aggressive lymphoid malignancies demonstrating improved biological activity when administered in divided doses. [4,5] Given the persistent need for cost-effective strategies to optimize outcomes for high-risk DLBCL—especially in LMICs—a practical modification of the R-CHOP backbone employing fractionated cyclophosphamide warrants systematic evaluation. As a few studies have shown, fractionation may offer superior anti-lymphoma activity without the adverse profile associated with dose escalation or additional novel agents not widely available. [6,7]

MATERIALS AND METHODS

Study Design and Setting- A retro-prospective, single-arm, interventional study was conducted at a tertiary care academic hospital to assess the clinical outcomes of fractionated cyclophosphamide-RCHOP (RfCHOP) versus historical standard RCHOP in patients with high-risk diffuse large B-cell lymphoma (DLBCL).

Patient Selection and Eligibility Criteria- Participants were considered eligible if they had a histologically confirmed diagnosis of high-risk DLBCL, defined by at least one of the following high-risk features at baseline: non-germinal center B-cell (non-GCB) phenotype as determined by immunohistochemistry by Hans algorithm, advanced clinical stage (Stage III or IV according to the Lugano staging), or an International Prognostic Index (IPI) score ranging from 2 to 5. Patients were required to have adequate performance status (ECOG performance score of ≤2) to receive systemic chemotherapy, and all consents and approvals were obtained in accordance with institutional review board guidelines.

The intervention group were treated with the RfCHOP protocol between March 2023 and December 2024. For comparison, 27 historical controls previously treated at the same institution with standard RCHOP chemotherapy were identified from institutional databases.

Treatment Interventions- Patients assigned to RfCHOP received the following regimen for each treatment cycle:

- Rituximab: 375 mg/m² intravenously on Day 1
- Cyclophosphamide: 500 mg/m² intravenously on Day 1, followed by 250 mg/m² orally on Days 2 and 3
- Doxorubicin: 50 mg/m² intravenously on Day 1
- Vincristine: 1.4 mg/m² intravenously on Day 1
- Prednisolone: 60 mg/m² orally (dosage schedule per standard institutional protocol)

Historical control patients received standard RCHOP, characterized by:

- Cyclophosphamide: 750 mg/m² intravenously on Day 1
- All other agents identical in identity and dosing to the RfCHOP group.

Treatment was administered every 21 days, for a planned total of six cycles, with dose adjustments as required for toxicity or patient tolerance. As per institutional policy, all patients received prophylactic GCSF.

Outcome Assessment- The primary outcome measure was treatment response, determined by whole-body 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging conducted six weeks following completion of the sixth chemotherapy cycle. Response was assessed and classified according to Lugano criteria.

Data Collection and Statistical Analysis- Clinical and demographic information, as well as treatment response data, were systematically collected. All statistical analyses were conducted using Microsoft Excel and SPSS software (version 22; IBM Corp., Armonk, NY, USA). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate, to account for sample size and data distribution. A two-tailed p-value less than 0.05 was considered statistically significant.

Ethical Considerations- Study procedures were reviewed and approved by the Institutional Ethics Committee prior to initiation (Number: KMIO/MEC/2023/04/PG/MO/20).

RESULTS

A total of 54 patients with high-risk DLBCL were included in this comparative analysis, with 27 patients receiving fractionated cyclophosphamide-RCHOP (RfCHOP) and 27 historical controls treated with standard RCHOP.

Baseline characteristics (Table 1) were well-balanced between the two groups. The median age was 56 years (range: 32-64) in the RfCHOP group compared to 58 years (range: 38-68) in the control group. Male predominance was observed in both arms, comprising 44% and 51% respectively. The majority of patients in both groups presented with advanced-stage disease (Stage III/IV): 81% in the RfCHOP group and 74% in the control group. Double-hit lymphomas were detected in 13% and 14% of tested patients in each group.

Treatment response assessment demonstrated superior outcomes in the RfCHOP group, with complete metabolic response achieved in 20 patients (74%) compared to 18 patients (67%) in the standard RCHOP group which was statistically significant (p value = 0.04). Stable or progressive disease occurred in 15% of RfCHOP patients versus 19% of control patients. The overall response rate (complete plus partial response) was 85% in the RfCHOP group compared to 82% in the standard RCHOP group. (Table 2; Figure 1)

Regarding safety profile, the RfCHOP regimen was associated with increased hepatological toxicity. All-grade neutropenia occurred more frequently in the RfCHOP group (78% vs 70%). Febrile neutropenia were higher in the fractionated group (22% vs 11%). (Figure 2).

Dose modifications were required in 11% of RfCHOP patients and 7% of control patients, indicating acceptable tolerability of the fractionated regimen.

DISCUSSION

Our study demonstrates that fractionated cyclophosphamide within the R-CHOP regimen (RfCHOP) achieves superior complete metabolic response rates compared to standard R-CHOP in patients with high-risk DLBCL (74% vs 67%), which was statistically significant (p value = 0.04). Our results are consistent with two key studies that explored fractionated cyclophosphamide approaches. Mato et al. [6] reported outcomes in 64 high-risk DLBCL patients treated with R-HCVAD/R-MTX-AraC, an intensive regimen incorporating fractionated cyclophosphamide (300 mg/m² every 12 hours for 6 doses). Their study achieved a 94% overall response rate with 3-year progression-free survival and overall survival of 79% and 76%, respectively. However, this regimen required inpatient administration and was associated with significant toxicity, particularly in patients over 45 years, limiting its broader applicability. Similarly, the randomized SCUBA-1 trial by Singh et al. [7] compared RfCHOP with standard R-CHOP in 55 high-risk DLBCL patients. Their fractionated approach (cyclophosphamide 500 mg/m² IV day 1, followed by 250 mg/m² orally on days 2-3) which was similar to the regimen used in our study, achieved an 82.1% complete response rate versus 59.3% with standard R-CHOP (p=0.062). Our results closely mirror these findings, with complete response rates of 74% versus 67%, suggesting reproducibility of the fractionated cyclophosphamide benefit across different institutions and populations.

The superior efficacy observed with fractionated cyclophosphamide aligns with established pharmacokinetic principles.[8]

Safety Profile and Tolerability: Our toxicity profile demonstrated increased hematological adverse events with RfCHOP, particularly neutropenia (78% vs 70% all grades, 44% vs 30% Grade 3-4) and febrile neutropenia (22% vs 11%). This pattern is consistent with both the Mato and Singh studies, where fractionated regimens showed increased early hematological toxicity.

The Singh study [7] similarly reported that primary G-CSF prophylaxis reduced Grade III-IV neutropenia from 80% to 38.4% and febrile neutropenia from 40% to 23.1%, emphasizing the importance of proactive supportive care measures in fractionated cyclophosphamide regimens.

Clinical Implications and Global Accessibility- A critical advantage of our approach lies in its global accessibility and cost-effectiveness. Cyclophosphamide is universally available and affordable, making RfCHOP a pragmatic therapeutic option for the 30-40% of DLBCL patients in India who currently achieve suboptimal outcomes with standard therapy.

Our real-world complete response rate of 67% with standard R-CHOP in high-risk patients aligns with reported Indian registry data showing 60-67% CR rates, which remain inferior to the 75-80% rates typically reported in developed countries. The 74% CR rate achieved with RfCHOP brings outcomes closer to international standards without requiring access to expensive novel agents.

Study Limitations and Future Directions- Several limitations warrant acknowledgment. Our study employed a historical control design rather than a randomized controlled trial, potentially introducing selection bias. The sample size was relatively small (n=54), limiting statistical power to detect meaningful differences in survival outcomes. Additionally, molecular characterization was incomplete. The encouraging results support the rationale for a larger, multicentre randomized controlled trial comparing RfCHOP to standard R-CHOP, powered to detect clinically meaningful differences in progression-free and overall survival.

CONCLUSION

Fractionated cyclophosphamide represents a promising strategy to optimize outcomes in high-risk DLBCL patients, particularly in resource-limited settings. Our results demonstrate improved response rates with acceptable toxicity. Given the universal availability and affordability of cyclophosphamide, RfCHOP offers a practical approach to bridge the outcome gap for high-risk DLBCL patients in LMICs. Larger randomized studies are warranted to definitively establish the clinical benefit of this approach and identify optimal patient selection criteria.

Table 1: Baseline Characteristics:

	Interventional arm (RfCHOP) n = 27	Historical Control arm (RCHOP) n = 27
Median Age (Years)	56 (Range: 32-64)	58 (Range: 38-68)
Male sex	12 (44%)	14 (51%)
Patients with B Symptoms	9 (33%)	8 (28%)
Stage: 3,4	22 (81%)	20 (74%)

IPI		
Low risk	2 (7%)	3 (11%)
Intermediate risk	8 (30%)	8 (30%)
High risk	17 (63%)	16 (59%)
Cell of Origin (Hans algorithm)		
GCB	12 (44%)	14 (51%)
Non-GCB	15 (56%)	13 (49%)
Double expressor	8 (30%)	9 (33%)
Double hit (Tested)	3 (22) (13%)	2 (14) (14%)
Bulky disease	5 (19%)	6 (22%)
Dose reductions done in	3 (11%)	2 (7%)

Table 2: Response Rate:

Response at end of treatment	RfCHOP	RCHOP
Complete Metabolic response	20 (74%)	18 (67%)
Partial Response	3 (11%)	4 (15%)
Stable / Progressive disease	4 (15%)	5 (19%)

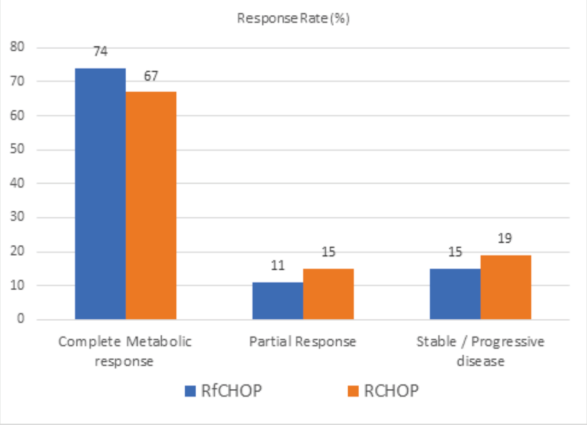

Figure 1: Response Rate:

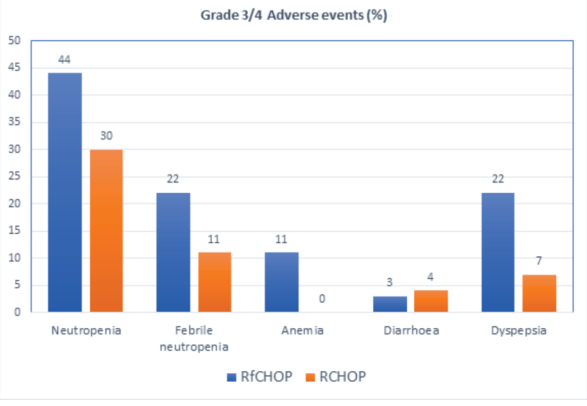

Figure 2: Adverse Events

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