

## Comparison of R-CHOP with CHOP in Patients of Diffuse Large B Cell Lymphoma

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### Abstract

**Objective:** Diffuse large B cell lymphoma (DLBCL) is a lymphoid B cells neoplasm with a diffuse pattern and high proliferation rate. Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) was considered effective as other complicated regimens with more toxicity profile. Rituximab is a monoclonal antibody directed against CD20 positive B cell. It has good activity therapeutically in patients of DLBCL. It increases response rates and survivals when added to CHOP chemotherapy. Although R-CHOP is more effective but due to high cost of Rituximab it is usually not incorporated with chemotherapy in most of our patients and CHOP is still used extensively. Due to heterogeneity of disease and difference in ethnicity, there may be difference in outcomes of two regimens. This study will help us in tailoring our management plan that will result in better outcome of patients.

**Methods:** 70 patients aged between 20-65 years having DLBCL were taken in this study. We randomized patients by lottery method into two groups. Group I received CHOP with dose of Cyclophosphamide 750mg/m<sup>2</sup>, Doxorubicin 50mg/m<sup>2</sup>, Vincristine 1.4 mg/m<sup>2</sup> and prednisolone 40mg/m<sup>2</sup>. Chemotherapy was given on Day-1 while prednisolone was given for 5 days from Day-1 of chemotherapy. Group II received R-CHOP which includes same chemotherapy with same dosage. Rituximab was included in Group II with dose of Rituximab 375 mg/m<sup>2</sup>. Each cycle was given at three weeks interval. Response in terms of CR (Complete Response), PR (Partial Response), SD (Stable Disease) or PD (Progressive Disease) was evaluated as per leukemia network after 4 cycles of chemotherapy. The quantitative variables were calculated by taking mean and standard deviation. The response was assessed in percentage and frequencies and compared by applying chi square test.

**Results:** Group I had 37.1% while Group II had 68.6% complete response with p value of 0.019. Partial response was 48.6% in Group I while 20.0% in Group II. 14.3% in Group I and 8.6% in Group II either had stable disease or progressive disease.

**Conclusions:** R-CHOP has superior response rates as compared to CHOP, therefore, whenever possible Rituximab should be added as target therapy in chemotherapy.

**Key Words:** Diffuse large B cell lymphoma, CHOP, R-CHOP

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### Introduction

**A**mong non-Hodgkin's lymphomas, DLBCL is most common type present approximately 25 % in the developed countries<sup>1</sup>. Based on morphology of

lymphoid tissue and immunophenotyping pathological diagnosis of DLBCL can be made. CHOP was considered effective as other complicated regimens with more toxicity profile based on number of serial clinical investigations<sup>2</sup>. DLBCL is a heterogeneous variety of tumors having large B cells that are transformed and having prominent nucleoli. Cells of DLBCL have basophilic cytoplasm, diffuse pattern of growth and high proliferation rate. Tumor cells in DLBCL expresses B cell antigens (CD19, CD20, CD22 and CD79a). Rituximab is monoclonal antibody directed against CD20 positive B cells. It has good activity therapeutically in patients of DLBCL. R-CHOP which includes Rituximab with CHOP

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chemotherapy is more effective therapy and has better responses and survivals.<sup>3</sup> Rituximab when incorporated with chemotherapy showed survival benefit in the GELA Trial. It also increase survival in British Columbia trial when added to CHOP chemotherapy.<sup>4,5</sup> There was no difference in response rate between R-CHOP and CHOP in another study but there was a significant difference in relapse rates between these groups.<sup>5</sup> This was in contrast to result of another study conducted on elderly patients, where the response rate was also increased with R-CHOP.<sup>3</sup> In a study, Li X et al analyzed retrospectively 437 patients of DLBCL who were newly diagnosed. In six university hospitals they received CHOP or R-CHOP therapy and followed up for assessment of response after treatment. Between R-CHOP and CHOP, significant differences in overall survival and progression-free survival were present. Median follow up was of 86 month in this study. Overall survival was 84.1% in R-CHOP group and 70.2% in CHOP group with p value of 0.018. While progression free survival was 81.5% in R-CHOP group and 66.7% in CHOP group with p value of 0.015. In this study, elderly patients with age greater than 60 years received higher overall survival as compared to younger population. Median follow up was 66 months in elderly population with overall survival 80.7% in R-CHOP group and 53.0% in CHOP group with p value of 0.011. Chemotherapy with rituximab did not showed significant effect on overall survival that is 85.5% in R-CHOP and 79.4% in CHOP group with p value of 0.428.<sup>6</sup> In another study by Afzar M et al showed CR for CHOP Group as 44.4% and for R-CHOP group as 48.2% while PR as 11.1% for CHOP group and 7.1% for R-CHOP.<sup>7</sup> Although R-CHOP is more effective but due to high cost of Rituximab it is usually not incorporated with chemotherapy in most of our patients and CHOP is still used extensively. There may be difference in outcomes of two regimens due to heterogeneity of disease and difference in ethnicity. This study will help us in in better outcome of patients by tailoring our management plan.

## Methods

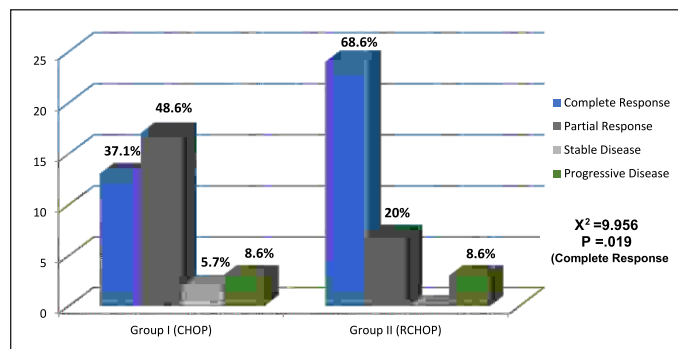
After taking approval from hospital ethical committee, patients who fulfilled the selection criteria were enrolled and written informed consent was taken from them before commencement of treatment. Patients were randomized by lottery method into two

groups. Group I received CHOP with dose of Cyclophosphamide 750mg/m<sup>2</sup>, Doxorubicin 50mg/m<sup>2</sup>, Vincristine 1.4 mg/m<sup>2</sup> and prednisolone 40mg/m<sup>2</sup>. Chemotherapy was given on Day-1 while prednisolone was given for 5 days from Day-1 of chemotherapy. Group II received R-CHOP which includes same chemotherapy with same dosage. Rituximab was included in Group II with dose of Rituximab 375 mg/m<sup>2</sup>. Each cycle was given at three weeks interval. Response in terms of CR (Complete Response), PR (Partial Response), SD (Stable Disease) or PD (Progressive Disease) is evaluated as per Lugano criteria with CT scan after four cycles of chemotherapy. We ensured follow up by taking patient's contact number. All the information was recorded on Performa by me. Data was entered on SPSS (Statistical Package of Social Sciences), version-10 software after being collected on Performa. Quantitative variables (age) were presented as mean and standard deviation. Qualitative variables (stage and disease response) were presented as frequency and percentage. Comparison between groups was made by applying chi-square test. We stratified the data for age, gender and stage of disease to describe effect modifiers. Chi-square test was used after stratification to assess significance with p < .05 as statistical significance.

## Results

70 subjects were randomly divided into Group I (CHOP n=35) and Group II (RCHOP n=35). Mean age of subjects was 45.24 years, SD 13.31 with minimum age of 20 years and maximum age of 78 years. 57.1% in Group I and 48.6% in Group II were of age 20–50 years and 49.2% in Group I and 51.4% in Group II were of age 51–80 years. 31.4% were females and 68.6% were male in Group I, 42.8% were females and 57.2% were male in Group II. 11.4% in Group I and 17.1% in Group II were in stage-1. 11.4% in Group I and 22.9% in Group II were in stage-2. 37.1% in Group I and 17.1% in Group II were in stage-3. 40.0% in Group I and 42.9% in Group II were in stage-4. 42.9% in Group I and 20.0% in Group II have no extra nodal involvement, 42.9% % in Group I and 62.9% in Group II had one extra nodal involvement and 8.6% in Group I and 17.1% in Group II had 2 extra nodal involvements. 37.1% in Group I and 42.9% in Group II had low risk (0-1), 28.6% in Group I and 17.1% in Group II were having low intermediate risk, 22.9% in Group I and 17.1% in Group II were having high interme-diate risk (=3) and

11.4% in Group I and 22.9% in Group II were having high risk (4-5). 28.6% in Group I and 51.4% in Group II had comorbidities. Final outcome was compared among groups, 37.1% in group I and 68.6% in Group II had complete response with  $P < .019$  which was statistically significant. 48.6% in group I and 20.0% in Group II had partial response, 5.7% in group I and 0.0% in Group II had a stable response, and 8.6% in both groups had progressive disease.



**Figure 1:** Final Outcome of Treatment Among Groups

**Table 1:** Demographic Data of Patients included in the study.

AGE (Years)	Groups		
	Group I	Group II	
Mean Age	46.6	49.6	
Median Age	47.00	52.00	
Std. Deviation	14.485	11.950	
Minimum	21	22	
Maximum	70	72	
An ARBOR STAGING	Groups		
	Group I	Group II	
	STAGE1	4 (11.4%)	6 (17.1%)
	STAGE2	4 (11.4%)	8 (22.9%)
	STAGE 3	13 (37.1%)	6 (17.1%)
STAGE4	14 (40.0%)	15 (42.9%)	
EXTRANODAL SITE	Groups		
	Group I	Group II	
	$\leq 1$ SITE INVOLVEMENT	30 (85.8%)	29 (82.9%)
$\geq 2$ SITE INVOLVEMENT	5 (14.2%)	6 (17.1%)	
IPI SCORE	Groups		
	Group I	Group II	
	0-2 LOW & LOW INTERMEDIATE RISK	23 (65.7%)	21 (60%)
3 - 5 HIGH & HIGH INTERMEDIATE RISK	12 (34.3%)	14 (40%)	
COMORBIDITIES	Groups		
	Group I	Group II	
	No	25 (71.4)%	17 (48.6%)
Yes	10 (28.6%)	18 (51.4%)	

## Discussion

DLBCL is the commonest variety of non-Hodgkin's lymphoma. It is clinically very heterogeneous lymphoma. Only 40% patients show good responses to current therapy and have survival benefit, whereas others don't respond well. This clinical heterogeneity and difference in natural history is due to molecular heterogeneity among tumors. CHOP is standard chemotherapy for patients with DLBCL. Rituximab is monoclonal antibody directed against CD20 positive B cells. It has good activity therapeutically in patients of DLBCL. We conducted a randomized trial and compared responses of R-CHOP with CHOP in patients of DLBCL.

Rituximab when added to CHOP chemotherapy increases complete responses and survival of patients in older patients with diagnosis of DLBCL as per study by Coiffier et al. There was no significant increase in toxicity seen with addition of Rituximab.<sup>3</sup>

Most of patients of DLBCL are of greater than sixty years.<sup>8</sup> Only half of patients responded with CHOP chemotherapy which was considered standard for years for all age groups of DLBCL.<sup>10</sup> Multiple attempts were made by adding other chemotherapy agents to increase the efficacy of therapy but it did not succeed. Regimens with increase doses of chemotherapy improve responses only in younger patients who have bad prognosis.<sup>11</sup> These intensified therapies were not tolerated by elderly population of patients. CHOP is also sometimes not tolerated by elderly patients. For this purpose easily tolerated chemotherapy regimens were designed for old patients, but these are less beneficial as compared to CHOP.<sup>10</sup>

Rituximab is a monoclonal antibody directed against CD20 positive B cells, it was first given on relapse and refractory low grade lymphomas. It was then found to have activity in relapse and refractory DLBCL.<sup>12</sup> CD20 is surface protein on lymphoid cells that is present only on mature B cells. The antibody is a chimeric because it is made up of human IgG1 portion with genetic engineered portion of mouse antibody which has CD20-binding site on it. Studies were conducted in which rituximab combined with CHOP chemotherapy showed 90 percent responses in all lymphomas.<sup>13</sup> The Groupe d'Etude des Lymphomes de l'Adulte (GELA) group studied and compared R-CHOP with CHOP in elderly population of patients with DLBCL. This was a randomized trial comparing both the effectiveness and safety of rituximab when

combined with CHOP with CHOP alone in patients of DLBCL. Higher responses rates and survivals were found among patients of DLBCL treated with R-CHOP. Patients treated with R-CHOP had fewer relapses after complete response and less rate of progression of disease that is why having longer survival. R-CHOP was tolerated well and no serious side effect was observed. In conclusion, R-CHOP chemotherapy when we give to elderly population of patients with newly diagnosed DLBCL increases responses to therapy, decreases failures with treatment and relapse of disease. It also improves survivals when compared with CHOP chemotherapy alone. There was no significant gain in toxicities with this addition.

### Conclusion

R-CHOP has superior response rates as compared to CHOP, therefore, whenever possible Rituximab should be added as target therapy in chemotherapy.

**Conflict of Interest:** None

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### Authors Contribution

**LRF:** Article writing

**ZA, KAM:** Data Collection

**GWA, AS, TS:** Data analysis