Original Article

Phase II Trial of R-CHOP Vs CHOP Chemotherapy in Pakistani Diffuse Large B cell Lymphoma Patients

Muhammad Azfar*
Farwa Rizvi**
Neelam Siddiqui***
Khawaja Farhan Zahid
Narjis Muzaffer
Iqtedar A Muazzam
Muhammad Usman Rashid

*Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan
**Department of Community Medicine, Islamabad Medical and Dental College, Barakaho, Islamabad.
***Department of Basic Sciences Research, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore.

Objective: To determine response and relapse rates in diffuse large B cell lymphoma (DLBCL) patients receiving rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone (R-CHOP) versus cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP).

Study Design: RC T (Randomized Control Trial).

Materials and Methods: This Randomized Control Trial was conducted between April 2007 and December 2008. 119 newly diagnosed consecutive DLBCL patients were treated with either R-CHOP or CHOP as first line chemotherapy at the Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Lahore, Pakistan. The CHOP chemotherapy was offered to 63 patients (53%) and 56 patients (47%) were given R-CHOP therapy. The arms were balanced with respect to International Prognostic Index (IPI) score, stage, and B symptoms (presence of systemic complaints of fever, weight loss, or night sweats).

Results: The response rates in terms of (disappearance of all radiological or biological lesions at the time of initial diagnosis and the absence of new lesions) were 48 % vs. 44% (p= 0.715) in R-CHOP and CHOP groups, respectively. Whereas the relapse rates were 9% vs. 20% (p=0.04) in R-CHOP and CHOP groups, respectively.

Conclusion: The addition of rituximab to CHOP chemotherapy increased the event free interval compared to CHOP chemotherapy in DLBCL Pakistani patients. However, it did not show any influence in response rate in this population.

Key words: Diffuse Large B Cell Lymphoma (DLBCL), Rituximab, CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone)

Address for Correspondence:
Dr. Farwa Rizvi
Assistant Professor, Community Medicine, Islamabad Medical and Dental College, Barakaho, Islamabad
Email: farwa.riz@gmail.com

Introduction

Diffuse Large B Cell Lymphoma (DLBCL) is the most common Non Hodgkin's Lymphoma and accounted for 40 % of the newly diagnosed lymphomas.[1] In 1993, the US Intergroup study demonstrated that the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) was associated with similar complete response (CR) rates, progression-free survival (PFS), and overall survival (OS) compared with more complicated regimens associated with more toxicity.[2]

CD 20 is an antigen that is expressed by DLBCL. Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, has therapeutic activity in diffuse large-B-cell lymphoma. R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, prednisolone and vincristine) has become the standard of care for DLBCL.[3]

In limited stage disease (stage I) with an adverse prognostic factor ISI (International Prognostic Index) score or non bulky stage II disease the addition of Rituximab to CHOP Chemotherapy and involved field radiation did not have an impact on the overall survival. The impact of Rituximab in a limited-stage setting was smaller than in advanced-disease setting, and there was a 4% absolute difference in 4-year OS as opposed to 10% to 15% absolute difference in 5-year OS in advanced disease, although the relative difference was 33%, which was more in line with reduction seen in advanced disease.[4]

Rituximab when added to CHOP chemotherapy is reported to have an increase in the overall response rate as well as overall survival in DLBCL,[3] but in another study it did not have an impact on the response rate but when given as a sequential therapy in patients who had received CHOP before, it did have an impact on the overall survival.[5] In all these studies the target population was above 60 years of age.[3,5]

Due to the overall increase in the amount of diagnostic facility and good cancer centers now available, the deaths due to cancers are decreasing. The down side includes the increased cost and serious financial burden to patients, and their families.[6]

Due to high cost it could not be incorporated as a standard of care in Pakistan, due to limited resources. Hence CHOP is still used extensively for treatment of DLBCL cases.

Rituximab however has not been investigated in Pakistani DLBCL population. Only one case report has been published in ALL (Acute Lymphoblastic Lymphoma) patient.[7]

The present study was designed and undertaken as a Randomized Control Trial to determine response and relapse rates in diffuse large B cell lymphoma (DLBCL) patients receiving rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone (R-CHOP) versus cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) between April 2007 and December 2008 at the Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Lahore, Pakistan.

Materials and Methods

All consecutive patients coming to Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC) with an outside diagnosis of lymphoma were enrolled and their histological specimen was collected and evaluated by board of institutional pathologists. Slides were reevaluated among those cases with no histological specimen. All study participants tissue diagnosis and CD 20 marker positivity was reconfirmed in order to make an accurate diagnosis.

Each patient had their International prognostic score calculated (0 or 1 *vs.* 2 or 3, with a higher score indicating a higher risk of death), which are based on disease stage, performance status, and the lactate dehydrogenase level.[8]

Inclusion Criteria:All individuals fulfilling following criteria were enrolled in the present study.

1. Patients diagnosed at or above 18 years of age
2. Patients with $\geq$ 50 ejection fraction as seen in their Echcardiographies.
3. Cases with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 4.
4. Individuals with stage I to stage IV disease
5. Patients with at least one objective measurable disease pattern.

Exclusion Criteria: All patients fulfilling following criteria were excluded from the current study.

1. Previously treated patients with any type of cancer(s)
2. Patients with a history of chronic disease(s) which limits the life expectancy of the patient in view of the investigator
3. Contraindication to doxorubicin therapy
4. Ejection fraction $\leq$ 50%.
5. Neurological contraindication to Vincristine
6. Patients with unresolved hepatitis B virus infection or with positive serologic test for the human immunodeficiency virus

Randomization: For this Randomized Control Trial, the 119 patients were first selected by consecutive sampling after the purpose of the study was made clear to them and written informed consent was obtained. Then these patients were randomized by lottery method to either group A or group B. Single blind technique was observed. CHOP chemotherapy (Group A) was offered to 63 patients (53%) and 56 patients (47%) were given R-CHOP therapy(Group B).

Treatment: Patients were given R-CHOP in the dose of Rituximab 375 mg per meter square on D1. Cyclophosphamide was given in the dose of 750 mg per meter square on D1, Doxorubicin in the dose of 50 mg per meter square on D1, Vincristine in the dose of 1.4 mg per meter square on D1. Prednisolone in the dose of 100 mg per day from D1-D5. CHOP was given in the same dosage except that Rituximab was not given.

Each cycle was repeated after every three weeks, if blood counts were not recovered then the cycle was delayed till the recovery of counts. For stage I disease three cycles of chemotherapy were followed by involved field radiation. The other patients were evaluated after 4 cycles of chemotherapy and then CT scan was performed and the response was evaluated according to the Recist criteria.[9] Complete response was defined as the disappearance of all radiological or biological lesions at the time of initial diagnosis and the absence of new lesions. An unconfirmed complete response was defined as a complete response with the persistence of some radiologic abnormalities, which had to have regressed in size by at least 75%. Partial response was defined as the regression of all measurable lesions by more than 50 percent, the disappearance of non measurable lesions, and the absence of new lesions. Stable disease was defined as a regression of any measurable lesion by 50 percent or less or no change for the non measurable lesions, but without growth of existing lesions or the appearance of new lesions. Progressive disease was defined as the appearance of a new lesion, any growth of the initial lesion by more than 25%, or growth of any measurable lesion that had regressed during treatment by more than 50 percent from its smallest dimensions.

If the patient developed complete response (CR) or near complete response (nCR), then two more cycles of chemotherapy was given for consolidation. If he had partial response then chemotherapy was

continued for the total of eight cycles and response was assessed by CT scan with contrast. If there was progressive disease then the chemotherapy was stopped and second line salvage chemotherapy was offered to the patient. After the completion of treatment the patients were followed according to the NCCN Guidelines of 2008 and the duration of relapse was calculated.

Statistical Analysis: Patients were randomized into two arms R-CHOP and CHOP and analysis was done on intention to treat principle. All data was entered into SPSS 14, p value was calculated using the Fischer Exact test. Two sided *p*-value was calculated along with 95% Confidence Interval (CI) for all the categorical variables. P–value less than 0.05 were considered statistically significant.

Death due to any cause and progressive disease according to Recist criteria was considered as the primary end point. Relapse was considered as the secondary end point.

Results

Between April 2007 and December 2008, 119 newly diagnosed consecutive DLBCL patients registered at SKMCH & RC were enrolled in this study. Study participants were randomized for treatment arm R-CHOP or CHOP. The baseline characteristics were balanced for age, prognostic factors and disease stage. The mean age group in the R-CHOP group was 43 years, standard deviation (SD) 13.6 and in CHOP it was 46 years, standard deviation (SD) 15.63. The CHOP chemotherapy was offered to 63 patients (53%) and 56 patients (47%) were given R-CHOP therapy. The arms were balanced with respect to IPI score, stage, and B symptoms.

There was no difference between the partial response that is after 4 cycles of chemotherapy (*p*=0.47) OR 1.04 CI [0.447 - 8.607] Table I.

Table I: Overall Response of CHOP vs. R-CHOP after 4 cycles of chemotherapy

Chemotherapy Regimen		Over all Response After 4 cycles	
		Yes	No
CHOP	Number of Patients (%)	60 (95.2%)	3 (4.8%)
R-CHOP	Number of Patients (%)	51 (91.1%)	5 (8.9%)
Two Sided P Value		0.47	
Odds Ratio/ Confidence Interval		1.04 [0.44 ----- 8.60]	

Table II: Complete Response Rate after End of treatment

Chemotherapy Regimen		End of Treatment CR		Total
		Yes	No	
CHOP	Number of Patients (%)	28 (44.4%)	35 (55.6%)	63 (100%)
R-CHOP	Number of patients (%)	27 (48.2%)	29 (51.8%)	56 (100%)
P – Value		0.715		
Odds Ratio / Confidence Interval		.922 [.626 ------ 1.358]		

The overall response rate at the completion of the therapy was insignificant between the two groups 44.4 % vs 48.2%, where (p= 0.715); OR 0.92 CI [0.626 - 1.358] Table II. There was no statistical significant difference in progression of disease after 4 cycles of chemotherapy (p=0.60) OR 0.44 [CI .0.41 --- 4.77]. No difference was observed in the progression of disease between the two treatment arm at the end of therapy (p= 0.537) OR 1.556 CI [0.481 --- 5.03) Table III.

Table III: Chemotherapy Regimen Used and end of treatment Progressive Disease

Chemotherapy Regimen	CHOP	End of Treatment Progressive Disease			Total
			Yes	No	
		Total number of Patients (%)	7 (11.1%)	56 (88.9%)	63 (100%)
	R-CHOP	Total number of patients	4 (7.1%)	52 (92.9%)	56 (100%)
P Value		0.537			
Odds Ratio / Confidence Interval		1.556 [.481 ----- 5.035]			

The complete response evaluated at the end of treatment was not significant (p = 0.71) with an OR of 0.922 CI [0.626 - 1.358].

During 1.5 years of follow up the relapse rate was significantly decreased in the R-CHOP chemotherapy receiving group 9.2% *vs.* 20.2% p=.043 OR 0.770 CI [0.610--973) Table IV.

Table IV: Chemptherapy Regimen Used and Relapse of Disease

Chemotherapy	CHOP	Relapse of Disease			Total
			Yes	No	
Regimen		Total Number of patients (%)	24 (38.1%)	39 (61.9%)	63 (100%)
	R-CHOP	Total Number of patients (%)	11 (19.6%)	45 (80.4%)	56 (100%)
P Value		0.043			
Odds Ratio / Confidence Interval		.77 [.610-------.973]			

Discussion

R-CHOP has now become the standard chemotherapy for patients with the diagnosis of DLBCL patients. However, due to financial constraints and high cost associated with Rituximab, it is difficult to offer to all of our patients with DLBCL. It is noteworthy that in Pakistan the majority of health care for oncology patient is not borne by the government. Moreover, there is not any solid health insurance policy in this country. The burden imposed by health care expenses is not trivial, a recent USA survey found that more than half of all bankruptcy filings are the result of medical expenses; the highest out-of-pocket medical expenses were associated with a cancer diagnosis.[10]
Therefore the CHOP still remains the most widely used chemotherapy for DLBCL in Pakistan. Rituximab has never been tested in Pakistani population. In another study, there was no difference in response rate between R-CHOP and CHOP but there was a significant difference in relapse between those receiving CHOP and R-CHOP, CHOP with maintenance Rutiximab.[11]

DLBCL is the most common type of Non-Hodgkins lymphoma according to Surveillance, Epidemiology, and End Results (SEER) registries[12] DLBCL typically presents as a rapidly enlarging mass most commonly from the lymph nodes, but can also present in extranodal tissues.[13] About 40 % of patients with Non- Hodgkins lymphoma present with B type of symptoms.[14] The aggressive lymphoma like DLBCL without treatment can be fatal within months, the first major break thru in treatment occurred in when CHOP like chemothrapy resulted in disease free interval in 44 % of the patients at 3 years with few side effects.[15] When other chemotherapy regimen containing cyclophosphamide, mitoxantrone, vincristine and prednisolone CNOP when compared with CHOP, to reduce the cardiotoxic effects doxorubicin, CNOP was significantly inferior to CHOP in terms of response rates.[16] The introduction of chemosensitisors like verapamil and quinine could not increase the response rate or survival.[17] The introduction of etoposide with granulocyte colony stimulating factor (G –CSF) to CHOP could not show superior results to CHOP chemotherapy in terms of response rate or overall survival.[18] The replacement of doxorubicin with Idarubicin was tried so that cardiotoxicity of CHOP chemotherapy could be decreased but CIOP resulted in inferior response rates and the trial was closed early.[19] The CHOP therapy then became the standard till the Rituximab came into picture. The Rituximab first showed survival advantage in the landmark GELA Trial, then this was further validated in the trial done in british columbia which again showed that it increased the progression free survival and over all survival when added to CHOP based chemotherapy.[20] Further more this came at a negligible increase in the toxicity level to the pateints.[21]
Applying the result of this study, CHOP can be initiated and when Rituximab is arranged it can be incorporated with the CHOP regimen or given as a maintenance therapy as a single agent.

We looked at the response rate comparing CHOP and R-CHOP .There was no statistical difference in response rate between the CHOP and R-CHOP (p=0.715). This was in contrast to results of another study, where the response rate was also increased.[3] This may be due to the reason that the above mentioned study had an age group which was more than 60 yrs of age while we had a diverse age group, with mean age of 46.06 years standard deviation (SD) 15.63 for CHOP and mean age of 43.39 years, standard deviation (SD) 13.6 for R –CHOP. Another reason might be that we enrolled a smaller number of patients in our study so statistical significance could not be reached. Despite the results of our study showing no difference in response rates it did show statistically significant lower rate of recurrence, so R-CHOP still remains the standard of care, to be used initially for CD 20 positive DLBCL. This study showed that by addition of Rituximab to the chemotherapy CHOP there was no difference in the response rate but it did have an impact on the relapse rate and it was associated with significant decrease in the relapse of the disease.

Conclusion

Although Rituximab did not have any effect on the response rate but decreased the recurrence of the disease. Our Recommendation is to give Rituximab to all DLBCL patients, or added to CHOP whenever it becomes available, to Pakistani population.

References

1. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998; 16: 2780-95.

2. Fisher RI, Gaynor ER, Dahlberg S et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328: 1002-6.
3. Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 235-42.
4. Persky DO, Unger JM, Spier CM et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. J Clin Oncol 2008; 26: 2258-63.
5. Habermann TM, Weller EA, Morrison VA et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006; 24: 3121-7.
6. Meropol NJ, Schrag D, Smith TJ et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. J Clin Oncol 2009; 27: 3868-74.
7. Ansari SH, Irfan M, Farzana et al. In-vivo purging with the anti-CD20 antibody rituximab along with standard allogeneic peripheral blood stem cell transplantation (PBSCT) for relapsed childhood pre-B acute lymphoblastic leukaemia (ALL). J Coll Physicians Surg Pak 2006; 16: 67-8.
8. Sehn LH, Berry B, Chhanabhai M et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007; 109: 1857-61.
9. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. Eur J Cancer 2006; 42: 1031-9.
10. Kim P. Cost of cancer care: the patient perspective. J Clin Oncol 2007; 25: 228-32.
11. Habermann TM, Weller EA, Morrison VA et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006; 24: 3121-7.
12. Morton LM, Wang SS, Devesa SS et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006; 107: 265-76.
13. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998; 16: 2780-95.
14. Anderson T, DeVita VT, Jr., Simon RM et al. Malignant lymphoma. II Prognostic factors and response to treatment of 473 patients at the National Cancer Institute. Cancer 1982; 50: 2708-21.
15. Fisher RI, Gaynor ER, Dahlberg S et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328: 1002-6.
16. Magnus B, Tomas A, Anders A et al. CNOP (mitoxantrone) chemotherapy is inferior to CHOP (doxorubicin) in the treatment of patients with aggressive non-Hodgkin lymphoma (meta-analysis). Eur J Haematol 2008; 80: 477-82.
17. Gaynor ER, Unger JM, Miller TP et al. Infusional CHOP chemotherapy (CVAD) with or without chemosensitizers offers no advantage over standard CHOP therapy in the treatment of lymphoma: a Southwest Oncology Group Study. J Clin Oncol 2001; 19: 750-5.
18. Sparano JA, Weller E, Nazeer T et al. Phase 2 trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with poor-prognosis, intermediate-grade non-Hodgkin lymphoma: an Eastern Cooperative Oncology Group trial (E3493). Blood 2002; 100: 1634-40.
19. Burton C, Smith P, Vaughan-Hudson G et al. Comparison of CHOP versus CIOP in good prognosis younger patients with histologically aggressive non-Hodgkin lymphoma. Br J Haematol 2005; 130: 536-41.
20. Sehn LH, Donaldson J, Chhanabhai M et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005; 23: 5027-33.
21. Pettengell R, Linch D. Position paper on the therapeutic use of rituximab in CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. Br J Haematol 2003; 121: 44-8.