Original Article

Outcome of diffuse large B-cell lymphoma patients treated with different chemotherapeutic regimens (R-DA-EPOCH *vs* R-CHOP)

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ABSTRACT

Background: *Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of hematological malignancy of large B lymphocytes with a diffuse growth pattern. It is the most common type of adult non-Hodgkin lymphoma (NHL), making up to 30-40% of NHL. Although DLBCL is potentially curable, it remains a challenging lymphoma to manage because of the biological and clinical heterogeneity of the disease.Aim of the study was to compare the outcome of different chemotherapeutic regimens in newly diagnosed DLBCL patients.*

Methods: *This quasi-experimental study was conducted at Department ofHematology,Dhaka Medical College Hospital(DMCH) from January 2018 to June 2019 including nineteen newly diagnosed DLBCL with stage I to IV A/B cases. Protocol was approved by ethical review committee (ERC) of DMCH. Patients aged e"18 years and < 65 years were enrolled for this study and were divided into two groups as arm A treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) (10 cases) and arm B treated with rituximab plus dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-DA-EPOCH)(9 cases).*

Results: *Mean age of all patients was 41 years (range 16 to 60 years). Majority (69%) of the patients were below 50 years of age and M: F ratio was 2:1.Seventy percent of patients had Ann Arbor stage III or IV disease in R-CHOP arm and 67% in R-DA-EPOCH arm although international prognostic index (IPI) score was variable (0-4). Raised serum lactate dehydrogenase (LDH) was observed in 70% and 89% of R-CHOP and R-DA-EPOCH arms respectively. Almost 50% of patients were germinal-center B-cell-like (*GCB*) diffuse large B-cell lymphoma (*DLBCL*) in each arm.In arm A, out of ten patients, five (50%) achieved complete remission (CR), one (10%) achieved partial response(PR), three (30%) had progressive disease (PD) and overall response (OR) rate was 60%. In arm B, out of nine patients, five (56%) achieved CR, two (22%) had progressive disease (PD) and two (22%) patients died. In subgroup analysis of outcome of GCB group, there was equal CR rate in both arms(60%, p=0.57), whereas in non-GCB arm, CR was found 40% vs. 50% in R-CHOP vs. R-DA-EPOCH arm respectively (p=0.89).*

Conclusion: *From the result of this study it can be concluded that, there was no statistically significant difference in respect of outcome of chemotherapy among patients treated with R-DA-EPOCH and R-CHOP.*

Key words: *Diffuse large B-cell lymphoma, rituximab plus dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-DA-EPOCH), rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP).*

BIRDEM Med J 2022; 12(3): 188-194

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) worldwide consisting of more than one-third of patients with newly diagnosed NHL. DLBCL is an aggressive NHL that affects B-lymphocytes which play a crucial part in

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Received: December 19, 2021
Revision received: August 7, 2022
Accepted: August 23, 2022

the immune system. Although it can occur in childhood, the occurrence of DLBCL generally increases with age and most patients are over the age of 60yearsat diagnosis. A multicenter retrospective study in Bangladesh reported that NHL and Hodgkin lymphoma (HL) comprise 16.9% and 3.9 % among the hematological malignancies over a 5 years study period.[1] In another single center study of lymphoma in Bangladesh stated that DLBCL comprised 48% of all NHL among total 125 cases.[2]

DLBCL can develop in the lymph nodes or in extra-nodal sites such as the gastrointestinal tract, testes, thyroid gland, skin, breast, bone, brain or essentially any organ of the body. Despite being an aggressive lymphoma, DLBCL is considered potentially curable. The cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen is the standard of care for younger and elderly patients with DLBCL but it induces complete responses in only 40 to 50 percent of elderly patients, with three-year event-free and overall survival rates of 30 percent and 35 to 40 percent, respectively.[3,4] Intensified chemotherapy regimens may improve the outcome in young patients with a poor prognosis but they are not well tolerated by elderly patients. Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and has activity in relapsed or refractory DLBCL.[5,6]

Rituximab in combination with CHOP had a good safety profile and induced responses in over 90 percent of patients with indolent or aggressive lymphoma.[7]The German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) investigated in the non-Hodgkin lymphoma–B1 (NHL-B1) trial whether the addition of etoposide to CHOP, would improve outcome for young patients with good-prognosis aggressive lymphoma.[8]These concepts formed the basis for the dose adjusted etoposide/vincristine/doxorubicin/ cyclophosphamide/prednisolone (DA-EPOCH) regimen. The National Cancer Institute initially performed a phase II study of DA-EPOCH followed by a study of DA-EPOCH with rituximab in untreated DLBCL, both of which performed well compared to reported outcomes with CHOP and R-CHOP.[9]

Treatment outcomes for this disease in the pre-rituximab era were not satisfactory with high relapse rates. Adding rituximab to regimens improved patient prognosis and thus R-CHOP has been widely adopted since then as the standard treatment. However, there are still unresolved questions in the therapy of DLBCL. There are questions such as, is R-CHOP an optimal regimen for all patients?Historical data indicated superiority of more intense chemotherapy regimens but they have not been compared to R-CHOP directly and there is no consensus which group of patients would be benefited from intensified regimens or those with additional agents. Relatively low patient numbers are the main obstacle in conducting randomized prospective trials, so therapeutic decisions have been based mainly on retrospective studies.[10]Therefore, prospective trials that compare the outcome betweentwo regimens R-CHOP and R-DA-EPOCH are of immense importance particularly in context of Bangladesh. This study was done to assess the outcome of DA-R-EPOCH regimen in DLBCL patients in comparison to those on R-CHOP.

METHODS

Study design and patients

This quasi-experimental study was conducted at Dhaka Medical College Hospital (DMCH) in the Department of Hematology from January 2018 to June 2019 including nineteen newly diagnosed DLBCL with stage I to IV A/ B cases. Protocol was approved by ethical review committee (ERC) of DMCH. Patients of Age e"18 years and <65 years of either sex, DLBCL stage I to IVA/B and who had ability to bear cost of chemotherapy and supportive treatment were included in the study. Patients who had Eastern Cooperative Oncology Group(ECOG) performance status 3 or 4, major organ abnormality and pregnant woman were excluded from the study.Patients fulfilling the inclusion criteria were enrolled using convenient sampling and then allotted any one of the two regimen groups.

DLBCL patients with stage I to IV with or without B symptoms attending / admitted in Department of Hematology of DMCH were explained about the disease, R-CHOP and DA-EPOCH chemotherapy regimen. Total 20 patients were enrolled in the study and 10 patients in each group were selected by convenient sampling. One patient discontinued treatment.

They were diagnosed through lymph node biopsy, histopathology and immunohistochemical analysis. Patients were included for the study following proposed inclusion and exclusion criteria. An informed written consent was obtained from each patient. Detailed family history, treatment and medical history were taken with physical and clinical examination and a detailed questionnaire was filled out for each case. Clinical assessments were carried out by one examiner on all patients, focusing specifically signs of

lymphoma. All patients were assessed before starting and after completing the chemotherapy schedule. Immediately after enrolment to the study, a data sheet prepared for this study was filled up with preliminary data (particulars of the patient, detailed history, physical and laboratory findings and special investigations) by the investigator herself after informed written consent of the patient. Clinical and biochemical parameters included anti-HIV, pregnancy test(in case of female), complete blood count, s. creatinine, s. bilirubin, alanine transaminase, s. alkaline phosphatase, s. *lactate dehydrogenase*, s. albumin, electrocardiogram, echocardiography. For staging computed tomography (CT) scan of chest and abdomen and bone marrow study were done at baseline.

R-DA-EPOCH chemotherapy and R-CHOP were administered according to standard protocol.[11] Before each cycle CBC and other biochemical marker including s. creatinine, alanine transaminase, *lactate dehydrogenase*, albumin were done. Complete blood count was done on days 10-11, 14-15 and 18-19 of each cycle. To restage disease CT scan of chest and abdomen was done after cycle 3 and at the end of therapy. Bone marrow study was done atthe end of therapy. The composite data collection sheet was filled up by the principal investigator. Response evaluation through lymph node size, liver and spleen size complied with the recommendations of the Lugano Treatment Response Criteria.[11]

Statistical analysis

The data was analyzed using standard statistical procedures. The Mc. Nemar test and Paired t test were used to assess the significance of lymph node size difference before and after R-CHOP/R-DA-EPOCH chemotherapy. Data of LDH, size of the liver and spleen were expressed as Mean±SD (standard deviation). SPSS version 23 was utilized for this purpose and to cross check results. Paired t-test was done as the test of significance. Differences considered significant if the p value was less than 0.05.

RESULTS

The study included a total of 19 patients.In this study male participants were 68.4% and female participants were 31.6%. Mean age of the study population are 41 years ranging from 18 to 60 years as shown in Table I.

Table I Distribution of patients according to age (N=19)

Age (years)	Frequency	Percentage
≤20	3	15.8
21 - 30	3	15.8
31 - 40	2	10.5
41 - 50	5	26.3
51 - 60	6	31.6

The baseline characteristics of the participants are shown in Table II. Seventy percent of patients in R-CHOP group and 67% in R-DA-EPOCH group were of Ann Arbor stage III or IV. Seventy percent of patients in R-CHOP group and 89% patients of R-DA-EPOCH group had IPI score <3. Five patients (50%) in R-CHOP group were GCB type and 5 patients (56%) in R-DA-EPOCH were GCB type.

Table II Baseline characteristics of the participants (N=19)

	R-CHOP n =10 n (%)	R-DA-EPOCH n =9 n(%)	P value
Age (years)			
≤50	5 (50.0)	8 (88.9)	0.141
>50	5 (50.0)	1 (11.1)	
Gender			
Male	8 (80.0)	5 (55.6)	0.350
Female	2 (20.0)	4 (44.4)	
ABC phenotype			
GCB	5 (50.0)	5 (55.6)	0.809
Non GCB	5 (50.0)	4 (44.4)	
Ann Arbor stage			
I	1 (10.0)	0 (0.0)	
II	2 (20.0)	3 (33.3)	
III	5 (50.0)	5 (55.6)	
IV	2 (20.0)	1 (11.1)	
ECOG performance			
<2	9 (90.0)	7 (77.8)	0.466
2	1 (10.0)	2 (22.2)	
Lactate dehydrogenase level			
High (≥1.5*)	7 (70.0)	8 (88.9)	0.313
Normal	3 (30.0)	1 (11.1)	
IPI score			
<3	7 (70.0)	8 (88.9)	0.313
≥3	3 (30.0)	1 (11.1)	
Bone marrow involvement	0 (0.0)	1 (11.1)	0.474

Chi-Square test was done to measure the level of significance
* Note. Abbreviations: ABC phenotype activated B-cell-like *phenotype*; GCB, Germinal Center B-Cell like; ECOG, Eastern Cooperative Oncology Group; IPI score, International Prognostic *Index score.*

Table III shows mean albumin and lactate Dehydrogenase level between two groups of patients before and after chemotherapy. There was no significant difference between two groups. There was statistically significant (p =0.001) lymph node size reduction in R-CHOP (a) and R- DA- EPOCH (b) group (p=0.034) of patients. But there was no statistically significant difference if we compare two groups of patients. There was statistically significant spleen size reduction (p =0.001) and live size reduction (p =0.004) in R-CHOP (a) and significant spleen size reduction (p =0.010) and live size reduction (p =0.002) in R- DA- EPOCH (b) group of patients. There was no statistically significant difference if we compare two groups of patients.

Table III Albumin, lactate dehydrogenase level, lymph node, spleen and liver size of the patients before and after chemotherapy (N=19)

	R- CHOP (a) n=10			R- DA-EPOCH (b) n=9			value a vs. b
	Before chemo	After chemo	p-value	Before chemo	After chemo	p-value	(after chemo)
Albumin	34.07±5.10	32.80±12.00	0.680	30.73±9.18	34.29±4.11	0.073	0.159
LDH	566.9±332.4	273.2±83.9	0.044	497.0±156.9	236.8± 93.2	0.024	0.426
Lymph node	R- CHOP (a)n=10			R –DA-EPOCH (b)n=9			p-value a vs. b
size (cm)	Before chemo	Afterchemo	p-value	Before chemo	Afterchemo	p-value	(after chemo)
≥1.5	9 (90.0)	4 (44.4)		6 (66.7)	3 (42.9)		
<1.5	1 (10.0)	5 (55.6)		3 (33.3)	4 (57.1)		
Mean±SD	5.01±1.81	2.90±1.19	**0.001**	6.05±2.43	2.28±0.86	**0.034**	0.374
	R CHOP (a)n=10			R DAEPOCH (b)n=9			value a vs. b
	Before chemo	After chemo	p-value	Before chemo	After chemo	p-value	(after chemo)
Spleen (cm)	12.36±1.66	10.61±0.69	0.001	12.43±2.19	10.00±1.41	0.010	0.475
Liver (cm)	14.80±1.34	13.10±1.05	0.004	15.31±2.24	12.57±1.81	0.002	0.274

Paired t test was done to measure the level of significance

Table IV shows Outcome of R-CHOP and R DA-EPOCH chemotherapy. There was no statistically significant difference if we consider the outcome between these two groups of patients although overall response is better in R-CHOP group.

Table IV Outcome of R-CHOP and R DA-EPOCH chemotherapy

Outcome	Total	R-CHOP n (%)	R-DA-EPOCH n(%)	pvalue
CR	10 (52.6)	5 (50.0)	5 (55.6)	0.686
PR	1 (5.3)	1 (10.0)	0 (0.0)	
PD	5 (26.3)	3 (30.0)	2 (22.2)	
Death	3 (15.8)	1 (10.0)	2 (22.2)	

Chi-Square test was done to measure the level of significance

In GCB group, there was equal CR rate in both arms (60%, p=0.57), whereas, in non-GCB arm CR was found 40% vs. 50% in R-CHOP vs. RDA-EPOCH arm respectively (p=0.89) (Table V).

Table V Outcome of R-CHOP and R DA-EPOCH chemotherapy in GCB and non-GCB group of patients

Outcome	GCB			Non-GCB		
	R CHOP n (%)	R-DA-EPOCH n (%)	p-value	R CHOP n (%)	R-DA-EPOCH n (%)	p value
CR	3 (60.0)	3 (60.0)	0.572	2 (40.0)	2 (50.0)	0.892
PR	1 (20.0)	0		0	0	
PD	1 (20.0)	1 (20.0)		2 (40.0)	1 (25.0)	
Death	0	1 (20.0)		1 (20.0)	1 (25.0)	

Chi-Square test was done to measure the level of significance

* Note. Abbreviations: GCB, Germinal Center B-Cell like; CR, complete remission; PR, partial response; PD, progressive disease

DISCUSSION

In 2002, the first of three trials established R-CHOP as frontline standard of care for diffuse large DLBCL.[12,13]ecurrent DLBCL patients have less favorable outcome.[14] This prompted efforts to improve first-line approaches and biomarkers to identify high-risk patients. National Cancer Institute (NCI) investigators modified the CHOP regimen and developed the 96-hour infusional DA-EPOCH combination. Rationale included evidence of less tumor resistance with prolonged exposure to natural products, less cardiac toxicity with prolonged doxorubicin administration, and maximization of dose intensity by pharmacodynamic dose adjustment on the basis of each cycle's neutrophil nadir.[15] The initial DA-EPOCH study in untreated DLBCL reported a 62-month progression-free survival (PFS) rate of 70% and overall survival (OS) rate of 73%, better results than with CHOP. Rituximab was added to DA-EPOCH, resulting in a 12-month PFS rate of 85%.[16]

This study compared the outcome of R-CHOP to the more intensive R-DA-EPOCH in patients with untreated DLBCL. For this, the lymph node size, liver and spleen size of DLBCL patients were estimated to assess their response status. Nineteen eligible patients were included in the final analysis. Most of the patients in this study belonged to 51-60 years of age group (31%). In terms of age, 19.0% of patients (n = 93) were at least 70 years old and 2.6% (n = 13) were 80 years or older.[17]Another study showed that, longitudinal cohort of 80 patients with high-risk DLBCL, 52 (65%) were treated with R-CHOP and 28 (35%) received DA-R-EPOCH.Most patients (71%) were e"60 years of age.[18]

In this study, most patients had stage III or IV disease, 70.0% in R-CHOP group and 67% in R-DA-EPOCH group. Another study described that most of the patients had stage III or IV disease (74.0%).[17] In our study, 70% patients had IPI score of less than 3 in R-CHOP group and 88.9% of patients in R-DA-EPOCH group. It was described in another study that that,86.1% of their patients had IPI score of less than 4 in R-CHOP group and 79.2% of patients in R-DA-EPOCH group.[18]

In this study, all six chemotherapy cycles were completed by 90.0% of the R-CHOP and 78.0% of the DA-EPOCH-R group. Reasons for early discontinuation included disease progression (R-DA-EPOCH, 10%). Overall response (CR+PR) rate was 60% in the R-CHOP group and 56% in R-DA-EPOCH group (p=0.69). Another study stated the overall response rate was 88.0% in the R-CHOP group and 86.7% in the DA-EPOCH-R group (P = 0.67).[17] A study on R-DA-EPOCH vs. R-CHOP for high-risk Diffuse Large B- Cell Lymphoma showed complete response after mid treatment was 59.6% in R-CHOP group and 50% in R-DA-EPOCH group.[19] If we consider GCB group of patients in our study, patients receiving R-CHOP had 80% overall response rate. In R-DA-EPOCH group, response rate was 60% although that was not statistically significant. In non-GCB group of patients, patients receiving R-CHOP had 40% response rate. In R-DA-EPOCH group, response rate was 50% although that was not statistically significant.

Limitations

Sample size was small as this was a single centre study. The participants were selected by convenient sampling for intensive dose adjusted chemotherapy. PET-CT scan could not be used as a method of staging and consequent evaluation of response status.

Conclusion

From the result of this study it can be concluded that, there was no statistically significant difference in respect to outcome of chemotherapy between R-CHOP and R-DA-EPOCH groups. Similar type of study is needed with larger sample size in and multiple centers. Longer duration of follow up is needed to evaluate the survival status of the patients.

Authors' contribution: TRdrafted the protocol, collected data, did literature search, drafted the manuscript and did statistical analysis. MA performed the literature search. TA, ARB, AK, MAK helped in preparation of manuscript. All authors read andapproved the final manuscript.

Conflicts of interest: Nothing to declare.

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