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ORIGINAL ARTICLE

TOXICITIES ASSOCIATED WITH DOSE-ADJUSTED EPOCH-R COMPARED WITH R-CHOP AS FRONTLINE THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA: A STUDY CONDUCTED IN A TERTIARY LEVEL HOSPITAL OF BANGLADESH

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Abstract

Background: *Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). This is a heterogeneous group of hematological malignancy of large B lymphocytes with a diffuse growth pattern. Managing DLBCL is challenging because of the biological and clinical heterogeneity of the disease and toxicities during treatment.* ***Methods:*** *This quasi experimental study was conducted at DMCH Hematology department from January 2018 to June 2019 including nineteen, newly diagnosed diffuse large B cell lymphoma with stage I to IV A/B cases. Protocol was approved by ethical review committee (ERC) of Dhaka Medical College Hospital(DMCH). Patients fulfilling the inclusion criteria were enrolled using convenient purposive sampling and then allotted any one of the two regimen groups.* ***Results:*** *Total nineteen (19) DLBCL cases were enrolled for this study and divided into two groups as arm A treated with RCHOP(10 cases) and arm B treated with R-DA-EPOCH (9 cases) . Mean age of all patients was 41 years (range 16 to 60 Y). Among them majority (13/69%) of the patients were below 50 years of age and M: F ratio was 2:1.102 cycles of chemotherapy were administered among 20 patients. In R-CHOP group of patients, Grade 1-2 Anemia was found in 14 cycles (28.0%). In R-DA-EPOCH group Grade 1-2 Anemia was found in 14 cycles (31.1%). Grade 3-4 thrombocytopenia was found in 6 cycles (12%) in R-CHOP group. On the other hand, Grade 3-4 thrombocytopenia was found in 4(8.89%) patients in R-DA-EPOCH group. There were 4 episodes of neutropenic fever (8% of cycles) in R-CHOP group and 3 episodes (6.7% of cycles) in R-DA-EPOCH group. 8 out of 10 patients suffered from grade 1-2 anemia in R-CHOP group and 8 out of 9 patients suffered from grade 1-2 anemia. 2 out of 9 patients suffered from grade 3-4 thrombocytopenia in R-DA-EPOCH group. Grade 3-4 hemorrhage occurred in 1(10%) patient in R-CHOP group and 2 (22.2%) patients in R-DA-EPOCH group. Mucocitis (grade 1-2) was found in 5 patients (50%) in R-CHOP group and 8 cycles (88.8%) in R-DA-EPOCH group which was not statistically significant. Diarrhea (grade 1-2) was found in 2 patients (20%) in R-CHOP group and 5 patients (55.5%) in R-DA-EPOCH group. Neuropathy was found in 3 patients (30%) in R-CHOP group and 1 patient (11.1%) in R-DA-EPOCH group. Febrile neutropenia was found in 4 patients (40%) in R-CHOP group and 3 patients (33.3%) in R-DA-EPOCH group.* ***Conclusion:*** *From the result of this study it can be concluded that, Overall incidence of grade 3-4 anemia, thrombocytopenia and diarrhea was more in R-DA- EPOCH group and neuropathy was more common in R-CHOP group.*

Key words: *Diffuse large B-cell lymphoma (DLBCL), R-CHOP, R-DA-EPOCH, toxicity.*

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Introduction:

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), with an annual incidence of 3 to 4 per 100 000 persons in Europe.[1] After introduction of newer modalities of treatment, survival rates have improved over the last several decades. Most recent 5-year relative survival rate are reported as 62.0% in the United States and 55.4% in Europe.[2] 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.[3] In another single center study of lymphoma in Bangladesh stated that DLBCL comprised of 48% of all NHL among total 125 cases and 41% of those were non-Germinal Center B cell pattern with majority presented with advanced stage.[4]

The first of three trials established rituximab (R) plus CHOP (cyclophosphamide, doxorubicin,

vincristine, prednisone; R-CHOP refers to the combination regimen) as frontline standard of care for diffuse large B-cell lymphoma (DLBCL) was done in 2002.[5,6] The 3-year event-free survival (EFS) rate ranged from 53% in patients age 60 years or older with high-risk features to 79% in patients 18 to 60 years old with a low-risk International Prognostic Index (IPI).[7] Less favorable outcomes for patients with recurrent DLBCL prompted efforts to improve first-line approaches and biomarkers to identify high-risk patients.[8]

National Cancer Institute (NCI) investigators modified the CHOP regimen and developed the 96-hour infusional dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (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.[9] 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 Progression-free survival (PFS) rate of 85%.[9,10] A phase II, multicenter trial of DA-EPOCH-R in DLBCL by Cancer and Leukemia Group B (CALGB) confirmed the regimen could be safely and accurately administered in community settings A phase III trial comparing R-CHOP with DA-EPOCH-R in frontline therapy of DLBCL was coordinated by CALGB (now part of the Alliance for Clinical Trials) and activated in 2005.[11]

Relatively low patient numbers are the main obstacle in conducting randomized prospective trials, so therapeutic decisions have been based mainly on retrospective studies. [12]Furthermore, neither data on DLBCL patients in the South East Asian Region on this new regimen R-DA-EPOCH is available nor is its toxicity. Therefore, prospective trials that compare the two regimens R-CHOP and R-DA-EPOCH are of immense importance at this time. This study was done to assess the toxicity of dose-adjusted R-EPOCH regimen in DLBCL patients in comparison to those on R-CHOP.

Methods:

Study Design

This quasi experimental study was conducted at Hematology department of Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh from January 2018 to June 2019 including nineteen, newly diagnosed diffuse large B cell lymphoma 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 both gender, 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 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 purposive sampling and then allotted any one of the two regimen groups.

Study Procedure

DLBCL patients with stage I to IV with or without B symptoms attending / admitted in department of Hematology of Dhaka Medical College & Hospital 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 purposive sampling. The response was non evaluable in 1 patient due to treatment discontinuation.

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),CBC, S. Creatinine, S. bilirubin, Serum(SGPT), S. Alkaline phosphatase, S. LDH,S. Albumin, ECG, Echocardiography. For staging CT scan of chest and abdomen and Bone marrow study were done at baseline.

Dose-adjusted R-DA-EPOCH chemotherapy and R-CHOP were administered according to standard protocol (Wilson et al., 2008) David Cunningham et al. 2013). Before each cycle CBC and other biochemical marker including S. Creatinine, SGPT, LDH (Lactase Dehydrogenase), Albumin were done.CBC 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 end of therapy. Bone marrow study was done at end of therapy. The composite data collection sheet was filled up by the principal investigator.

Any adverse event considered to be related to chemotherapy was recorded during the follow up assessment in the data collection sheet. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 3. **(**Williams et al., 2003).

Statistical analysis

Data was collected on proposed data sheets (attached hereby as Appendices) and was also recorded in digital formats for security and convenience for analysis. The data was analyzed using standard statistical procedures. SPSS version 23 was utilized for this purpose and to cross check results. Fisher's Exact test was done to see the incidence of toxicity among participants. Paired t-test was done as the test of significance. Differences considered significant if the *p* value was less than 0.05.

Results:

Total 20 patients were enrolled in the study and 10 patients in each group were selected by purposive sampling. The response was non evaluable in 1 patient due to treatment discontinuation.

Distributions of patients according to age are shown in table 1. Thirteen (69%) of the patients were below 50 years of age. Mean age of the study population is 41 years ranging from 18 to 60 years.

Table I

Distribution of patients according to age (n=19)

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

Figure 1 shows distributions of patients according to sex. In this study male participants were 68.4% and female participants were 31.6%.

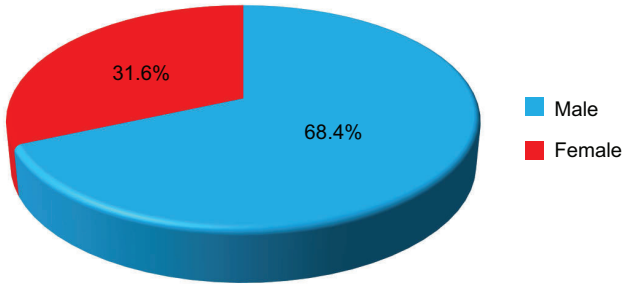

Fig.-1: *Pie chart of the patients according to gender*

The baseline characteristics of the participants are shown in table 2. Thirteen patients were male and 6 patients were female. 70% patients in R-CHOP group and 67% in R-DA-EPOCH group were at Ann Arbor stage III or IV. 70% patients in R-CHOP group and 89% patients of R-DA-EPOCH group had IPI score <3. 70% patient had serum *Lactate dehydrogenase* (LDH) level above normal range in R-CHOP group. 89% patients of R-DA-EPOCH group had LDH above normal level. No patient with CNS involvement or having non-measured lesion at diagnosis was included. Five patients (50%) in R-CHOP group were GCB type and 5 patients (56%) in R-DA-EPOCH were GCB type. Five patients (50%) in R-CHOP group were non GCB type and 4 patients (44%) in R-DA-EPOCH were non GCB type.

102 cycles of chemotherapy were administered among 20 patients. The median number of cycles administered per patient was (range 1-6). Treatment was discontinued in three patients due to death (n=3). One patient died at home after 2nd cycle, one patient died after 1st cycle due to progressive disease and one patient died of acute myocardial infarction after 3rd cycle. Most patients (84%) received 6 cycles of chemotherapy. Four patients receiving R-DA-EPOCH required dose escalation to achieve ANC nadir below 0.5 × 10y /l. Treatment was deescalated in 2 patients.

Table-II

The 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)	
LDH 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 marrowin volvement	0 (0.0)	1 (11.1)	0.474

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

Table-III

Incidence of major toxicities in the participants in 102 cycles

	R-CHOP n (%)	R-DA-EPOCH n (%)	p-value
Anaemia			
Grade 1 -2	14 (28.0)	14 (31.1)	0.298
Grade 3 -4	1 (2.0)	5 (11.1)	
Thrombocytopenia			
Grade 1 -2	2 (4.0)	0 (0.00)	0.773
Grade 3 -4	6 (12.0)	4 (8.89)	
Neuropathy	3 (6.0)	1 (2.2)	0.582
Hemorrhage (G 3-4)	1 (2.0)	4 (8.9)	0.141
Febrile neutropenia	4 (8.0)	3 (6.7)	0.876
Infection with normal ANC	8 (16.0)	8 (17.8)	0.920
Mucocitis			
Grade 1 -2	5 (10.0)	11 (24.4)	0.267
Grade 3 -4	2 (4.0)	0 (0.0)	
Diarrhoea			
Grade 1 -2	2 (4.0)	4 (8.9)	0.610
Grade 3 -4	0 (0.0)	1 (2.2)	
Death during treatment	1 (2.0)	2 (4.4)	0.582

Fisher's Exact test was done

Table III shows, in R-CHOP group of patients, Grade 1-2 Anemia was found in 14 cycles (28.0%). In R-DA-EPOCH group Grade 1-2 Anemia was found in 14 cycles (31.1%). Grade 3-4 thrombocytopenia was found in 6 cycles (12%) in R-CHOP group. On the other hand, Grade 3-4 thrombocytopenia was found in 4(8.89%) cycles in R-DA-EPOCH group. There were 4 episodes of neutropenic fever (8% of cycles) in R-CHOP group and 3 episodes (6.7% of cycles) in R-DA-EPOCH group. Most of them were hospitalized, treated with broad spectrum antibiotic and other supportive management. Only patient who died of neutropenic fever, source of infection couldn't be confirmed. Blood culture was negative in all the cases. Most common first line antibiotic was cefepime (2gm intravenously 8 hrly). Second line antibiotics were meropenem (1 gm intravenosuly 8 hourly), with or without amikacin (500 mg intravenously 12 hourly), Common third line choice was the combination antibiotic tazobactum +piperacilin.

Table IV shows, grade 3-4 anemia was found in 1 patient (10%) in R-CHOP group. Grade 3-4 anemia was found in 1 patient (11.1%) in R-DA-EPOCH group. 8 out of 10 patients suffered from grade 1-2 anemia in R-CHOP group and 8 out of 9 patients suffered from grade 1-2 anemia. They were treated with transfusion of red cell concentrate. 2 out of 9 patients suffered from grade 3-4 thrombocytopenia in R-DA-EPOCH group. Grade 3-4 hemorrhage occurred in 1(10%) patient in R-CHOP group and2 (22.2%) patients in R-DA-EPOCH group. One patient developed hematuria. He was treated with apheretic platelet transfusion. Rest of the patients who developed grade-3 thrombocytopenia recovered spontaneously.

Table III shows, mucocitis (grade 1-2) was found in 5 cycles (10%) in R-CHOP group and 11 cycles (24.4%) in R-DA-EPOCH group which was not statistically significant. Diarrhea (grade 1-2) was found in 2 cycles

(4%) in R-CHOP group and 4 cycles (8.9%) in R-DA-EPOCH group. Neuropathy was found in 3 cycles (6%) in R-CHOP group and 1 cycle (2.2%) in R-DA-EPOCH group which was not statistically significant.

Table IV shows, mucocitis (grade 1-2) was found in 5 patients (50%) in R-CHOP group and 8 cycles (88.8%) in R-DA-EPOCH group which was not statistically significant. Diarrhea (grade 1-2) was found in 2 patients (20%) in R-CHOP group and 5 patients (55.5%) in R-DA-EPOCH group. Neuropathy was found in 3 patients (30%) in R-CHOP group and 1 patient (11.1%) in R-DA-EPOCH group. Febrile neutropenia was found in 4 patients (40%) in R-CHOP group and 3 patients (33.3%) in R-DA-EPOCH group.

Table IV

Incidence of major toxicities in the participants (N=19)

	R-CHOP n=10 n(%)	R-DA-EPOCH n=9 n(%)	p-value
Anaemia (grade 3 -4)			
Grade 1 -2	8 (80.0)	8 (88.8)	0.454
Grade 3 -4	1 (10.0)	1 (11.1)	
Thrombocytopenia			
Grade 1 -2	1 (10.0)	3 (33.3)	0.698
Grade 3 -4	0 (0.0)	2 (22.2)	0.414
Neuropathy	3 (30.0)	1 (11.1)	0.582
Hemorrhage (G 3-4)	1 (10.0)	2 (22.2)	0.141
Febrile neutropenia	4 (40.0)	3 (33.3)	0.876
Infection with normal ANC	8 (80.0)	8 (88.8)	0.656
Mucocitis			
Grade 1 -2	5 (50.0)	8 (88.8)	0.389
Grade 3 -4	2 (20.0)	0 (0.0)	
Diarrhoea	2 (20.0)	5 (55.5)	0.610
Death during treatment	1 (10.0)	2 (22.2)	0.582

Fisher's Exact test was done

Discussion:

In 2002, the first of three trials established rituximab (R) plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP refers to the combination regimen) as frontline standard of care for diffuse large B-cell lymphoma (DLBCL).[13,14] Recurrent DLBCL patients have less favorable outcomes.[15] 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 dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (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.[16] 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.[11] Rituximab was added to DA-EPOCH, resulting in a 12-month PFS rate of 85%.[16]

This study compared the toxicity of R-CHOP to the more intensive R-DA-EPOCH in patients with untreated DLBCL. 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 described that,longitudinal cohort of 80 patients with high-risk DLBCL,52 (65%) were treated with R-CHOP and 28 (35%) received DA.REPOCH. Most patients (71%) were e"60 years of age. In this study, most patients had stage III or IV disease, 70.0% in R-CHOP group and 67% in R-DA-EPOCH group.[18] 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. A study stated 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.[19]

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%). There was no statistically significant difference in toxicity between R-CHOP and R-DA-EPOCH group including grade 1-2 anemia(80% v 88%, respectively), grade 3-4 anemia(10% v 11%, respectively), febrile neutropenia(40% v 33%, respectively), thrombocytopenia grade 1-2(10% v 33%, respectively), hemorrhage(10% v 22%, respectively), neuropathy(30% v 11.1%, respectively), mucositis(70% v 89%, respectively), diarrhea(20% v 56%, respectively). Thrombocytopenia and diarrhea were more common in R-DA-EPOCH group and neuropathy was more common in R-CHOP group although that was not statistically significant. One patient died

(10%) in R-CHOP group and 2 patients (22%) died in R-DA-EPOCH group. A study concluded that, grade 3 and 4 adverse events were more common (P <0.001) in the DA-EPOCH-R arm than the R-CHOP arm, including infection (16.9% v 10.7%, respectively), febrile neutropenia (35.0% v 17.7%, respectively), mucositis (8.4% v 2.1%, respectively), and neuropathy (18.6% v 3.3%, respectively). Five treatment-related deaths (2.1%) occurred in each arm in the same study.[17]

Another study described that, on retrospective analysis, treatment of patients with high-risk DLBCL with DA.R-EPOCH resulted in similar clinical outcomes, but was associated with increased incidence of grade 3/4 neutropenia and need for transfusions during treatment when compared to those receiving R-CHOP regimen.[19]The more intensive, infusional DA-EPOCH-R was more toxic and did not improve progression free survival (PFS) or overall survival (OS) compared with R-CHOP. The more favorable results with R-CHOP compared with historical controls suggest a potential patient selection bias and may preclude generalizability of results to specific risk subgroups.[17]

A longitudinal cohort of 95 patients was included in a study. All standard risk DLBCL (N=15) patients were treated with R-CHOP. Eighty patients with high-risk DLBCL were treated with R-CHOP (N= 52, 65%) and DA.R-EPOCH (N= 28, 35%) respectively. DA.R-EPOCH cohort had more patients with higher Ann Arbor stage. Rate of treatment completion and complete response rate at the end of treatment were similar in both groups. DA.R-EPOCH was associated with increased grade 3/4 neutropenia and need for transfusions during treatment. The median follow up was 13.3 months and 10.9 months for DA.R-EPOCH and R-CHOP group respectively. Patients receiving DA.R-EPOCH regimen had more adverse features in terms of disease stage and phenotype. A prospective randomized comparison is warranted between these two regimens for high-risk DLBCL. Until such prospective studies show benefit in any sub-set of DLBCL, DA.R-EPOCH should be used with judicious clinical discretion.[18] Another study stated that, the rates of treatment completion and CR, as well as the overall incidences of grade e"3 neutropenia, neuropathy and unplanned hospitalizations were similar between the two treatment groups.Patients treated with DA.R-EPOCH required more red cell transfusions (p = 0.004)[19]

Conclusion:

The present study was done to compare the toxicity of R-CHOP and R DA-EPOCH chemotherapy in newly diagnosed DLBCL patients. From the result of this study it can be concluded that, Overall incidence of grade 3-4 anemia, thrombocytopenia and diarrhea was more in R-DA- EPOCH group and neuropathy was more common in R-CHOP group. Similar type of study with larger sample size and multi centered with longer duration of follow up to evaluate the survival status of the patients is needed.

Limitations:

Sample size was small due to time and financial constraint of the patients. As the participants were selected by purposive sampling for intensive dose adjusted chemotherapy, clinical characteristics matched control group was not available.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study.

Funding:

No specific funding was received for this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained

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