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A Study of Dose-Adjusted EPOCH Chemotherapy in Diffuse Large B-Cell Lymphoma

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Abstract

Background: Worldwide, diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma (NHL), accounting for 30%-40% of all newly diagnosed cases. The response rate to currently available chemotherapy in DLBCL is much unsatisfactory. Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) was developed in an effort to improve outcome in patients with diffuse large B-cell lymphoma. To assess the efficacy and safety of DA-EPOCH chemotherapy in patients with diffuse large B-cell lymphomas. **Material & Methods:** This quasi experimental study was conducted in the department of Hematology, DMCH, from January 2016 to December 2017. 20 patients with diffuse large B-cell lymphomas were treated with etoposide, vincristine, and doxorubicin for 96 hours with bolus doses of cyclophosphamide and oral prednisone (DA-EPOCH chemotherapy). The doses of etoposide, doxorubicin and cyclophosphamide were adjusted to achieve a nadir absolute neutrophil count below 0.5× 109/L. Cycles were repeated after 21 days. After 3rd and 6th cycle patients were evaluated for interim analysis and response evaluation respectively. Evaluation was done in aspect of clinical parameter (lymph node size, physical complaint), laboratory parameter (CBC) and radiological imaging (CT scan of chest and abdomen). The median age of the patient was 46.5 years (range, 25-62 years); 20% were older than 50 years; and 25% were at high-intermediate risk according to International Prognostic Index (IPI) criteria. The statistical analyses were done by appropriate methods. **Results:** There was a complete response in 73.7% of patients and partial response 10.5% of patients, which were evidenced by significant reduction of size of the lymph nodes after chemotherapy. The mean Serum LDH was also significantly lower after chemotherapy in comparison to before chemotherapy in those patients who achieved complete or partial response. Moreover, size of the liver and spleen were significantly lower after chemotherapy in response group patients who had either hepatomegaly or splenomegaly or both. Doses were escalated in 12.50% cycles and toxicity levels were acceptable. **Conclusion:** DA-EPOCH chemotherapy is an effective regimen for treatment of diffuse large B-cell lymphoma patients.

Keywords:- Diffuse large B-cell lymphoma patients, DA-EPOCH chemotherapy regimen, and toxicity.

INTRODUCTION

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of systemic non-Hodgkin lymphoma (NHL).[1] It typically presents as an aggressive behaving lymphoma. The most commonly used initial therapy is cyclophosphamide, doxorubicin,

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vincristine and prednisone (CHOP). Unfortunately, with standard CHOP therapy, only one third of patients remain free of progressive disease at 5 years.[2] Over the past 50 years, efforts to improve chemotherapy strategies for diffuse large B-cell lymphoma have met with limited success.[3] While modifications of CHOP chemotherapy led to modest improvements in outcome, these were generally overcome by the addition of rituximab.[4,5] The basis for these strategies have generally come from the hypothesis that 'non cross resistant' drugs and dose intensity will overcome drug resistance, but this has not generally been borne out.[6,7] Evidence today indicates that treatment failure depends on a complex interplay of factors including tumor biology, tumor volume, pharmacokinetics, and pharmacogenomics.[6] It was hypothesized that continuous drug exposure may modulate the effects of the cell cycle and apoptosis on treatment response. In this regard, studies have suggested that tumor proliferation is an adverse prognostic factor with bolus regimens such as CHOP and possibly rituximab plus CHOP (R-CHOP), while in vitro studies suggest that extended drug exposure may enhance cell kill.[8,9,10] This concept formed the basis for dose-adjusted (DA) EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) where doxorubicin, vincristine and etoposide are infused over 96 hours.[11] Because the efficacy of infusional schedules are constrained by sub threshold steady-state concentrations, below which a drug is ineffective, pharmacodynamics dosing based on the neutrophil nadir was incorporated. A phase II study of DA-EPOCH with filgrastim in 50 patients with untreated de novo DLBCL revealed promising results.[11] The present study is designed to see the outcome produced by DA-EPOCH in DLBCL.

Objectives

General Objective

To evaluate the outcome of DA-EPOCH chemotherapy in DLBCL patients at the end of therapy.

Specific Objectives

- To assess the size of the target nodes and nodal masses for response status of DLBCL patients after completion of da-EPOCH chemotherapy.
- To assess the size of liver and spleen of DLBCL patients after completion of da-EPOCH chemotherapy.
- To assess the bone marrow infiltration. To observe da-EPOCH chemotherapy related toxicity in DLBCL patients.

MATERIAL AND METHODS

It was a prospective interventional study. The patients selected by purposive sampling method. 20 consecutive patients were included for the study. The study was enrolled between July 2016 and June 2017. The patients of diffuse large B cell lymphoma with stage IIB to IV A/B. The study conducted at Department of Hematology of Dhaka Medical College Hospital (DMCH) Dhaka, Bangladesh.

Inclusion Criteria

- Age ≥18 years and <65 years of both gender
- DLBCL stage IIB to IVA/B
- Informed written consent
- Ability to bear cost of chemotherapy and supportive treatment

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Exclusion Criteria

- Disease stage I or IIA
- ECOG status 3 or 4
- Major organ abnormality
- HIV patients,
- Pregnant woman.

Study Procedure

DLBCL patients with stage IIB to IV attending / admitted in department of Hematology of Dhaka Medical College & Hospital or their guardians were explained about the disease and DA-EPOCH chemotherapy regimen. They were diagnosed through lymph node biopsy, histopathology and immunohistochemical analysis. A total of 20 consecutive patients were included for the study following proposed inclusion and exclusion criteria. After informed written consent of the patient or patient's guardian, all patients were analyzed before starting and after completing the chemotherapy schedule. Clinical and biochemical parameters included Anti-HIV, pregnancy test, CBC, S. Creatinine, S. bilirubin, SGPT, S. Alkaline phosphatase, S. LDH, S. Albumin, ECG, Echocardiography. For staging CT scan of chest and abdomen and Bone marrow study was done at baseline. Dose-adjusted EPOCH chemotherapy was administered. [11] Dose adjustment is a fundamental component of EPOCH regimen. Adjustment above the starting dose level always applied to etoposide, doxorubicin and cyclophosphamide. Pharmacodynamic dose adjustment was based on complete blood counts. ANC nadir in the previous cycle was designed to achieve a shallow period of neutropenia. If platelet nadir value below $25x10^9$ / L was observed, doses were reduced 20% regardless nadir ANC. All patients received granulocyte colony-stimulating factor (G-CSF) beginning on day 6 and continued until the ANC was more than 5 x 10^9 /L above the nadir level or pegfilgrastim 6mg/day on D 6. Cycles began every 21 days, providing that the ANC was at least 1 x 10^9 /L and the platelet count is at least 100 x 10^9 /L. After discharge from the hospital the patients were followed up at lymphoma clinic like (OPD) and got treatment accordingly.

RESULTS

This study was executed to see efficacy and safety of DA-EPOCH chemotherapy in DLBCL patients. Twenty patients of DLBCL were enrolled between July 2016 and June 2017. The response was non-evaluable in 1 of 20 patients due to treatment discontinuation. When analyzed in evaluable patients Fourteen patients (73.7%) achieved CR, which was evidenced by significant reduction of target nodes or nodal masses to ≤1.5 cm (p value <0.001 at 95% confidence interval), also liver and spleen size regressed to normal size wherever enlarged. Two patients (10.5%) achieved PR, evidenced by ≥50% decrease of target nodes and liver size, also spleen regressed by >50% in length beyond normal. Three patients had progressive disease (PD) evidenced by appearance of new lymph nodes of >1.5 cm. Overall response rate was 84.2%. 112 cycles of chemotherapy were administered among 20 patients. Treatment was discontinued in two patients due to disease progression (n=1) after 3rd cycle of chemotherapy and death (n=1) resulting from infection grade 4 event. 10 (12.5% cycles) required dose escalation to achieve ANC nadir below 0.5 × 10^9 /l. Most patients (90%) received 6 cycles of DA-EPOCH. Treatment was deescalated 2 patients. Toxicity was assessed

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over 112 cycles. Anemia was found in 11 cycles (9.8%). 9 out of 20 patients suffered from grade 3-4 anemia. They were treated with transfusion of red cell concentrate. Grade 3-4 thrombocytopenia was found in 8 cycles (7.14%). 6 out of 20 patients suffered from thrombocytopenia including only one who had grade 4 thrombocytopenia. Hemorrhage grade 3-4 occurred in one patient. He developed hematuria and epistaxis. He was treated with apheretic platelet transfusion. Rest of the patients who developed grade-3 thrombocytopenia recovered spontaneously. There were 7 episodes of neutropenic fever (6.25% of cycles) in 6 patients (30%). Most of them were hospitalized, treated with broad spectrum antibiotic and other supportive management. Only patient who died of neutropenic fever, source of infection couldnot 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. Infection without neutropenia occurred in 3 cycles. DA-EPOCH had to be discontinued in 2 of 20 patients. One patient died from neutropenic sepsis after 1st cycle of chemotherapy and the other patient had progressive disease after 3rd cycle of chemotherapy, underwent salvage chemotherapy.

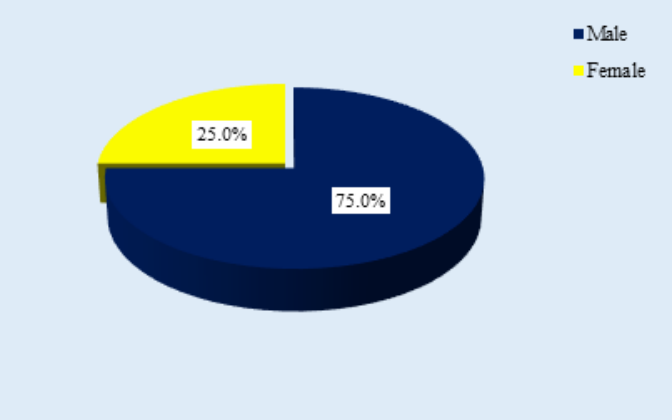

Figure 1: Pie chart shows the patients according to gender(N=20)

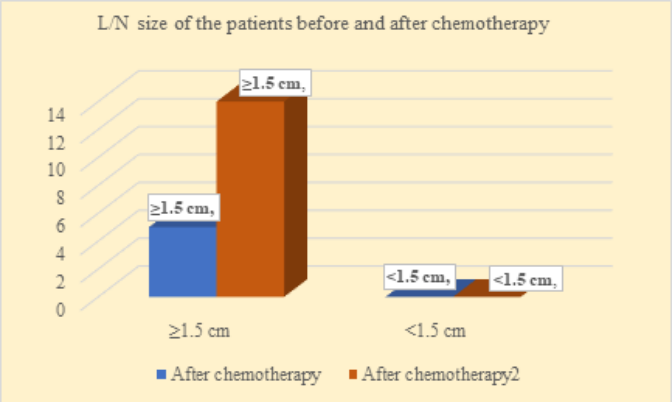

Figure 2: L/N size wise before and after chemotherapy patients Distribution(n=19)

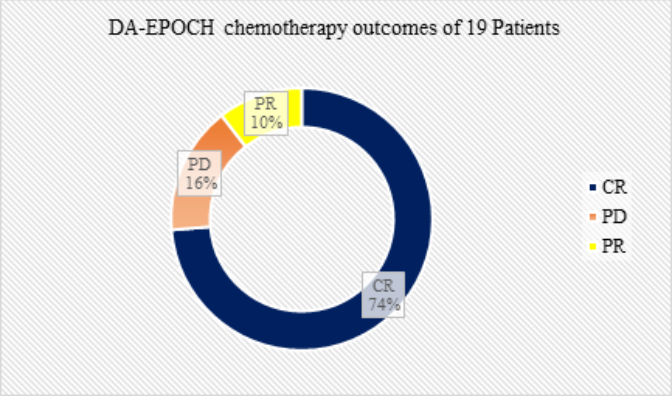

Figure 3: Figure shows outcome among 19 patients of DA-EPOCH chemotherapy.

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Table 1: Distribution of patients according to age (N=20)

Age (years)	Frequency (n)	Percentage (%)
25 - 34 yrs.	4	20.0
35 - 44 yrs.	5	25.0
45 -54 yrs.	8	40.0
≥ 55 yrs.	3	15.0

Table 2: L/N size of the patients before and after chemotherapy (n=19)

Before chemotherapy	After chemotherapy	After chemotherapy	P value
	≥ 1.5 cm	<1.5 cm	
≥1.5 cm	5	14	<0.001
<1.5 cm	0	0	

The mean (±SD) initial liver size of patients was 15.86±2.30 (cm) and after chemotherapy was 13.13±1.17 (cm). Also the mean (± SD) initial spleen size of patients was 15.30 ± 3.92 (cm) and after chemotherapy was 10.12±1.67 (cm). Both liver and spleen size were significantly lower (p<0.001) after chemotherapy.

Table 3: Spleen size and liver size of the patients before and after chemotherapy (n=19)

	Before chemo	After chemo	P value
Spleen (cm)	15.30 ± 3.92	10.12 ± 1.67	<0.001
Liver (cm)	15.86 ± 2.30	13.13 ± 1.17	<0.001

Table 4: Major toxicities of DA-EPOCH chemotherapy to the patients. (N=20)

Toxicity	Cycles (n)	Cycles (%)	Patients (n)	Patients (%)
Anemia grade 3-4	11	9.8	9	45
Thrombocytopenia grade 3-4	8	7.14	6	30
Hemorrhage grade 3-4	1	0.9	1	5
Febrile neutropenia	7	6.25	6	30
Infection without neutropenia	3	2.7	3	15
Mucositis Grade 3-4	2	1.78	2	10
Diarrhoea Grade 3-4	1	0.9	1	5
Death during treatment	1	0.9	1	5

DISCUSSION

Using majority of the currently available chemotherapeutic combinations, treatment of aggressive non-Hodgkin's lymphoma remains largely unsatisfactory.[12] Efforts to enhance therapy of aggressive lymphomas have included adding more drugs, increasing dose intensity, using non-cross resistant combinations, high dose therapy with bone marrow support and continuous infusion schedules such as EPOCH and the CODBLAM regimen. The earlier one was based on biochemical and genetic evidence that one of the mechanisms of resistance to chemotherapy is increased expression of the MDR gene and its

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products, and that tumor cells overexpressing MDR in culture display relatively less resistance to prolonged exposure of lower concentrations of chemotherapy.[13] In the beginning DA-EPOCH was developed and used as the first line treatment for DLBCL patients at the US National Cancer Institute, with the CR rate of 92%.[11] A Spanish group used R-DA-EPOCH for the treatment of poor prognosis DLBCL patients, which results a CR 80.6%.[14] Recently another group from Spain achieved complete response and partial response 80.2% and 9.8% respectively, in R-DA-EPOCH treated patients with DLBCL.[15] Another study from Egypt reported 50% CR rate in EPOCH treated patients with DLBCL.[16] In a phase II study using EPOCH in the 74 patients with intermediate-or high grade relapsed non-Hodgkin's lymphoma, 27% of case achieved a CR and 42% a PR.[17] However, the CR rate of previous studies compared to that of last two studies might be explained, in their study, by the use of a dose-escalating schedule permitting higher dose intensity of each of the four chemotherapeutic agents included in EPOCH regimen. The present study was undertaken to assess the efficacy and safety of DA-EPOCH chemotherapy in diffuse large B-cell lymphoma. For this the lymph node size, liver and spleen size of DLBCL patients were estimated to assess their response status. In this study DA-EPOCH chemotherapy appears to be an effective regimen in DLBCL patients in terms of achieving complete response. Most patients received all planned chemotherapy cycles. We observed a high CR rate (73.7%), PR rate (10.5%) and ORR (84.2%) with tolerable toxicity. These findings are comparable with another study with the same regimen although much higher follow up period assessed.[18] Grade 3-4 hematological toxicities with DA-EPOCH regimen in this study were anemia (45% of the patient) in 9.8% of cycles, thrombocytopenia (30%) in 7.14 % of cycles, and febrile neutropenia (30%) in 6.25% of cycles. Hemorrhage grade 3-4 occurred in 5% patient only in one patient. Infection without neutropenia occurred in 15% (2.7% cycles) of the patient. One patient died from neutropenic sepsis during treatment. Among the non-hematological toxicities gastrointestinal toxicity were mostly mild nausea, vomiting, and diarrhea. Mucositis grade 3-4 occurred in 10% patients during last cycles. On the other hand toxicities (grade 3-4) with DA-EPOCH regimen in other study were anemia 18%, thrombocytopenia 17% and febrile neutropenia 18% of cycles. This discrepancy might be explained, in their study dose escalation occurred in higher number of cycles resulting higher dose intensity of chemotherapeutic agents. The proportion of patients at high-intermediate to high risk in this study (25%) was close to a previous study with similar protocol (31.6 %).[19] Those investigators also revealed outcome differences based on IPI score. But this association could not be shown in this study.

Limitations of the Study

There are some limitations in this study, namely, small sample size, absence of a control group. As the participants were selected by purposive sampling for intensive dose adjusted chemotherapy clinical characteristics matched control group was not available. PET-CT scan could not be used as a method of staging and consequent evaluation of response status.

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CONCLUSIONS

The present study was done to reveal the outcome of dose-adjusted EPOCH chemotherapy in diffuse large B-cell lymphoma. From the result of this study it can be concluded that, DA-EPOCH represents an effective therapeutic regimen in DLBCL patients. In this study the overall response rate is 84.2% ($p<0.001$). However, to provide evidence for the superiority of this regimen may be tried in future randomized phase III trials. For further study following recommendations are proposed- Similar types of study on larger sample size in multi institution using a control group and immunotherapy in all appropriate cases. Longer duration of follow up to evaluate the survival status of the patients.

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