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Dose-Adjusted R-EPOCH Therapy for Aggressive Lymphoma: A single center experience

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Abstract

Objective: In this study, Dose-Adjusted R-EPOCH Therapy for Aggressive Lymphoma has been investigated. According to our study, when we look at diffuse large B-cell lymphomas, 5-7% are double hit lymphoma, 30-40% are double expressor lymphoma and 5-10% are triple hit lymphomas and they have an aggressive course. In our study, the efficacy of the dose-adjusted-R-EPOCH treatment regimen in the treatment of double-hit lymphoma, double expressor lymphoma, triple hit lymphoma; triple expressor lymphoma and primary large B cell lymphomas of the mediastinum are presented.

Materials and Methods: Thirty-six patients diagnosed with B-cell lymphoma who received dose-adjusted R-EPOCH treatment were included in the study. The patients were grouped cytogenetically according to the Bcl-2 and Bcl-6 rearrangement by MYC translocation. Response assessment with PET-CT was performed in patients whose planned therapy reached the number of cycles.

Results: At the end of the treatment, 61% of the patients had a complete response, 3% had a partial response, and 8% had no response. During the follow-up, 9 of the patients died and while the treatment of 2 patients was still ongoing, the treatment regimen of 1 patient was changed. When the patients were evaluated, 2 had double-hit lymphoma (complete response in 2 patients), 9 had double expressive lymphoma (5 patients had a complete response, 2 patients had progressed disease, 1 patient died and 1 patient had a change in treatment), and 8 had triple expressor lymphoma (Complete response in 5 patients, death in 2 patients, and progressive disease in 1 patient).

Conclusion: The dose-adjusted-R-EPOCH treatment regimen can also provide a high response rate in patients with lymphoma with a triple expressor cytogenetic subtype.

Keywords: Aggressive lymphoma, DA-R-EPOCH, double expressor lymphoma, double hit lymphoma, triple expressor lymphoma.

Introduction

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of patients diagnosed with Non-Hodgkin lymphoma (NHL) and is the most common histological subtype of NHL. It is an aggressive NHL (1). Limited stage disease (stage I or stage II according to Ann Arbor staging system) constitutes 30-40% of DLBCL and its treatment is combined therapy consisting of chemotherapy, recombinant anti-CD20 antibody rituximab and radiotherapy in case of a bulky mass. Advanced stage disease (stage III or IV according to Ann Arbor staging system) accounts for 60-70%. Advanced stage DLBCL should first be treated with chemotherapy and rituximab (2). In order to treat patients with a diagnosis of NHL in the best way, it is necessary to know the exact histological subtype, the extent of the disease, as well as its molecular cytogenetic characteristics.

In patients diagnosed with DLBCL, MYC translocation, B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma 6 (Bcl-6) rearrangement evaluates by fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC). In the World Health Organization's 2016 classification of mature B-cell neoplasms, high-grade B-cell lymphoma was defined as the accompanying Bcl-2 and / or Bcl-6 rearrangement in addition to MYC translocation. Double hit lymphoma (DHL); it has been defined as the presence of Bcl-2 or Bcl-6 rearrangement in addition to MYC translocation by FISH method (3). The presence of Bcl-2 and Bcl-6 rearrangement in addition to MYC translocation was defined as triple hit lymphoma (THL) (4). Although the frequency of DHL is stated between 3-32% in case series, its actual frequency is between 5-10%.

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Compared to other DLBCL subtypes, patients with DHL have a much higher rate of lactate dehydrogenase (LDH) levels, central nervous system involvement, high international prognostic index (IPI) values, and extra nodal involvement (5). If the standard R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) treatment regimen is administered to patients with DHL, it will result in higher than expected relapse, worse progression-free survival, and lower response rates. Therefore, patients with DHL are candidates for a more aggressive treatment regimen, DA-R-EPOCH regimen (dose adjusted Rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin). Primary large B-cell lymphoma of the mediastinum (PMLBCL) is a rare NHL subtype. PMLBCL is an aggressive tumor originating from thymic-medullary B cell in the mediastinum. Patients were presented with a locally invasive anterior mediastinal mass that often spreads to local structures. The DA-R-EPOCH treatment regimen is recommended in the first step in the treatment of PMLBCL (6). Double expressor lymphoma (DEL) is defined as the detection of both MYC translocation and Bcl-2 or Bcl-6 rearrangement by the IHC method. It has been reported to constitute approximately 30-40% of all DLBCL patients (3). Triple expressor lymphoma (TEL) is defined as the demonstration of Bcl-2 and Bcl-6 rearrangement in addition to MYC translocation by the IHC method (7). DA-R-EPOCH is recommended for first-line therapy in patients with DHL, THL, and PMLBCL. However, there is no consensus on the use of DA-R-EPOCH in patients with DEL and TEL. In this study, we aimed to share the single-center experience of our patients who received the DA-R-EPOCH regimen.

Material and Methods

Study design and population

A total of 36 patients with a diagnosis of NHL who received a DA-R-EPOCH treatment regimen in the Department of Medical Oncology of Cukurova University Faculty of Medicine Balcalı Hospital between 2016 and 2018, which was showed in Table 1.

Demographic data of 36 patients included in the study were analyzed. In addition, NHL subtypes, beta-2 microglobulin levels, presence of B symptoms, lactate dehydrogenase (LDH) levels, ki67 proliferation index, National comprehensive cancer network-international prognostic index (NCCN-IPI) score, Eastern Cooperative Oncology Group Performance Status (ECOG PS), according to extra-nodal organ involvement, bone marrow involvement, stages according to Ann-Arbor staging system, sedimentation levels, development of neutropenia during treatment, MYC translocation, Bcl-2 and Bcl-6 rearrangement status, patients were recorded as DHL, THL, DEL and TEL. Patients who completed the planned number of treatment cycles were evaluated by PET-CT at the end of the treatment to determine the treatment response. Patients were recorded according to treatment response as partial response (PR), complete response (CR), and no treatment response. Response evaluation was not performed in patients who could not complete the planned number of treatment cycles, who died, and whose treatment was changed.

Statistical analysis

SPSS package program compatible with Microsoft Windows was used in the statistical analysis of the data. Descriptive statistics were expressed as numbers and percentages (%) for categorical measurements; and as mean and standard deviation (median and minimum-maximum where necessary) for continuous measurements. One-way Anova test was used for parameters showing normal distribution in the comparison of continuous measurements between groups. Chi-square tests were used to compare categorical variables.

Results

Of the total 36 patients participating in the study, 75% (n: 27) were male and 25% (n: 9) were female. The average age of all patients was 54.36 years. The average Ki67 proliferation index of the patients included in the study was 79.4%. When the diagnostic distribution of the patients according to the NHL subtypes was examined, 72% (n: 26) of 36 patients had DLBCL, 14% (n: 5) had high-grade B cell lymphoma, 11% (n: 4) had PMLBCL and 3% (n: 1) had Burkitt's lymphoma (BL). One patient developed DLBCL from chronic lymphocytic leukemia as a result of Richter transformation. In the response evaluation performed with PET-CT at the end of treatment has shown that 61% (n: 22) of the patients attained CR, 3% (n: 1) attained PR, and 8% (n: 3) had no response. CR was attained in 61% (n: 16) of 26 patients diagnosed with DLBCL at the end of the treatment, while there was no response in 8% (n: 2) of the patients. The characteristics of the patients are shown in Table 2.

Table 1. Dose adjusted R-EPOCH chemotherapy administration scheme

Drug	Dose and route	Given on days
Rituximab	375 mg/m^2-IV	Day 0 or 1
Etoposide	50 mg/m^2-IV per day	Days 1 to 4 (96 hours)
Doxorubicin	10 mg/m^2-IV per day	Days 1 to 4 (96 hours)
Vincristine	0.4 mg/m^2-IV per day (dose not capped)	Days 1 to 4 (96 hours)
Cyclophosphamide	750 mg/m^2-IV	Day 5
Prednisone	60 mg/m^2-orally twice daily	Day 1 to 5
Granulocyte colony stimulating factor		Start day 6-10

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Table 2. Characteristics of all patients (n:36 patients)

	% (n) patients		% (n) patients
Age (>60 years)	61 (22)	Bone marrow involvement (yes)	52 (19)
Gender (Male)	75 (27)	Extranodular involvement (yes)	8 (3)
NHL subtype		Beta-2 microglobulin (>ULN)	77 (28)
DLBCL	72 (26)	Lactate dehydrogenase (>2XULN)	86 (31)
Gigh grade B cell lymphoma	14 (5)	Uric acid (>ULN)	63 (23)
PMLBCL	11 (4)	ESR (>ULN)	80 (29)
Burkitt lymphoma	3 (1)	Ki67 proliferaton index (>%70)	88 (32)
Stage		Cytogenetic subtype	
I-II	39 (14)	DHL	5 (2)
III-IV	61 (22)	DEL	25 (9)
NCCN-IPI		TEL	22 (8)
Low-Low intermediate	30 (11)	Response status	
High intermediate-High	70 (25)	CR	61 (22)
ECOG PS		PR	3 (1)
0-1	45 (16)	No response	8 (3)
2-4	55 (20)		
B symtpom (yes)	69 (25)		

NHL: Non-hodgkin lymphoma; DLBCL: Diffuse large B cell lymphoma; PMLBCL: Primary mediastinal large B-cell lymphoma; NCCN-IPI: National comprehensive cancer network-international prognostic index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ULN: Upper limit normal; ESR: Erythrocyte sedimentation rate; DHL: Double hit lymphoma; THL: Triple hit lymphoma; DEL: Double expressor lymphoma; TEL: Triple expressor lymphoma; CR: Complet response; PR: Partial response

27% (n: 7) of the patients diagnosed with DLBCL had deceased and the treatment regimen was changed in 4% (n: 1) of the patients. CR was attained in 40% (n: 2) of the patients diagnosed with high-grade B cell lymphoma at the end of the treatment, while 20% (n: 1) did not respond, and 40% (n: 2) of the patients decreased.

At the end of the treatment, CR was attained in 50% (n: 2) of the patients diagnosed with PMLBCL, while PR was attained in 25% (n: 1) of the patients, and the treatment process of 25% (n: 1) of the patients was ongoing.

CR was attained in the response evaluation performed at the end of two cycles of the patient whose treatment process was ongoing. In one patient with a diagnosis of BL, the treatment process was ongoing and CR was detected in the response evaluation performed after two cycles.

While 25% (n: 9) of the patients died during the follow-up period, 6% (n: 2) were continued their therapy, and 3% (n: 1) had their treatment regimen changed. When the cytogenetic subtypes of all patients in the study were examined, it was found that two patients diagnosed with DLBCL and high-grade B-cell lymphoma had a DHL cytogenetic subtype with Bcl-6 rearrangement.

CR was attained in both cases with DHL cytogenetic subtype. 33% (n: 3) of nine patients with DEL cytogenetic subtype had Bcl-2 and 66% (n: 6) had Bcl-6 rearrangement. While 55% (n: 5) of the patients with DEL cytogenetic subtype attained CR, 22% (n: 2) had no treatment response.

In two patients with a DEL cytogenetic subtype and a diagnosis of DLBCL, the treatment regiment was changed in one of the patients and the other patient had deceased.

While 22% (n: 2) of the patients with DEL cytogenetic subtype had a diagnosis of high-grade B cell lymphoma, 78% (n: 7) had a diagnosis of DLBCL. Bcl-2 rearrangement was present in both patients with DEL cytogenetic subtype who diagnosed with high-grade B-cell lymphoma.

One of the patients with a diagnosis of DLBCL had Bcl-2 rearrangement, while 6 patients had Bcl-6 rearrangement. All eight patients with TEL cytogenetic subtype had a diagnosis of DLBCL. While 62% (n: 5) of the patients with TEL cytogenetic subtype attained CR at the end of the treatment, 12% (n: 1) had no response and 25% (n: 2) of the patients had deceased.

Discussion

In our study, we aimed to share the single center experience of 36 NHL patients who received DA-R-EPOCH treatment.

As a result of the study, we concluded that DA-R-EPOCH treatment regimen, which is accepted as the standard treatment regimen in lymphomas with DHL cytogenetic subtype and PMLBCL, is also an effective treatment regimen for lymphomas with DEL cytogenetic subtype and TEL cytogenetic subtype. In studies involving 132 patients with a diagnosis of PMLBCL in eleven centers and a study involving 39 DLBCL patients receiving DA-R-EPOCH therapy, the CR rates were 70% and 66%, respectively (9,8).

In our study, we administered DA-R-EPOCH treatment regimen to 36 patients with aggressive lymphomas and achieved a complete response in 61% of the patients.

On the other hand, although the number of patients was few, our patients with a diagnosis of PMLBCL had a CR rate of 75%. Compared to the literature, although the overall response rates seem to be less, 52% of the patients who participated in our study had a cytogenetically aggressive cytogenetic subtype. For this reason, the overall CR rate may have seemed less.

In the study conducted by Huang et al., the efficiency of R-CHOP and DA-R-EPOCH treatment regimens in patients with a diagnosis of DLBCL with Ki67 proliferation index greater than 80% was compared and as a result, the CR rate was found to be 83% in patients who received DA-R-EPOCH treatment regimen and it was found to be higher than patients receiving R-CHOP treatment regimen.

The same study found that overall survival and progression-free survival rates were better with the DA-R-EPOCH treatment regimen. (10). The average Ki67 proliferation index of the patients included in our study was 79.4%, and the Ki67 proliferation index of 88% of the patients was over 70%. In our study, 61% of the patients had attained complete response, and 52% of the patients included in our study had DHL, DEL or TEL cytogenic subtypes.

In the study conducted by Huang et al, cytogenetic subtypes are undefined and therefore higher response rates may have been obtained.

In a study involving a total of 394 lymphoma patients with DHL cytogenetic subtypes, DA-R-EPOCH and R-CHOP treatment regimens were compared and it was found that the risk of progression was relatively lower and the CR rate was higher in patients receiving the DA-R-EPOCH treatment regimen. However, there was no difference between the two treatment regimens in terms of overall survival (11). In our study, CR was attained in both of two patients with DHL cytogenetic subtype.

In a study conducted at MD Anderson Cancer Center with patients with the DEL cytogenetic subtype, it was observed that patients who received the DA-R-EPOCH treatment regimen had a higher rate of response than patients who received the R-CHOP treatment regimen and recurrence rates were found to be higher in patients receiving the R-CHOP treatment regimen. (12,13).

In our study, CR was attained in 55% of the patients diagnosed with DEL. In the literature review, no data could be found regarding the efficacy of DA-R-EPOCH treatment regimen in patients with TEL cytogenetic subtype. 22% of the patients participating in our study had TEL cytogenetic subtype and 62% CR rate was obtained in this patient group. With this information, it can be said that DA-R-EPOCH treatment regimen can provide a high response rate in patients with TEL cytogenetic subtype.

Conclusion

DA-R-EPOCH treatment regimen can provide a high response rate in patients with lymphoma with THL, DHL and DEL cytogenetic subtypes as well as in patients with lymphoma with TEL cytogenic subtype. However, there is no data in the literature on patients with TEL cytogenetic subtype. Multi-center studies with large patient participation are needed.

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Ethical issues: All authors declare originality and ethical approval of research. The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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