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Response of DA-Epoch-R in High Grade B-Cell Lymphoma

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ABSTRACT

Introduction: The dosages of chemo immunotherapy medications (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab) are modified based on the toxicity of the preceding cycle. Etoposide, doxorubicin, and cyclophosphamide are subject to dosage adjustments above starting dose level 1, while cyclophosphamide is subject to dose adjustments below starting dose level 1. **Materials and Procedures:** There were 65 high-grade B cell lymphoma patients in all, both male and female, aged >18–50 years. Patients with hepatitis B, primary CNS lymphoma, and those who had already received treatment were not included. Following their enrollment in the study, these patients received four cycles of DA-EPOCH-R along with 12.5 mg of intrathecal methotrexate. These were monitored prospectively, and following four cycles, the interim response was evaluated using the Deauville criteria based on whole body FDG PET-CT scans. **Findings**: Participants in this study ranged in age from over 18 to 50, with a mean age of 33.46 ± 7.41 years. 42 patients, or 64.62% of the total, were between the ages of 18 and 50. With a male to female ratio of 2.4:1, 46 (70.77%) of the 65 patients were men and 19 (29.23%) were women. 50 (76.92%) of the patients in my study had a complete response, 14 (21.54%) had a partial response, 01 (1.54%) had stable disease, and 00 (0.0%) had progressing disease. **Conclusion:** This investigation came to the conclusion that DA-EPOCH-R had a very effective response in high grade B-cell lymphoma.

INTRODUCTION

High grade B-cell lymphoma, also referred to as double-hit lymphoma, is an aggressive B-cell non-Hodgkin lymphoma (NHL) that is characterized by chromosomal exchanges (rearrangements) in two particular genes. One rearrangement involves the MYC gene, while the other involves the BCL2 or, less commonly, the BCL6 genes. In terms of gene alterations, HGBCL shares many traits with Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL). Actually, only 5% of DLBCLs and 32–78% of Burkitt lymphomas, also known as HGBCL, are linked to MYC and BCL2/BCL6 gene rearrangements. However, research has revealed some important differences between HGBCL and types of DLBCL and Burkitt lymphoma that do not feature dual gene rearrangements. As a result, in 2016, the World Health Organization identified HGBCL as a unique subtype of B-cell NHL.[1]

HGBL is classified by the WHO in 2016. The terms "double-hit" or "triple-hit" lymphomas, as well as "Burkitt-like" and "high grade," describe this category. The primary category "HGBL with MYC and BCL2 and/or BCL6 translocations" includes the subset "HGBL-not otherwise defined."[2] There isn't yet a widely accepted standard procedure for dealing with these situations.

Patients who receive R-CHOP had much poorer survival rates than those who do not have these anomalies, according to a number of retrospective and observational studies. For this subset, retroactive study in the past revealed a particularly negative result, which is less noticeable in some more recent studies. The selection bias that occurred in the past when FISH testing was utilized to find individuals with more severe clinical symptoms rather than the more recent practice of employing it in the majority of new cases may help to explain this. A recent large-scale retrospective evaluation of DLBCL patient outcomes after R-CHOP, gathered from prospective studies and patient registries, revealed some intriguing findings.[3] Overall survival (OS) and progression-free survival (PFS) were found to be significantly lower in patients with a MYC rearrangement. However, this effect was only observed in patients who also had concurrent BCL2 and/or BCL6 rearrangements and an IG partner with

MYC as opposed to a non-IG spouse. Compared to previous research that included cases with blasted and Burkitt morphologies, this study may have produced better results because it only included individuals with DLBCL morphology.[4]

Two prospective studies of DLBCL patients with a MYC rearrangement—of whom a significant proportion have DHL—have been conducted recently. Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin, and rituximab (DA-EPOCH-R) was tested in a prospective, multicenter study of 53 patients with MYC rearrangement (aggressive B-cell lymphoma) based on retrospective comparisons that demonstrated that DHL cases performed better with more dose-intensive approaches than R-CHOP.SHL-MYC-R cases were outnumbered by 4 DHL cases. The 48-month event-free survival (EFS) and overall survival (OS) rates were 71% and 77%, respectively, and 81% of patients had advanced illness. Lenalidomide was administered to R-CHOP in 82 patients who were part of the phase 2 HOVON investigation on the basis of the idea that it would be useful as a treatment for MYC-R lymphoma since it inhibits MYC and its target genes.[5] The 2-year EFS and OS were 63% and 73%, respectively, and 65% of patients had either a DHL or a THL. In a recent British study, individuals with high-risk DLBCL were evaluated with cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and high-dose cytarabine (R-CODOX-M/R-IVAC). Every patient had an IPI score of three or above. Over 10% had DHL and the majority were GCB, suggesting that HGBL might have been prevalent. Although the 2-year PFS and 2-year OS were not directly compared to R-CHOP, the results were better than previous R-CHOP experiences in a similar population.

Leppa and colleagues examined dose-dense immune treatment in 139 patients with high-risk DLBCL and discovered that the 5-year OS rate was 83%.[6] The results of patients with BCL2/MYC DHL were comparable to those of individuals without rearrangements, suggesting that dose-intense therapy was beneficial for the DHL group. Furthermore, intensive therapy showed a significantly longer PFS than R-CHOP, according to a large, newly published French retrospective study that included 160 patients with HGBL (with MYC, BCL2, and/or BCL6).[7] There is a lack of data to guide the sickness stage and IPI traits may be important considerations in the treatment options made for HGBL patients because HGBL-NOS cases are much less common. Positive outcomes have been observed in individuals with limited-stage aggressive B-cell lymphoma, despite their high-risk cytogenetics. For these patients in the early stages, it might make sense to give them regular R-CHOP.R (Dose-Adjusted) DA-EPOCH The dosages of chemo immunotherapy medications (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab) are modified based on the toxicity of the preceding cycle. Etoposide, doxorubicin, and cyclophosphamide are affected by dose adjustments above starting dose level 1, while cyclophosphamide is affected by dose adjustments below starting dose level 1. Burkitt lymphoma, primary mediastinal DLBCL, and high grade B-cell lymphoma are among the conditions for which D-EPOCH-R is suggested.

MATERIALS AND METHODS

This descriptive case series was done on 65 patients at Department of Hematology & Oncology at INMOL Hospital Lahore. Patients of age ranges from 18 – 50 years of both genders with High grade –B cell lymphoma were included. Multiple co-morbidities, ECOG III/IV, primary CNS lymphoma, already treated patients and hepatitis B positive were excluded. Sample size of 65 cases is calculated with 95% confidence level, 10% margin of error and expected percentage of PR a 21%.[5]

After taking approval from the hospital ethical committee, patients fulfilling the inclusion criteria were enrolled and informed consent was taken. All the patients were undergone DA-EPOCH-R. Response was collected upon data collecting form. All the patients had a baseline study hematology and biochemical profile along with a Biopsy for histopathology and IHC, FISH for C-MYC, BCL2/BC 6 and whole body FDG-PET in addition to the baseline hematology and clinical chemistry profile. Once enrolled in the study these patients were given 4 cycles of DA-EPOCH-R with intrathecal methotrexate 12.5mg. These were followed prospectively and the interim response was assessed after 4 cycle by whole body FDG PET-CT scan based Deauville criteria.

Data was analyzed by SPSS version 21. Quantitative variables like age were presented as mean and standard deviation. Qualitative variables like gender and response were presented as frequency and percentage.

RESULTS

Age range in this study was from >18 to 50 years with mean age of 33.46 ± 7.41 years. Majority of the patients 42 (64.62%) were between 18 to 50 years of age. Out of 65 patients, 46 (70.77%) were males and 19 (29.23%) were females with male to female ratio of 2.4:1. In my study, complete response was found in 50 (76.92%), partial response in 14 (21.54%), stable disease in 01 (1.54%) and progressive disease in 00 (0.0%) patients as shown in Table 1.

Table 1

Response of DA-EPOCH-R in High grade B-cell Lymphoma (n=65).

Response	No. of Patients	%age
Complete response (CR)	50	76.92
Partial response (PR)	14	21.54
Stable disease (SD)	01	1.54
Progressive disease (PD)	00	0.0

DISCUSSION

The most prevalent kind of non-Hodgkin lymphoma (NHL) in the US is diffuse large B-cell lymphoma (DLBCL). 50% to 70% of patients who get treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemo immunotherapy recover.[8] After decades of failed attempts to intensify CHOP with additional chemotherapeutics, rituximab's addition to the CHOP backbone in the 2000s greatly improved survival, making R-CHOP the standard treatment for DLBCL for almost 20 years. Nonetheless, DLBCL is becoming more widely acknowledged as a diverse illness with unique

molecular subgroups that impact survival and treatment. Therefore, there has been a great deal of interest in enhancing the standard-of-care R-CHOP regimen, especially for patients with high-risk tumor genetics or unfavorable prognostic characteristics. Dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH), an intensified infusional variant of R-CHOP that has been investigated in a variety of DLBCL subtypes, is one treatment that has emerged in particular.[9]

The purpose of this study is to determine how DA-EPOCH-R responds to high-grade B-cell lymphoma. 50 (76.92%) of the patients in my study had a complete response, 14 (21.54%) had a partial response, 01 (1.54%) had stable disease, and 00 (0.0%) had progressing disease. In one trial, 77.0% of patients had a complete response, 21.0% had a partial response, 1.0% had stable disease, and 0.0% had progressing disease.[5]

86% of the 81 patients with untreated, poor-risk DLBCL who were assessed in a phase 2 investigations by the Spanish PETHEMA Group had high-risk IPI scores ranging from 3 to 5.[10] there was no discernible difference in survival based on IPI score or GCB vs. ABC subtype; the CR rate was 80% and the 10-year OS rate was 64%. The toxicity of DA-R-EPOCH was as previously reported; 91% of patients received all scheduled cycles, however 46% of patients experienced a neutropenic fever episode. This study's 10-year OS rate for patients with high-risk IPI scores was the highest reported in the literature at the time, indicating the need for additional research.

Over the course of eight years, from 2005 to 2013, 524 patients participated in the Intergroup phase 3 randomized study comparing R-CHOP vs. DA-R-EPOCH for untreated DLBCL.[11] 491 suitable patients were split into 6 cycles of either DA-R-EPOCH or R-CHOP at random. Although the percentage of recruited patients with a high-risk IPI score was significantly lower than in earlier DA-R-EPOCH studies, the majority of patients had advanced-stage disease; 25% of patients had an IPI score of 3, and 12% had an IPI score of 4 or 5. Only a small percentage of patients were later discovered to have either DEL (16%) or DHL (3 patients), therefore it was not necessary to evaluate for DHL or DEL prospectively. Response and survival rates did not differ significantly between the R-CHOP and DA-R-EPOCH populations at a median follow-up of 5.2 years; the 5-year OS rates were 79% for R-CHOP and 78% for DA-R-EPOCH. Patients in the DA-R-EPOCH group with an IPI score of 3 to 5 had a considerably better PFS rate, according to post hoc subgroup analysis, but there was no discernible difference in OS. Between patients who underwent R-CHOP and those who received DA-R-EPOCH, no further subgroup differences in survival were seen, including no difference for patients with DEL.[11]

Two extensive retrospective clinical analyses[12,13] conducted in the last few years have demonstrated that the R-DA-EPOCH regimen considerably improved the PFS when compared to other regimens in DHL. In a multicenter retrospective analysis, Petrich et al.[12] examined 311 patients. The findings indicated that each enhancement protocol significantly increased the PFS rate (R-DA-EPOCH compared with R-CHOP, P=0.0463; R-Hyper CVAD, P=0.001; R-CODOX-M/IVAC, P=0.036), but there was no discernible difference in OS (P=0.119). The median PFS for the R-CHOP, R-EPOCH, and dosage intensity groups (referred to as R-Hyper-CVAD, R-M/A, and R-CODOX-M/IVAC) was 12.1, 22.2, and 18.9 months, respectively, according to a meta-analysis conducted by Howlett et al[13], which examined 394 patients from 11 studies. Additionally, compared to R-CHOP, the PD risk of R-DA-EPOCH was 34% lower (P=0.032). Nevertheless, there was no discernible variation in the OS across regimens.

In the recently released publication by Dodero et al[14], a subset of DHL patients with comparable high IPIs (74%) and less favorable outcomes were included. The fact that the majority of patients over 60 were restricted to dose level 1 (perhaps as a result of comorbidities and greater toxicity) may possibly be because the patient cohort in this trial was older and more fragile (higher ECOG), which reduces some of the potential advantages of DA-EPOCH-R over R-CHOP. Another retrospective analysis of DA-EPOCH-R in a DLBCL cohort revealed a similar finding of limited dose escalation in older patients.[15] Although DA-EPOCH-R is a deliverable regimen for actual DHL patients, the study's relatively low EFS/OS indicates that its optimization and efficacy in an older unselected population may be limited by the increased treatment-related toxicity.

CONCLUSION

This study concluded that response of DA-EPOCH-R in High grade B-cell lymphoma is very effective. So, we recommend that DA-EPOCH-R in High grade B-cell lymphoma should be used as a primary treatment option for reducing the morbidity and mortality of our population.

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