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DA-R-EPOCH versus R-CHOP in intermediate and high risk IPI diffuse large B-cell lymphoma, a randomized controlled trial

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Abstract---Background: Diffuse large B-cell lymphoma is a challenging disease in management. Although most patients are cured with the standard R-CHOP, one third of them remains refractory to this regimen. As prognosis of refractory disease is worse than primarily responding one, several trials investigated other more intense frontline regimens tailored based upon risk and biological

characteristics. Patients & Methodology: This is a prospective randomized trial investigating the more intensive DA-R-EPOCH regimen as frontline therapy in intermediate and high risk DLBCL patients in comparison to the standard R-CHOP regimen. We compared both regimens in these risk categories as well as undergoing a subgroup analysis according to cell of origin (Germinal center versus activated B cell) and according to BCL2 and C-myc expression (double expressor lymphoma). Toxicities in both arms have been analyzed according to common terminology criteria for adverse events (CTCAE). Results: In spite of being more toxic and complex, there was no significant improvement in DFS or response rate with DA-R-EPOCH. No significant benefit for DA-R-EPOCH over R-CHOP in both germinal center and activated B-cell DLBCL. Conclusion: Tailoring upfront treatment of DLBCL based upon risk classification or BCL2/c-myc expression remains an area of unanswered questions and warrants further investigations.

Keywords---Diffuse large B cell lymphoma (DLBCL), cell of origin, IPI, R-CHOP, DA-R-EPOCH.

Introduction

In 2002, R-CHOP was first established as the standard frontline therapy for DLBCL (1). In the first trials that established this standard regimen, the 3-year event-free survival (EFS) varied from 53% to 79% according to IPI risk. Worse outcomes for patients with refractory or recurrent DLBCL warranted further efforts to improve first-line approaches. In 2019 the Alliance/CALGB 50303 trial by Bartlett et al was published (2). It is a large phase 3 study comparing R-CHOP versus DA-R-EPOCH. Results were actually unsatisfactory regarding the previously promising DA-R-EPOCH regimen as it was of more toxicity and with no significant improvement in PFS. Although it included 491 patients, 37% only were of IPI 3-5. Moreover, in an unplanned subset analysis, there was a significant improvement in PFS in patients with IPI 3-5 who received DA-R-EPOCH (HR = 0.63, 95% CI: 0.41 to 0.99; P = 0.041) compared with patients in the R-CHOP arm; however, the subset analysis was a post-hoc analysis and was not powered. On such basis we decided to carry out this trial comparing R-CHOP versus DA-R-EPOCH in intermediate and high-risk patients with untreated DLBCL. Seventy seven percent of our study population were of stage 3 and 4 and 82% of them were of IPI 3-5. However, in spite of being more toxic and complex, DA-R-EPOCH added no significant improvement response rate or DFS.

Methods:

Study Design and Patients

Our study compared DA-R-EPOCH with R-CHOP in intermediate and high risk DLBCL. Eligible patients included untreated DLBCL and primary mediastinal large B-cell lymphoma (PMBCL). Additional eligibility criteria included age equal to or more than 18 years, stage II to IV DLBCL (or stage I PMBCL), ECOG

performance status 0 to 2 (unless disease related), adequate cardiac function defined as left ventricular EF more than 45%, absolute neutrophil count not less than 1,000/mL, platelet count at least 100,000/mL, creatinine not more than 1.5 mg/dL, and bilirubin not more than 2 mg/dL (unless disease related obstruction). Patients with known CNS lymphoma or HIV positive were not included. A paraffin fixed tumor biopsy was required before inclusion. Immunohistochemistry (IHC) (Hans Algorithm) and IHC for BCL-2 and MYC expression were done as well as PCR testing for MYC and BCL2 rearrangements.

Participants provided informed consent

Both regimens were given every 21 days for 6 cycles. CNS prophylaxis was administered in eligible patients according to CNS IPI risk scoring. Prophylactic medications for both regimens included a proton pump inhibitor, antihistaminic, dexamethasone 8mg and, for patients positive for hepatitis B surface antigen, lamivudine 100 mg per day initiated 2 weeks before starting chemotherapy. Growth factor (Filgrastim) was given on days 7 to 9 of DA-R-EPOCH. In the R-CHOP arm, filgrastim was added if a patient developed an absolute neutrophilic count of less than 500/mL or neutropenic fever with the previous cycle.

Efficacy and Safety Measures

PET-CT at the end of the six cycles was done for all patients. Baseline and post cycle 3 CTs were performed and EOT PET was done in all patients. An end-of-treatment PET was considered negative if Deauville 3 or less. Adverse events were reported every cycle according to the CTC (common toxicity criteria) version 4.0.

Statistical Analysis

The primary clinical end points were overall response rate and toxicity. Overall response rate is defined as complete remission (CR) on achieving a Deauville score of 3 or less at the end of treatment PET-CT, While non-CR is considered if Deauville score was 4 or 5. Secondary clinical end points included comparisons of DFS measured from randomization to disease progression, relapse or death. The protocol required at least 12 months of follow up. A P value of 0.05 or less was used to define a statistically significant finding. Planned clinical subset analyses in the protocol were analyses according to cell of origin (COO) and according to BCL2 and c-myc expression.

Results

Forty-five patients were enrolled in this study, 25 in the R-CHOP arm and 20 patients in the DA-R-EPOCH arm. Both regimens were upfront regimens. Median age for the total population was 50 years old, 77.7% of them were of stage 3 and 4 and 82% represented IPI 3-5. All patients were diagnosed DLBCL with CD 20 positive, that was the baseline marker for all cases. Unfortunately, we could continue the panel of immunophenotyping for 26 patients only due to technical and logistical problems.

Table 1
Pathological parameters

Parameter		Total population No (%)	R-CHOP arm No (%)	DA-R-EPOCH arm No (%)
Cell of origin	Total	26 (100%)	13 (50%)	13 (50%):
	ABC	14 (53.8%)	7 (53.8%)	7 (53.8%)
	GC	12 (46.2%)	6 (46.2%)	6 (46.2%)
Double expressor	Yes	5 (19.2%) (3 GC and 2 post GC)	0 (0%)	5 (38.5%)
	No	21 (80.8%)	13 (100%)	8 (61.5%)

Table 2
G 3-4 GIT toxicities

Parameter	R-CHOP	DA-R-EPOCH	P-value
G3 Nausea	1 (4%)	1 (5%)	0.733
G3-4 Vomiting	2 (8%)	2 (10%)	0.621
G3-4 Constipation	1 (4%)	1 (5%)	0.731
G3-4 Diarrhea	0 (0%)	4 (20%)	0.00012
G3-4 Oral mucositis	5 (20%)	4 (20%)	1.00

Table 3
Neutropenia, neutropenic fever

Parameter	R-CHOP	DA-R-EPOCH	P-value
Grade 3-4 neutropenia	7 (28%)	8 (40%)	0.07325
Rate of Neutropenic fever	12 (48%)	13 (65%)	0.01531

Table 4
Other toxicities

Parameter	R-CHOP	DA-R-EPOCH	P-value
G3-4 Sensory neuropathy	1 (4%)	0%	0.17
G3-4 Fatigue	1 (4%)	1 (5%)	0.73
Tumor lysis syndrome	2 (8%)	1 (5%)	0.39
G3-4 Hepatic toxicity	0%	0%	0.62
G3-4 Anemia	7 (28%)	3 (15%)	0.02

Among patients who received R-CHOP non were subjected to discontinuation or shift of treatment due to toxicity while in the R-EPOCH arm 2 patients (10%) were shifted to R-CHOP due to severe hematologic toxicity and sepsis. This was statistically significant of p-value 0.0052.

Table 5
Response rate (RR) analysis

RR at the end of treatment	ARM		P-value
	R-CHOP No(%)	DA-R-EPOCH No(%)	0.970
CR (Deauville 3 or less)	21 (84%)	17 (85%)	
Non-CR (Deauville 4 or 5)	4 (16%)	3 (15%)	

Table 6
RR according to cell of origin (COO)

COO	ARM	RR No(%)		P-value
		CR	Non-CR	
ABC (No=14)	R-CHOP (No=7)	6(85.7%)	1 (14.28%)	0.51
	DA-R-EPOCH (No=7)	5 (71.42%)	2 (28.57%)	
GC(No=12)	R-CHOP (No=6)	6 (100%)	0%	0.79
	DA-R-EPOCH (No=6)	6(100%)	0%	

Table 7
RR according to IPI

IPI	ARM	RR		P-value
		CR	Non-CR	
Intermediate Risk (No=19)	R-CHOP (No=14)	11 (78.57%)	3 (21.43%)	0.8
	DA-R-EPOCH (No=5)	5 (100%)	0%	
High Risk (No=22)	R-CHOP (No=11)	10(91%)	1 (9%)	0.53
	DA-R-EPOCH (No=11)	9(82%)	2 (18%)	

RR of double expressor patients

Five patients among the study group were determined double expressor and they all were in the DA-R-EPOCH arm. All of them achieved CR at the end of treatment PET-CT assessment (P-value 0.366)

Disease free survival analysis

Median DFS: Not reached

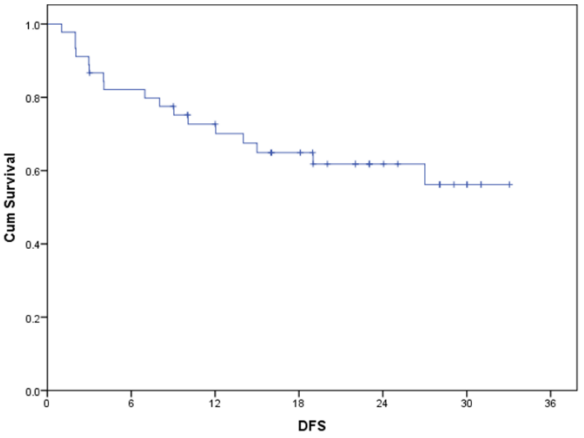

Figure 1. Overall DFS in all patients included in the study: (No=45)

Mean DFS for the total population: 23 months (confidence interval 19.2-26.8).
Mean DFS for R-CHOP: 24 months (confidence interval 19-28)
Mean DFS for DA-R-EPOCH: 19.6 months (confidence interval 14.6-24.7)
P-value 0.33

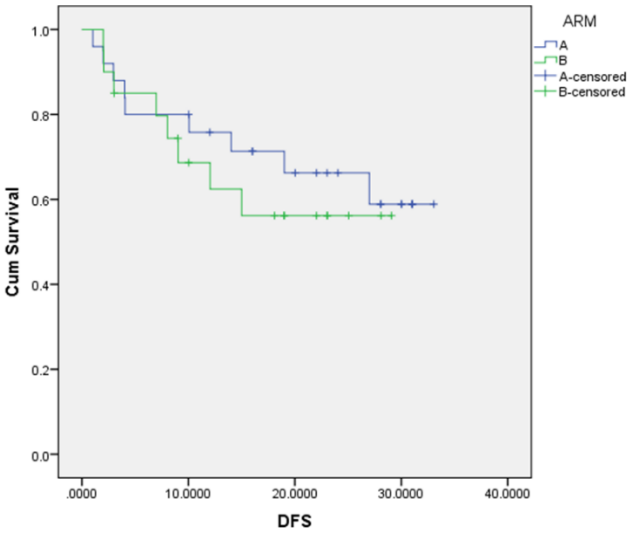

Figure 2. DFS in each arm

A =R-CHOP
B =DA-R-EPOCH

Survival analysis according to cell of origin

Median: not reached
Mean: The mean DFS is numerically higher in GC group in both arms (overall 30 months versus 18 months in the ABC arm) however it was not statistically significant (P-value 0.77).

Table 8
Mean DFS according to cell of origin

ABC OR GC	ARM	Mean	
		Months	P-value
			O.77
ABC (No=14)	R-CHOP (No=7)	21.581	
	DA-R-EPOCH (No=7)	14.464	
	Overall	18.148	
GC (No=12)	R-CHOP(No=6)	30.718	
	DA-R-EPOCH (No=6)	24.819	
	Overall	29.849	

Survival analysis according to IPI

Table 9
Mean DFS according to IPI, overall

IPI	Mean (months)	P-value
Intermediate risk (No=19)	19.762	0.846
High risk (No=22)	23.339	
Overall	23.027	

Table 10
Mean DFS according to IPI, R-CHOP vs DA-R-EPOCH

ARM	IPI	Mean (Months)	P-value
R-CHOP (No=25)	INTERMEDIATE RISK (No=14)	21.349	0.024

	HIGH RISK (No=11)	24.249	
	Overall	24.031	
DA-R-EPOCH (No=16)	INTERMEDIATE RISK (No=5)	18.257	
	HIGH RISK (No=11)	19.368	
	Overall	19.688	
Overall	Overall	23.027	

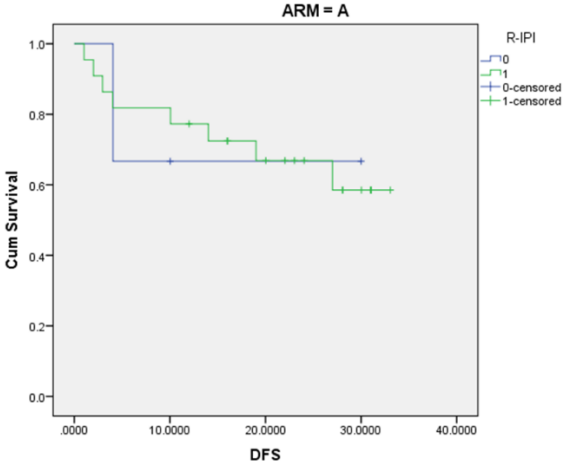

Figure 3. DFS according to IPI, R-CHOP

0=low and high intermediate risk
1=high risk

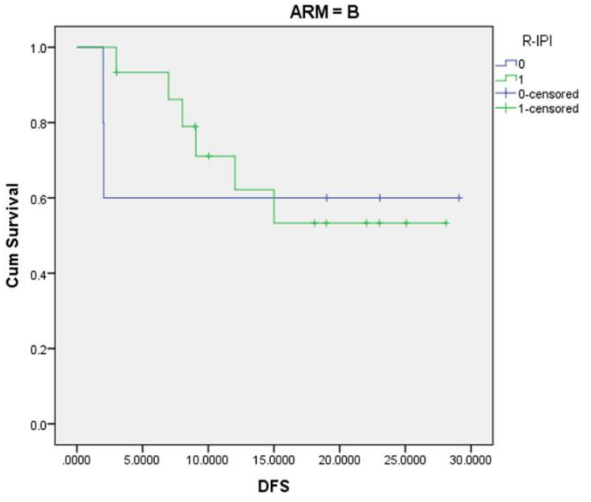

Figure 4. DFS according to IPI, DA-R-EPOCH

0=low and high intermediate risk
1=high risk

Double expressor

Five patients among all the study group were proved to be double expressor and they were all in the DA-R-EPOCH arm. Among the DA-R-EPOCH arm the double expressor patients survived for a mean of 22.8 months versus 19.3 months for the non-double expressors which was not statistically significant.

Discussion

This randomized trial compared the efficacy of R-CHOP to the more intensive DA-R-EPOCH in patients with intermediate and high risk DLBCL. Median age for the total population is 50 years old which is younger than populations in other countries. In USA the median age of aggressive B cell lymphomas is 55 years old and in Asia it ranges from 63-65 years old (3). Younger population affected by DLBCL is observed in our country (median age 47 years old) as well as more aggressive types of lymphoma affect our population (In Egypt 49% of newly diagnosed lymphomas are of aggressive types). This is as reported by Mokhtar et al (4). All patients were tested for HCV antibody and HBV surface antigen (HbsAg) and eleven patients were proved to be positive (4 HBsAg positive and 7 HCV antibody positive). Hepatitis B and C have been strongly linked to lymphomas, DLBCL in hepatitis positive patients tends to be of earlier onset and of more aggressive course as reported by Wang et al,2008 (5). In our study 9 of them were stage 3 and 4, and all of them were high intermediate and high risk IPI. They were all of CHILD A status and with normal liver functions.

Germinal center DLBCL represented 46.2% in our population while ABC represented 53.8% while in US ABC nearly represents 40% of newly diagnosed DLBCL as reported by Alizadeh et al, 2000 (6). We also performed BCL2 and C-MYC by RT-PCR to detect double hit patients. Due to poor preparation of some blocks as well as the small size of many samples (core biopsies from liver, bone, mediastinal mass, lung, stomach or colon) RNA extraction was challenging. We also used peripheral blood samples for which RNA extraction was easier. However finally we relied on IHC for detecting double expressor DLBCL patients. RT-PCR or FISH detects double hit DLBCL while IHC detects double expressor ones. Unfortunately, we could only detect double expressor lymphomas due to technical problems. Nineteen percent of patients in this study were proved to be double expressor by IHC, a figure which is higher than global figures (5-10% in most western studies) as reported by Rosenthal et al,2017 (7).

Among our total population 95.5% (38 out of 40 patients who represent those who did not express progression on first line) could continue the six cycles of either R-CHOP or DA-R-EPOCH. Five patients had evident disease progression before 3rd cycle. They were shifted to second line. Six patients (13.33%) received CNS prophylaxis (either IT MTX or HD-MTX). None of them developed CNS relapse until last follow up. Due to high rates of neutropenia and infection we could not escalate the DA-R-EPOCH doses in any of the patients according to nadir as described in the protocol. Shifting or discontinuation of the whole treatment due to severe toxicity was 10% in the DA-R-EPOCH arm (2 patients) vs 0% in R-CHOP (P-value 0.0052). G3-4 diarrhea (20% in the DA-R-EPOCH arm versus 0% in the R-CHOP arm) (P-value 0.00012) was statistically significant, other G3-4 GIT

toxicities such as nausea, vomiting, constipation and oral mucositis were the same in both arms with figures comparable to other international studies. (2)

G3-4 neutropenia (40% vs 28% in the DA-R-EPOCH and R-CHOP arms respectively, P-value 0.07325), neutropenic fever (65% vs 48% in the DA-R-EPOCH and R-CHOP arms respectively, P-value 0.01531). Site of infection was mainly chest infection (n=12), followed by central line infection (n=3). The three patients who developed central line infection, infection was severe such that removal of the central line was indicated, cultures were withdrawn and patients were kept on IV antibiotics which caused delay of their subsequent cycles.G3-4 anemia occurred more in the R-CHOP group (28% vs 15%, P-value 0.0252). Apart from anemia, Bartlett et al 2019 showed similar findings concerning toxicity. More G3,4 hematologic and non-hematologic toxicity was found in the DA-R-EPOCH arm in their study.(2)

G3-4 sensory neuropathy was more on the R-CHOP arm (4% vs 0% P-value 0.17423) however not statistically significant. CALGB/Alliance 50303 trial (Bartlett et al) found a fivefold increase in the rate of severe neuropathies with DA-R-EPOCH compared to R-CHOP.(2) The reason behind this contradictory finding is that we capped the vincristine dose in the DA-R-EPOCH regimen at 2mg in most cases. Taylor et al (8) conducted a prospective study in which they capped the vincristine dose to 2mg per cycle and this significantly decreased rates of high grade neuropathy.G1-2 hepatic toxicity occurred almost equally on both arms.Tumor lysis syndrome occurred in 8% in the R-CHOP group versus 5% in the DA-R-EPOCH one however it is more related to the bulk of the disease rather than the regimen itself.

Response rates and DFS

Complete remission rates were almost equal in both arms (84% in R-CHOP group and 85% in the DA-R-EPOCH group). Bartlett et al also reported overall response rate of 88.0% in the R-CHOP group and 86.7% in the DA-R-EPOCH group. Complete remission rates in ABC group were around 86% in R-CHOP compared to 71% in R-EPOCH while in GC it was 100% in both groups). ABC DLBCL is known to be more aggressive than GC DLBCL (9) the fact that explains why CR was higher in GC in our study. Median DFS was not reached however mean DFS was 24 months in the R-CHOP arm and 19.6 months in the DA-R-EPOCH arm (p value 0.33). DFS at 24 months for the whole population was 56%, which is lower than that in Bartlett et al (around 75% for both arms). This can be explained by the fact that bartlett et al included low risk IPI (0 and 1) patients in their study which constituted around one quarter of their population while we totally excluded low risk IPI patients from this study. Another explanation is that in our study rate of neutropenic fever was higher in our study (65% in the DA-R-EPOCH arm in our study versus only 35% in this arm in Bartlett's study), this fact actually made delay of treatment and dose reduction more in our study which might have affected the response rate.

While Zhang et al (10) in their subgroup analysis showed OS and PFS benefit in the GC group who received DA-R-EPOCH, our mean DFS was shown to be numerically higher in GC group in both arms (overall 30 months versus 18

months in the ABC arm) (p value 0.7) but no significant DFS benefit was noticed in the DA-R-EPOCH arm. According to IPI the high-risk group survived better in the R-CHOP than the DA-R-EPOCH arm (24 months vs 19 months respectively) (p-value 0.02) which is contradictory to Zhang et al findings that revealed OS and PFS benefit in high risk group treated with DA-R-EPOCH. However, Mayo clinic in a retrospective study reported no survival benefit for DA-R-EPOCH over R-CHOP in high risk IPI patients (11).

Four patients among the study population suffered from primary mediastinal DLBCL. All of them received DA-R-EPOCH regimen, and three achieved CR while one patient showed disease progression after two cycles. Five patients among the entire study were proved to be of double expressor DLBCL and they were -by chance- all in the DA-R-EPOCH arm. Among the DA-R-EPOCH arm the double expressor patients survived for a mean of 22.8 months versus 19.3 months for the non-double expressors which was not statistically significant. In a single arm phase 2 study underwent by Dunleavy et al, 2018 (12) the DA-R-EPOCH regimen achieved durable remissions in patients with C-MYC rearrangement or double hit lymphomas. This is actually contradictory to Zhang et al study in which it was stated that DA-EPOCH-R regimen may not overcome the poor prognosis of DE lymphomas. Results published by MD Anderson (13) analysis showed that DA-EPOCH-R improves Progression Free Survival (PFS) in DLBCL with C-MYC rearrangements however patients still relapse and OS is not improved.

Conclusions

There was no improvement in the primary end point (response rate) with DA-R-EPOCH as compared to the standard R-CHOP. Unfortunately, the number of patients with unmet needs i.e., PMBL and double expressor lymphoma is not enough to conclude whether they would really benefit from DA-R-EPOCH. This represents a current challenge to address in further studies.

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