

Original Article

Outcome of Newly Diagnosed DLBCL-NOS Treated with R-DA-EPOCH and R-CHOP: Report from King Chulalongkorn Memorial Hospital

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Abstract:

Objective: Since the introduction of rituximab (R), outcomes of diffuse large B cell lymphoma (DLBCL) have significantly improved. R-CHOP (C-Cyclophosphamide, H-Adriamycin, O-Vincristine and P-Prednisolone) has been the standard treatment over the past decade. Subsequent data have shown the benefit of adding etoposide (E) and administering treatment in a dynamic dose adjusting fashion so called dose-adjusted (DA) EPOCH. Several phase II trials demonstrated promising outcomes of R-DA-EPOCH. We hypothesized that R-DA-EPOCH would be more effective than R-CHOP in DLBCL. Herein, we compared outcomes of patients with DLBCL treated with R-CHOP and R-DA-EPOCH at our institution. **Methods:** We identified newly diagnosed DLBCL among patients treated with at least three cycles of R-CHOP or R-DA-EPOCH at King Chulalongkorn Memorial Hospital between January 2011 and August 2016. We described and compared baseline characteristics, outcomes and toxicities among these patients. **Results:** During the study period, 178 newly diagnosed DLBCL-NOS were treated with CHOP-like chemotherapy at King Chulalongkorn Memorial Hospital. The overall response rate was similar between the 2 groups (R-CHOP 97.3% vs. R-DA-EPOCH 92.9%). With a median follow-up duration of 32 months, 2-year progression free survival (PFS), overall survival (OS) for the entire cohort was 89% and 92.1%, respectively. R-CHOP treated patients had similar 2-year PFS but marginally better 2-year OS than R-DA-EPOCH cohorts (90.2% vs. 80.9%, $P = 0.09$ for PFS and 93.1% vs. 85.3%, $P = 0.05$ for OS). R-DA-EPOCH had more grade III/IV hematological toxicities. **Conclusion:** According to our study, R-DA-EPOCH resulted in comparable outcomes including response rate and survival to R-CHOP in DLBCL-NOS but presented more adverse events. Due to limitations in our study further large prospective cohort studies are required.

Keywords : ● Diffuse large B cell lymphoma ● Immunochemotherapy

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นิพนธ์ต้นฉบับ

ผลการรักษามะเร็งต่อมน้ำเหลืองชนิดบีเซลล์ตัวใหญ่ด้วย R-DA-EPOCH และ R-CHOP ที่โรงพยาบาลจุฬาลงกรณ์

ธนิษฐ์ ลิ้นสมบุรณ์ทอง และ กฤษฎา วุฒิการณ

หน่วยโลหิตวิทยาภาควิชาอายุรศาสตร์คณะแพทยศาสตร์จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ

บทนำ ตั้งแต่มีการใช้ rituximab (R) ร่วมกับยาเคมีบำบัดในการรักษาโรคมะเร็งต่อมน้ำเหลืองนอนฮอดจ์กินชนิดบีเซลล์ตัวใหญ่ (DLBCL) ผลการรักษา DLBCL ดีขึ้นอย่างมากโดย R-CHOP ถือเป็นการรักษามาตรฐาน การศึกษาต่อมาพบว่าการเพิ่ม etoposide (E) เข้ากับสูตร R-CHOP เรียกว่า dose-adjusted (DA) EPOCH นั้นจากการศึกษาวิจัยขั้นที่สองพบว่าให้ผลการรักษาที่ดีขึ้นเราตั้งสมมุติฐานว่า R-DA-EPOCH ให้ผลการรักษาเหนือกว่า R-CHOP ดังนั้นเราจึงได้ทำการศึกษาถึงผลการรักษาผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองนอนฮอดจ์กินชนิดบีเซลล์ตัวใหญ่ (DLBCL) โดยเปรียบเทียบระหว่างการรักษาด้วย R-CHOP และ R-DA-EPOCH ที่สถาบันของเรา **วิธีการวิจัย** เรารวบรวมผู้ป่วย DLBCL ที่ได้รับการวินิจฉัย และรับการรักษาด้วย R-CHOP หรือ R-DA-EPOCH ตั้งแต่ 3 ครั้งที่โรงพยาบาลจุฬาลงกรณ์ระหว่างเดือนมกราคม 2554 ถึงสิงหาคม 2559 และรายงานลักษณะทางคลินิก ผลการรักษาของผู้ป่วย และผลข้างเคียงจากการรักษาในผู้ป่วยกลุ่มนี้ **ผลการวิจัย** มีผู้ป่วย DLBCL 178 ราย ที่ได้รับการวินิจฉัย และรักษาในช่วงเวลาที่ศึกษา (R-CHOP 150 ราย และ R-DA-EPOCH 28 ราย) อัตราการตอบสนองของผู้ป่วยแต่ละกลุ่มไม่ต่างกัน (R-CHOP 97.3% และ R-DA-EPOCH 92.9%) อัตราการปลอดโรค (PFS) และอัตราการรอดชีวิต (OS) ที่ 2 ปี ของผู้ป่วยทั้งหมดเท่ากับ 89% และ 92.1% ในระยะเวลาการติดตามที่ 32 เดือนโดยผู้ป่วย R-CHOP มี PFS ที่ 2 ปี ใกล้เคียงกับ R-DA-EPOCH (90.2% และ 80.9%, $p = 0.09$) แต่ R-CHOP มีแนวโน้ม OS ที่ 2 ปีดีกว่า R-DA-EPOCH (93.1% และ 85.3%, $p = 0.05$) อย่างไรก็ตาม R-DA-EPOCH มีผลข้างเคียงทางโลหิตวิทยามากกว่า R-CHOP **สรุป** การรักษาโรค DLBCL ด้วย R-DA-EPOCH และ R-CHOP ให้ประสิทธิภาพในการรักษาไม่ต่างกัน แต่ผู้ป่วยที่ได้ R-DA-EPOCH มีผลข้างเคียงทางโลหิตวิทยามากกว่า R-CHOP อย่างไรก็ตามการศึกษาที่สถาบันของเรา ยังมีข้อจำกัด จึงต้องอาศัยข้อมูลจากงานวิจัยที่ขนาดใหญ่เพิ่มเติม

คำสำคัญ : ● Diffuse large B cell lymphoma ● Immunochemotherapy

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2561;28:155-63.

Introduction

Diffuse Large B Cell Lymphoma (DLBCL) is the most common type of nonHodgkin lymphoma, representing 25 to 35%^{1,2}. Incorporation of rituximab in chemotherapy, so called immunochemotherapy, has improved outcomes of DLBCL over the past decade, for 3-year PFS, 50 to 60% and 3-year OS, 60 to 70%³⁻⁶. The most widely used regimen is R-CHOP, currently considered the gold standard of care. However, relapse remains the most important cause of treatment failure⁷. Dynamic dose adjustment of chemotherapy and adding etoposide to the regimen, rituximab-dose-adjusted-EPOCH (R-DA-EPOCH), could overcome chemotherapy resistance resulting in improved outcome over CHOP⁸. Phase II data of R-DA-EPOCH has shown promising outcomes in a variety of B cell lymphoma including DLBCL-NOS, resulting in improved 3-year OS up to 80%^{9,10}. The maximum benefit was seen in germinal B cell subtypes and among younger patients. Moreover, efficacy of R-DA-EPOCH in certain DLBCL subtypes, i.e., primary mediastinal B cell lymphoma, was exceptional¹¹. However, direct comparison of R-DA-EPOCH over R-CHOP, showed surprisingly disappointing results. Recent analysis of CALGB/Alliance 50303 did not show superiority to R-DA-EPOCH over R-CHOP but rather, more toxicity¹². Despite negative interim results, a superior trend has been observed of R-DA-EPOCH among patients with high risk IPI compared with R-CHOP and a further subgroup analysis is pending. Although negative results were reported in the CALGB study, other groups reported superiority of R-DA-EPOCH in certain DLBCL subgroups, i.e., high Ki-67¹³. Thus, efficacy of R-DA-EPOCH might be preferential in certain DLBCL subgroups. Herein, we analyzed outcomes of patients with DLBCL receiving R-DA-EPOCH and compared with patients treated with R-CHOP at our center.

Materials and Methods

We conducted a retrospective cohort study of newly diagnosed DLBCL among patients aged 18 years old or

older according to WHO classification for lymphoid malignancy 2008 criteria who received at least three cycles of immunochemotherapy (R-CHOP or R-DA-EPOCH regimens) at the King Chulalongkorn Memorial Hospital between January 2011 and August 2016. We excluded primary CNS lymphoma and pregnant patients. Pathological review was conducted with hematopathologists to confirm DLBCL diagnosis. When paraffin embedded tissue archives were available, further immunohistochemistry staining for CD10, MUM1, BCL6, c-MYC and BCL2 were performed if not previously done. Cell of origin was determined using CD10, MUM1 and BCL6 data according to Hans Criteria. We reviewed medical records to obtain baseline clinical characteristics (including prognostic information, i.e., international prognostic index), treatment parameters, i.e., dose reduction or dose delay, adverse events and treatment outcomes. The primary end point of this cohort study was overall survival. The secondary end points included response rate, progression free survival, cumulative incidence of relapse and adverse events. Cut off for data analysis was December 31, 2016.

Statistical Analysis

Continuous variables were reported as median and compared between groups using student t test or Fisher's exact test. Categorical data were reported as proportion with 95% confidence interval (CI) and compared using chi-square test. Response rate was reported in percentage and comparison was made between groups using the chi-square test. Survival data including OS, PFS were analyzed using Kaplan Meier survival analysis and comparison was made by log-rank test. Multivariate analyses were carried out using a Cox proportional hazard regression model, for which the variables with known prognostic potential from univariate analysis were entered. Statistical significance was set at a *p-value* less than 0.05. Cumulative incidence of relapse was performed using competing risk analysis by Gray's method using R program¹⁴. All other statistical analyses were performed under STATA, Version 11.0 (Stata Corp, College Station, TX).

Results

Baseline characteristics

We identified 178 newly diagnosed DLBCL-NOS cases among patients treated with at least three cycles of R-CHOP or R-DA-EPOCH at the King Chulalongkorn Memorial Hospital between January 2011 and August 2016. Of 178 patients, 150 received R-CHOP (84.3%) and 28 received R-DA-EPOCH (15.7%). Median age of the entire cohort was 52 years (ranged 18-78 years). Advanced stage and high to intermediate/high risk IPI were seen among 92 patients (51.7%) and 77 patients (43.2 %), respectively. Compared with R-CHOP, the R-DA-EPOCH treated cohort had a significantly higher proportion of high intermediate/high risk IPI, elevated lactate dehydrogenase, presence of B symptoms and trend toward a higher proportion of advanced stage diseases. Baseline characteristics are summarized in Table 1.

Treatment delivery

Median time from DLBCL diagnosis to treatment initiation was 24 days and 19 days for R-CHOP and R-DA-EPOCH, respectively ($p = 0.68$). In both R-CHOP

and R-DA-EPOCH cohorts, the median numbers of treatments delivered comprised 6 cycles (R-CHOP; ranging from 4 to 8 cycles, R-DA-EPOCH ranged 3 to 8 cycles). Of 150 patients in the R-CHOP cohort, chemotherapy dosing details were available for review among 143 patients. Of 143 patients who had chemotherapy dosing detail in the R-CHOP cohort, median actual dose intensity of cyclophosphamide and doxorubicin were 226.1 mg/m²/week and 14.9 mg/m²/week, respectively, which translated into a median relative dose intensity of 90.4% and 89.4% for cyclophosphamide and doxorubicin, respectively. About 30% of patients in the R-CHOP cohort had reduced chemotherapy dose or delayed treatment.

In the R-DA-EPOCH cohort, chemotherapy dosing details were available among all 28 patients. We adjusted doses of doxorubin, etoposide and cyclophosphamide depending on nadir ANC and nadir platelet count. Nadir ANC of $0.5 \times 10^9/L$ will increase 1 level dose but nadir ANC less than $0.5 \times 10^9/L$ or nadir platelet count less than $25 \times 10^9/L$ will decrease 1 level dose. The median administered dose level of DA-EPOCH was

Table 1 Baseline characteristics

Characteristic	R- CHOP (N = 150)		R- EPOCH (N = 28)		p-value
	n	%	n	%	
Sex					0.512
■ Male	69	46.0	11	39.3	
■ Female	81	54.0	17	60.7	
Mean age at diagnosis (years $\pm$ SD)	56.5 $\pm$ 14.5		48.3 $\pm$ 18.4		0.009
Age > 60	67	44.6	10	35.7	0.65
Advance stage	73	51.3	9	32.1	0.062
ECOG Performance status > 2	15	10.0	4	14.3	0.500
Elevated lactate dehydrogenase	97	64.7	26	92.9	0.003
Extranodal involvement	16	10.7	4	14.3	0.578
High intermediate/High IPI*	51	34	26	92.8	0.001
Presence of B symptoms	76	50.7	21	75	0.018
Cell of origin					0.263
■ Germinal Center	48	32.0	5	17.9	
■ NonGerminal Center	73	48.7	15	53.6	
■ Missing	29	19.3	8	28.6	

level 2 (range level -1 to level 6). Eighteen patients (64%) were able to have EPOCH dose adjusted to level 2 or more. Of 28 patients in the R-DA-EPOCH cohort, 25 (89%) and 12 patients (49%) had at least one delayed treatment and reduced chemotherapy dose reduction, respectively.

Treatment outcomes

The overall response rate (ORR) for the entire cohort was 96.6% (CR 89.3% and PR 7.3%). The overall response rate was similar between the two groups (97.3% in R-CHOP vs. 92.9% in R-DA-EPOCH). At the time of analysis, 20 patients had died (15 R-CHOP and 5 R-DA-EPOCH). The major causes of death were disease progression (n = 16, 80%) and infection (n = 4, 20%).

With a median follow-up duration of 32 months, 2-year progression free survival (PFS) and overall survival (OS) for the entire cohort were 89% and 92.1%, respectively. R-CHOP treated patients had similar PFS but marginally better OS than R-DA-EPOCH cohorts (90.2% vs. 80.9%, $p = 0.09$ for PFS and 93.1% vs. 85.3%, $p = 0.05$ for OS) (Figure 1). The Subgroup analyses of 77 high-risk patients, PFS and OS did not differ between R-CHOP and R-DA-EPOCH treated patients (Figure 2). The 2-year cumulative incidence of relapse (CIR) of the entire cohort was 3.9% (95%CI: 0.8-6.9%) (Figure 3). R-DA-EPOCH treated patients showed a trend toward higher 2-year CIR. When stratifying patients based on cell of origin (COO), 2-year PFS of germinal center

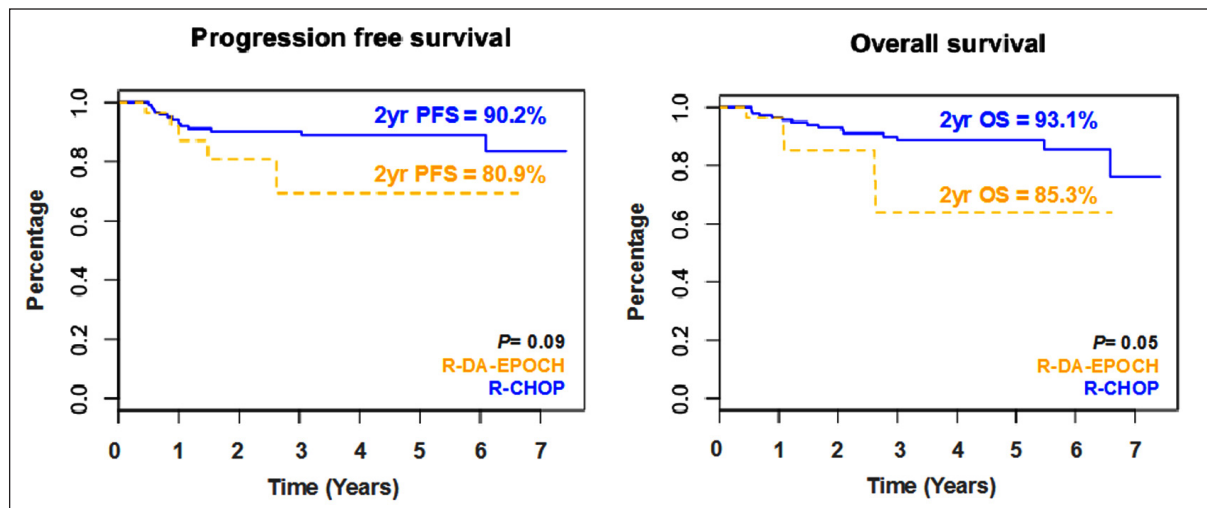


Figure 1 Kaplan Meier Survival Curve of all patients stratified by treatment regimen

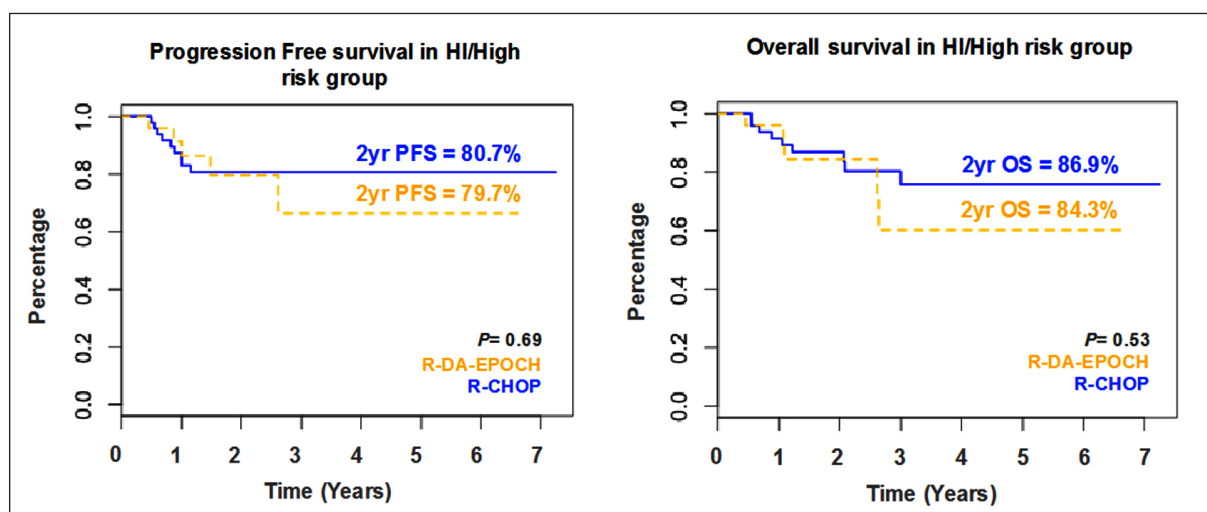


Figure 2 Kaplan Meier Survival Curve of High intermediate & high IPI patients stratified by treatment

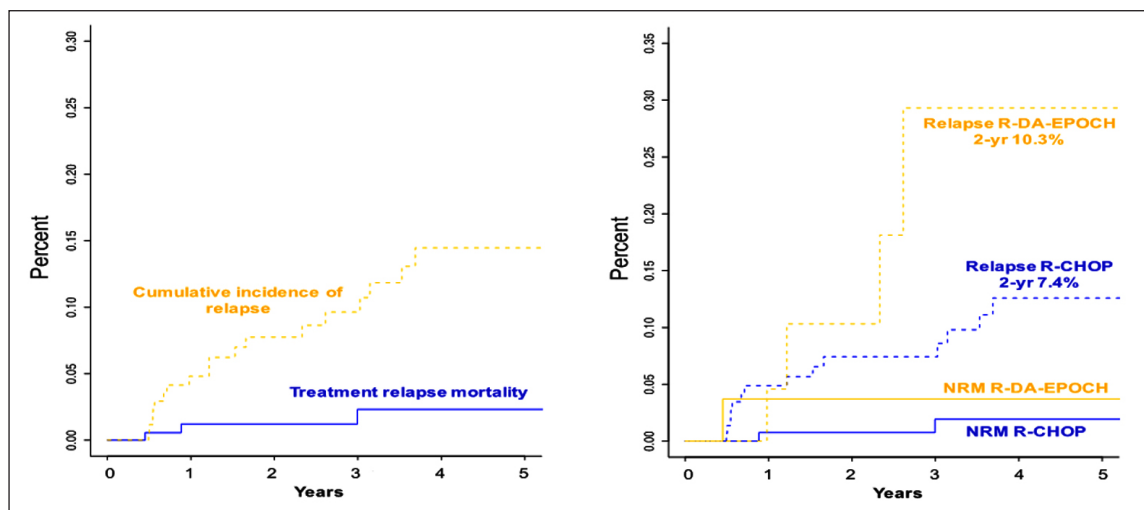


Figure 3 Cumulative incidence of relapse and treatment relapse mortality

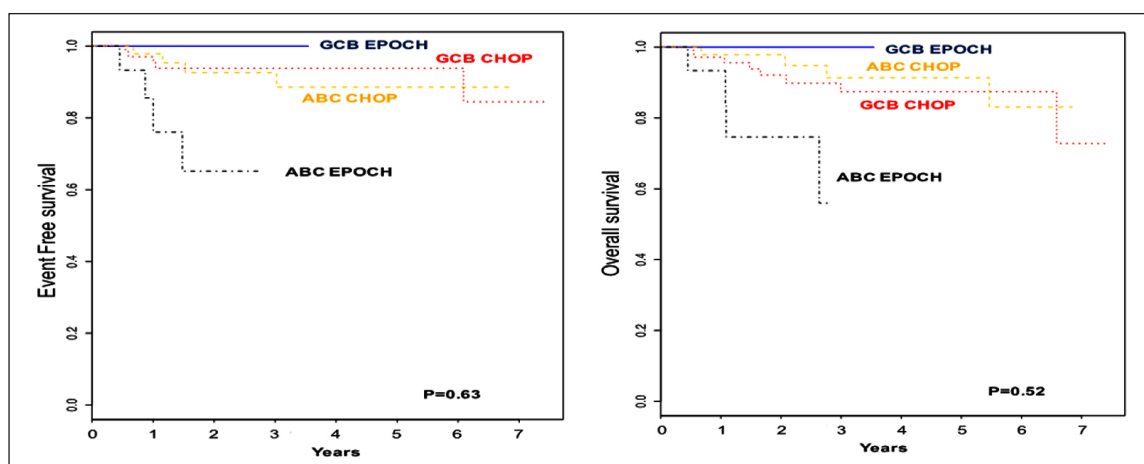


Figure 4 Survival outcome stratified by cell of origin and treatment regimen

like B cell subtype (GCB) and activated B cell subtype (ABC) were 92.6% and 93.9% in the R-CHOP cohort, vs. 100% and 65.2% in R-DA-EPOCH cohort, respectively. However, 2-year OS of GCB and ABC subtype were 97.9% and 92.1% in R-CHOP cohort vs. 100% and 74.7% in R-DA-EPOCH, respectively.

Subgroup analysis in high intermediate and high risk IPI

Subgroup analyses were conducted among 77 patients with high intermediate and high risk IPI. The overall response rate was 94.8% (CR 81.8% and PR 13%). The CR rate did not differ between R-CHOP and R-DA-EPOCH groups (87% vs. 83%, $p = 0.61$). PFS and OS in the R-CHOP and R-DA-EPOCH cohorts were 80.7% vs. 79.7% ($p = 0.69$) and 86.9% vs. 84.3% ($p = 0.53$), respectively. The 2-year CIR was 10.4% and 14.8% for

R-CHOP and R-DA-EPOCH cohorts which did not differ between the two cohorts ($p = 0.62$).

Prognostic factors

Univariable analysis using log rank method demonstrated being female, elevated LDH, impaired ECOG performance status, multiple extranodal sites and high intermediate/high risk IPI as prognostic factors for adverse PFS whereas elevated LDH, advanced stage disease, worsened ECOG performance status, bone marrow involvement, presence of B symptoms and high intermediate/high risk IPI as prognostic factors for adverse OS. Multivariable cox proportional hazard analysis showed only sex as independent prognostic factors for adverse PFS but no parameters as independent factors for OS (Table 2).

Table 2 Univariate and multivariate analysis of factors predicting for survival outcome

Factor	Event free survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value
Age (> 60 years old)	1.30 (0.53-3.11)	0.56	NS	NS	1.76 (0.72-4.28)	0.21	NS	NS
Female	0.28 (0.10-0.86)	0.01	0.31 (0.10-0.93)	0.04	0.51 (0.19-1.32)	0.16	NS	NS
Advance stage	2.31 (0.88-6.02)	0.07	NS	NS	3.27 (1.18-9.01)	0.02	NS	NS
ECOG $\geq$ 2	2.30 (1.01-5.54)	0.05	NS	NS	2.99 (1.24-7.25)	0.01	NS	NS
Elevated LDH	4.97 (1.15-21.46)	0.02	NS	NS	5.20 (1.2-22.5)	0.01	NS	NS
More than 1 extranodal site	3.19 (1.16-8.82)	0.02	NS	NS	2.71 (0.90-8.14)	0.07	NS	NS
High intermediate/high IPI	3.69 (1.41-9.68)	0.004	NS	NS	4.19 (1.60-11.02)	0.002	NS	NS
Presence of B symptoms	1.96 (0.75-5.13)	0.17	NS	NS	3.47 (1.15-10.47)	0.02	NS	NS
R-DA-EPOCH treatment	2.33 (0.84-6.48)	0.09	NS	NS	2.70 (0.97-7.54)	0.06	NS	NS
Activated B cell origin	1.11 (0.99-1.24)	0.16	NS	NS	1.01 (0.89-1.15)	0.52	NS	NS

Table 3 Treatment toxicity and adverse events

	R- CHOP (N = 150)		R- EPOCH (N = 28)		p-value
	n	%	n	%	
Treatment-related death	1	0.67	1	3.57	0.29
All grade 3-5 AEs	50	33.34	18	64.2	0.002
Hematologic	46	30.67	17	60.71	0.002
Nonhematologic	5	3.34	2	7.14	0.3

Adverse events

Patients treated with R-DA-EPOCH (n = 18, 64.2%) developed grade III to IV hematologic toxicity, which was significantly higher than that of patients in the R-CHOP group (n = 50, 33.3%) (p = 0.002) (Table 3). No difference was observed of nonhematologic toxicity between R-CHOP (n = 5, 3.3%) and R-DA-EPOCH (n = 2, 7.1%) (p = 0.3).

Discussion

Immunotherapy has been the gold standard of care for and resulted in improved treatment outcomes of DLBCL over the past decades¹⁵. CHOP chemotherapy has been the cornerstone of regimens¹⁶. Several phase II studies have demonstrating impressive activity of R-DA-EPOCH in the endeavor to increase efficacy by revisiting drug resistant mechanisms of lymphoma cells^{9,10,17}. Complete remission rates were reported in

the ranges of 84 to 94% with 5-year PFS and OS of 75 to 79% and 80 to 84% respectively. These endpoints were comparable or even exceeded expected outcomes seen among R-CHOP treated patients especially in particular DLBCL subtypes, i.e., primary mediastinal B cell lymphoma and gray zone lymphoma^{11,18}. Our study demonstrated similar ORR, PFS and OS of R-DA-EPOCH treated DLBCL-NOS to related reports. However, R-DA-EPOCH was not superior to R-CHOP among patients with DLBCL. This finding might be attributed partly to a higher proportion of high risk patients (elevated LDH, advanced stage and high intermediate/high IPI) in the R-DA-EPOCH cohort compared with the R-CHOP cohort. Another potential explanation is the high rate of treatment delay and failure to escalate chemotherapy dose, both of which could result in disappointing result of R-DA-EPOCH cohort in our study. About 30% of the patients in the R-DA-EPOCH cohort failed to have chemotherapy dose escalation above level 1.

The finding of our study was similar to that recently reported preliminary CALGB/Alliance 50303 trial, which failed to demonstrate the superiority of R-DA-EPOCH over R-CHOP¹². In the CALGB trial, outcomes of patients with high intermediate and high IPI seemed relatively better in the R-DA-EPOCH cohort compared with the R-CHOP cohort although final analysis is still pending. In contrast to the CALGB trial, another smaller phase II trial showed superior efficacy of R-DA-EPOCH over R-CHOP among only patients with low/low intermediate IPI¹³. We did not observe any difference regarding ORR, EFS and OS between R-CHOP and R-DA-EPOCH groups despite subset analysis among high risk patients. No specific prognostic factors were identified that could determine outcomes of patients with DLBCL in our cohort except female sex which independently correlated with better PFS in multivariable analysis. This finding might partly be explained by the pharmacodynamics of rituximab in female patients^{19,20}.

Interestingly, when looking at treatment outcomes stratified by COO subtypes and treatment regimen in our study, COO was not a prognostic factor for response rate, EFS and OS when considered as a single prognostic factor. However, patients with GCB DLBCL treated with R-DA-EPOCH seemed to have the best outcomes at 100% CR rate, 100% 2-year EFS and OS, which were relatively better than other COO subtypes, i.e., GCB treated with R-CHOP, ABC treated with R-CHOP or ABC treated with R-DA-EPOCH, Figure 4. The difference was not statistically significant but could be attributed to the small number of patients in each COO subgroup and relative shorter duration of follow-up. However, this finding is worth exploring in larger clinical trials with longer follow-up durations.

Our study has its own strength as it compared the efficacy of R-CHOP and R-DA-EPOCH in the real-world situation involving resource limited countries. The result of the study also supported the tested hypothesis that R-DA-EPOCH might be particularly effective in certain subgroups of DLBCL, for example, germinal B

cell subtype and primary mediastinal B cell lymphoma. The relative completeness of our chemotherapy dose data allowed us to analyze chemotherapy delivery effect on treatment outcomes. However, our study had several drawbacks. The nature of the retrospective chart review inevitably affected the completeness of the data collection. Some data on cell of origin subtypes was missing due to limited availability of tissue archives among some patients. In addition, we did not have data on the proportion of double-hit or double-expressed lymphoma of patients in our cohort. This information could certainly have affected the survival result. The relatively small numbers of patients in the R-DA-EPOCH and short duration of follow-up might limit any definite conclusion from the study. However, when considering most DLBCL relapse cases within the first two years, the median duration of follow-up 32 months in our study would be justified. Further enrollment and follow-up could be conducted. The final analysis of CALGB/Alliance 50303 will contribute more insights regarding the most appropriate use of R-DA-EPOCH in particular DLBCL subsets. According to our study, R-CHOP continues to be the standard regimen in treating naïve DLBCL-NOS.

Summary

R-DA-EPOCH is an effective treatment regimen for DLBCL. However, based on our study, R-DA-EPOCH was not superior to R-CHOP. The ORR, 2-year PFS and OS and CIR were comparable. However, some limitations were involved in the interpretation in our study as mentioned in the discussion section. To determine whether R-DA-EPOCH would be more beneficial for specific subsets, further studies are warranted.

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