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ORIGINAL ARTICLE – CANCER RESEARCH

DA-EPOCH-R improves the outcome over that of R-CHOP regimen for DLBCL patients below 60 years, GCB phenotype, and those with high-risk IPI, but not for double expressor lymphoma

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Abstract

Purpose This study was to compare DA-EPOCH-R and R-CHOP regimen as first-line therapy in diffuse large B cell lymphoma (DLBCL) patients, retrospectively.

Methods A total of 252 cases treated with R-CHOP and 146 cases who received DA-EPOCH-R were enrolled into this study.

Results Overall, 162 (64.3%) and 105 patients (71.9%) achieved complete remission, 43 (17.1%) and 14 patients (9.6%) achieved partial remission following R-CHOP and DA-EPOCH-R regimen, respectively. After a median follow-up of 48 months, better progression-free survival (PFS) was seen in DA-EPOCH-R group, but no better overall survival (OS) was found in patients treated with DA-EPOCH-R compared to R-CHOP ($P=0.015$ for PFS, $P=0.19$ for OS). However, subgroup analysis according to cell of origin, international prognostic index (IPI), and age showed DA-EPOCH-R resulted in significantly better PFS and OS than R-CHOP regimen in patients with germinal center B-cell-like (GCB) phenotype ($P=0.002$ for PFS, $P=0.007$ for OS), high IPI ($P=0.002$ for PFS; $P=0.03$ for OS), and with a younger age ($P=0.002$ for PFS, $P=0.045$ for OS). We also compared two regimens in patients with double expressor lymphoma (DEL). The prognosis of DEL patients was significantly worse than non-DEL patients ($P<0.001$ for PFS, $P<0.001$ for OS), but DA-EPOCH-R regimen may not overcome the poor prognosis ($P=0.47$ for PFS, $P=0.79$ for OS).

Conclusion GCB DLBCL, younger patients, and high-risk patients, but not DEL patients, may benefit from continuous-infusion DA-EPOCH-R regimen.

Keywords Diffuse large B cell lymphoma · Prognosis · R-CHOP · DA-EPOCH-R · Therapy

Introduction

Diffuse large B cell lymphoma (DLBCL) is a relatively heterogeneous disease. The addition of rituximab has greatly improved the efficacy of CHOP therapy (cyclophosphamide, doxorubicin, vincristine and prednisone) (Coiffier et al. 2010), which made R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen a standard therapy for DLBCL. However, about one-third of DLBCL patients were resistant to standard R-CHOP therapy, associated with rapid clinical progression and short survival time. Many attempts have been made to improve the treatment for DLBCL. DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) therapy was designed based on the findings that prolonged exposure to low-concentration agents can reverse the drug resistance (Lai et al. 1991). Dose adjustment is needed because of different drug clearance among individuals (Wilson et al. 2002). DA-EPOCH-R performed excitingly in the following studies regardless of in de novo DLBCL or refractory or relapsed DLBCL (Wilson et al. 1993, 2002, 2008, 2012), but limited research has compared the efficacy between R-CHOP and DA-EPOCH-R regimens in DLBCL patients. Subgroup

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comparison analyses are also necessary due to the prognostic value of some clinical characteristics such as age, international prognostic index (IPI), cell of origin, stage and so on (Hans et al. 2004; Scott et al. 2015; Varga et al. 2014).

Recently, there has been huge interest in abnormal MYC gene in DLBCL. Double hit lymphoma (DHL) is defined as cases with chromosomal translocation affecting MYC gene in addition with BCL2 or BCL6 gene (Aukema et al. 2011). Double expressor lymphoma (DEL) is identified by immunohistochemistry as cases with MYC and BCL2 proteins overexpression with or without gene aberrations (Green et al. 2012). The prognosis of DHL and DEL is extremely poor following the standard R-CHOP therapy (Hu et al. 2013; Johnson et al. 2009, 2012). Clinicians are exploring more effective approach to prolong their short survivals. DA-EPOCH-R regimen is considered a hopeful therapy for DHL patients (Howlett et al. 2015; Oki et al. 2014; Petrich et al. 2014), while the value of this regimen for DEL remains controversial. Here, we investigated the efficacy of DA-EPOCH-R in patients with DEL compared to R-CHOP regimen.

Materials and methods

Patients

We retrospectively studied 398 patients with de novo DLBCL diagnosed at the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital from July 2006 to December 2015. The diagnosis was according to the 2008 World Health Organization classification (Swerdlow et al. 2008). This study was approved by the institutional review board. Corresponding clinical data were available including age, gender, B symptom, Eastern Cooperative Oncology Group performance status (ECOG PS) score, Ann Arbor stage, lactate dehydrogenase (LDH), IPI, number and site of involvement, treatment regimen and ^{18}F-fluorodexyglucose positron emission tomography/computed (PET/CT) of whole body imaging results or contrast-enhanced computed tomography of neck, chest, abdomen, and pelvis.

Immunohistochemistry

Immunohistochemistry was performed on 4-μm formalin-fixed paraffin-embedded sections. The antibodies used were CD10 (clone 56C6, Dako), MUM1 (clone MUM1p, Dako), BCL6 (clone LN22, Dako), MYC (clone Y69; Abcam, cut-off: 40%) and BCL2 (clone 124; Dako, cut-off: 50%). Hans algorithm (Hans et al. 2004) was used to classify DLBCL patients into two categories (GCB and non-GCB) based on the expression of three proteins (CD10, BCL6 and MUM1). Cases positive for both MYC and BCL2 were defined as DEL.

Treatment

The R-CHOP regimen was given as the usual dose of cyclophosphamide (750 mg/m^2, day 1), vincristine (1.4 mg/m^2, day 1), doxorubicin (50 mg/m^2, day 1), prednisone (60 mg/m^2, days 1–5), and rituximab (375 mg/m^2, day 0). R-CHOP was administrated every 21 days. The DA-EPOCH-R therapy including etoposide (50 mg/m^2), vincristine (0.4 mg/m^2), and doxorubicin (10 mg/m^2) at daily doses by continuous intravenous infusion over 96 h (days 1–4). Cyclophosphamide (750 mg/m^2, intravenous bolus, day 5), prednisone (60 mg/m^2 bid, days 1–5), and Rituximab (375 mg/m^2, day 0). Details on dose adjustment have been published elsewhere (Wilson et al. 2002). Courses were repeated every 3 weeks.

Supportive treatment

During chemotherapy, patients with peripheral blood leucocyte count $< 2.0 \times 10^9$/L received granulocyte-colony stimulating factor. If hemoglobin was < 80 g/L or with poor cardiopulmonary decompensation, patients received infusions of RBC suspensions. If platelets were $< 50 \times 10^9$/L, patients were treated with thrombopoietin, and if platelets were $< 20 \times 10^9$/L or if bleeding tended to occur, patients received infusions of platelet suspension.

Response evaluation

The response was assessed according to Deauville criteria (Meignan et al. 2015) for PET/CT or standard Cheson criteria (Cheson et al. 2007) for CT alone during and after the treatment or disease progression was suspected. Clinical and biochemical follow-up and CT scans were performed every 3 months during the first year, and thereafter every 6 months in the second year, and then yearly or whenever clinically indicated.

Statistical analysis

Progression-free survival (PFS) was defined as the time from the date of diagnosis to the date of disease progression/relapse, patients succumbed to the disease, or last follow-up. Overall survival (OS) was calculated as the time between diagnosis and death due to any cause or last follow-up. Survival was calculated with the Kaplan–Meier method and the significance between subgroups was calculated using the log-rank test. In univariate and multivariate analysis, the Cox proportional-hazards model was used to identify the factors that were significantly associated with PFS or OS. Categorical variables were reported as proportions, and

compared using Chi square test or Fisher's exact test. All Statistical analyses were performed with Graphpad Prism (version 6.0; GraphPad Software, Inc., La Jolla, CA, USA), and SPSS for Windows (version 20.0; IBM Corporation, Armonk, NY, USA), and all tests were two-sides with 5% defined as level of significance.

Results

Patients' characteristics

The clinical characteristics of all 252 cases treated with R-CHOP and 146 cases received DA-EPOCH-R regimen are shown in Table 1. The median age of patients was 55 years (range from 14 to 84 years). A total of 247 (62.0%) patients had advanced disease (stage III–IV) according to Ann Arbor classification (Lister et al. 1989), 155 (38.9%) presented B symptom, 59 (14.8%) had an ECOG PS score of ≥ 2, and 111 (27.9%) had high IPI score (3–5). More than one extranodal involvement and bone marrow involvement (BMI) [BMI criteria should meet one of the following situation: (1) a diffuse pattern of infiltration with large cells that were homogenously positive for B-cell markers detected by bone marrow biopsy; (2) light-chain restriction of BM aspirates gated B cell detected by flow cytometry; (3) immunoglobulin heavy or light chains rearrangement detected by polymerase chain reaction amplification; (4) bone marrow uptake showed an increased activity higher than in the liver detected by PET/CT] were found in 104 (26.1%) and 30 (7.5%) patients, respectively. Elevated serum LDH was observed in 137 (34.4%) patients and bulky disease (any nodal or extranodal tumor mass with a diameter of ≥ 7.5 cm) was seen in 43 (10.8%) patients. The germinal center B-cell-like (GCB) and non-GCB subtype were found in 139 (34.9%) and 259 (65.1%) patients, respectively. A total of 44 (11.1%) and 16 (4.0%) patients received autologous stem cell transplantation (ASCT) or radiation therapy as consolidation therapy. Clinical characteristics were comparable with no significant difference between two groups except that patients below 60 years tended to receive DA-EPOCH-R regimen. The median age of R-CHOP group was 57 years and 51 years in DA-EPOCH-R group.

Table 1 Clinical characteristics of 398 patients with DLBCL

Characteristics	Total	R-CHOP	DA-EPOCH-R	*P* value
Gender				
Male	221	131 (52.0)	90 (61.6)	0.075
Female	177	121 (48.0)	56 (38.4)	
Age (years)				
≤ 60	277	160 (63.5)	117 (80.1)	**< 0.001**
> 60	121	92 (36.5)	29 (19.9)	
Stage				
I–II	151	100 (39.7)	51 (34.9)	0.391
III–IV	247	152 (60.3)	95 (65.1)	
B symptoms				
Absent	243	159 (63.1)	84 (57.5)	0.287
Present	155	93 (36.9)	62 (42.5)	
ECOG PS				
0–1	339	212 (84.1)	127 (87.0)	0.468
≥ 2	59	40 (15.9)	19 (13.0)	
IPI score				
0–2	287	182 (72.2)	105 (71.9)	1.000
3–5	111	70 (27.8)	41 (28.1)	
LDH				
Normal	261	174 (69.0)	87 (59.6)	0.063
Elevated	137	78 (31.0)	59 (40.4)	
Extranodal site				
≤ 1	294	192 (76.2)	102 (69.9)	0.193
> 1	104	60 (23.8)	44 (30.1)	
Hans classification				
GCB	139	82 (32.5)	57 (39.0)	0.193
Non-GCB	259	170 (67.5)	89 (61.0)	
BMI				
Absent	368	233 (92.5)	135 (92.5)	1.000
Present	30	19 (7.5)	11 (7.5)	
Bulky				
Absent	355	225 (89.3)	130 (89.0)	1.000
Present	43	27 (10.7)	16 (11.0)	
ASCT				
Yes	44	22 (8.7)	22 (15.1)	0.067
No	354	230 (91.3)	124 (84.9)	
Radiation				
Yes	16	11 (4.4)	5 (3.4)	0.794
No	382	241 (95.6)	141 (96.6)	

$P < 0.05$ is in bold

ASCT autologous stem cell transplantation, *BMI* bone marrow involvement, *DLBCL* diffuse large B cell lymphoma, *ECOG PS* Eastern Cooperative Oncology Group performance status, *GCB* germinal centre B-cell-like, *IPI* International Prognostic Index, *LDH* lactate dehydrogenase

Response to treatment

A total of 252 cases in this study were treated with 2–8 cycles (median, 6 cycles) of R-CHOP regimen as the first-line immunochemotherapy and 146 cases received 2–8 cycles (median, 6 cycles) of DA-EPOCH-R therapy.

In R-CHOP group, 162 patients (64.3%) achieved a complete response (CR) or CR unconfirmed (CRu), and 43 patients (17.1%) achieved a partial response (PR). CR/CRu and PR occurred in 105 patients (71.9%) and 14 patients (9.6%) on DA-EPOCH-R group. Two (0.79%) and 5 (3.4%) patients got stable disease, and 45 (17.9%)

and 22 patients (15.1%) exhibited progressive disease for R-CHOP and DA-EPOCH-R regimen, respectively.

Survival outcomes

After a median follow-up of 48 months (range 14–183 months), the 5-year PFS and the 5-year OS were 59.0% and 72.0%, respectively. Better PFS was found in DA-EPOCH-R group, but no statistical difference for OS was found between patients treated with DA-EPOCH-R compared to R-CHOP in the whole cohort ($P=0.015$ for PFS, $P=0.19$ for OS, Fig. 1a, b).

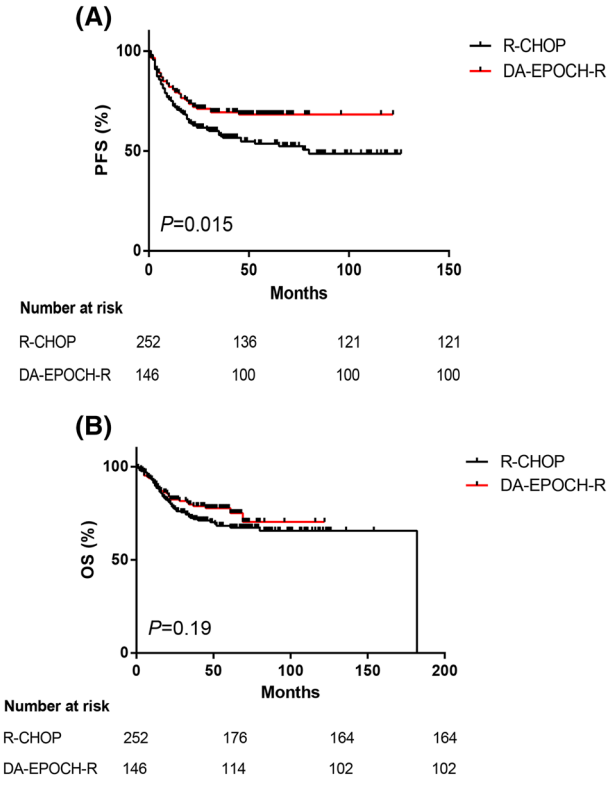

Fig. 1 Survival outcomes in the R-DA-EPOCH and R-CHOP groups. **a** PFS of two regimens in all patients. **b** OS of two regimens in all patients

To accommodate for other important risk factors and compensate for slightly unequal distributions in age, gender, LDH, and ASCT between groups, we carried out a multivariate analysis on the impacts of treatment regimen, age, gender, ECOG PS, B symptom, extranodal site involvement, cell of origin, stage and LDH in cohort without ASCT (Table 2). Treatment regimen, ECOG PS, stage and LDH level were of significant importance to PFS. In relation to OS, treatment regimen, cell of origin, stage and LDH level were also of significant importance.

However, subgroup analysis according to cell of origin categorized by the Hans algorithm, showed that DA-EPOCH-R regimen resulted in significantly better PFS and OS than R-CHOP regimen in patients with GCB phenotype ($P=0.002$ for PFS, HR 0.337, 95% CI 0.161–0.706; $P=0.007$ for OS, HR 0.286, 95% CI 0.108–0.758, Fig. 2a, b). Nevertheless, the survival superiority of DA-EPOCH-R therapy did not remain in non-GCB DLBCL ($P=0.56$ for PFS, HR 0.889, 95% CI 0.595–1.330; $P=0.71$ for OS, HR 1.092, 95% CI 0.681–1.751, Fig. 2c, d).

Furthermore, when categorizing patients according to IPI, we divided patients into low-risk (IPI 0–2) and high-risk group (IPI 3–5). Statistical difference was found for PFS and OS in high-risk patients ($P=0.002$ for PFS, HR 0.439, 95% CI 0.257–0.751; $P=0.03$ for OS, HR 0.512, 95% CI 0.273–0.961, Fig. 2e, f), while in low-risk patients, no worse PFS and OS were found ($P=0.40$ for PFS, HR 0.806, 95% CI 0.505-1,288; $P=0.87$ for OS, HR 1.057, 95% CI 0.595–1.877, Fig. 2g, h).

A stratified analysis according to age discovered significantly better PFS and OS in patients below 60 years

Table 2 Multivariate analysis of PFS and OS in patients without ASCT

Variable	Multivariate analysis PFS			Multivariate analysis OS		
	P	HR	95% CI	*P*	HR	95% CI
Regimen (DA-EPOCH-R)	**0.004**	0.560	0.376–0.833	**0.015**	0.559	0.350–0.895
Age > 60 years	0.173	0.769	0.528–1.122	0.072	0.660	0.419–1.039
Gender (male)	0.278	0.820	0.572–1.174	0.090	0.688	0.446–1.060
ECOG PS ≥ 2	**0.031**	1.581	1.043–2.396	0.054	1.603	0.992–2.590
B symptom (yes)	0.115	1.343	0.930–1.938	0.348	1.229	0.799–1.889
Extranodal site ≥ 2	0.272	1.236	0.847–1.802	0.704	1.090	0.698–1.702
Non-GCB (yes)	0.214	1.280	0.867–1.888	**0.016**	1.803	1.117–2.911
Stage (III–IV)	< **0.001**	3.605	2.096–6.198	< **0.001**	3.494	1.809–6.747
LDH > ULN	< **0.001**	2.267	1.548–3.320	< **0.001**	2.959	1.884–4.647

$P < 0.05$ are in bold

ECOG PS Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal

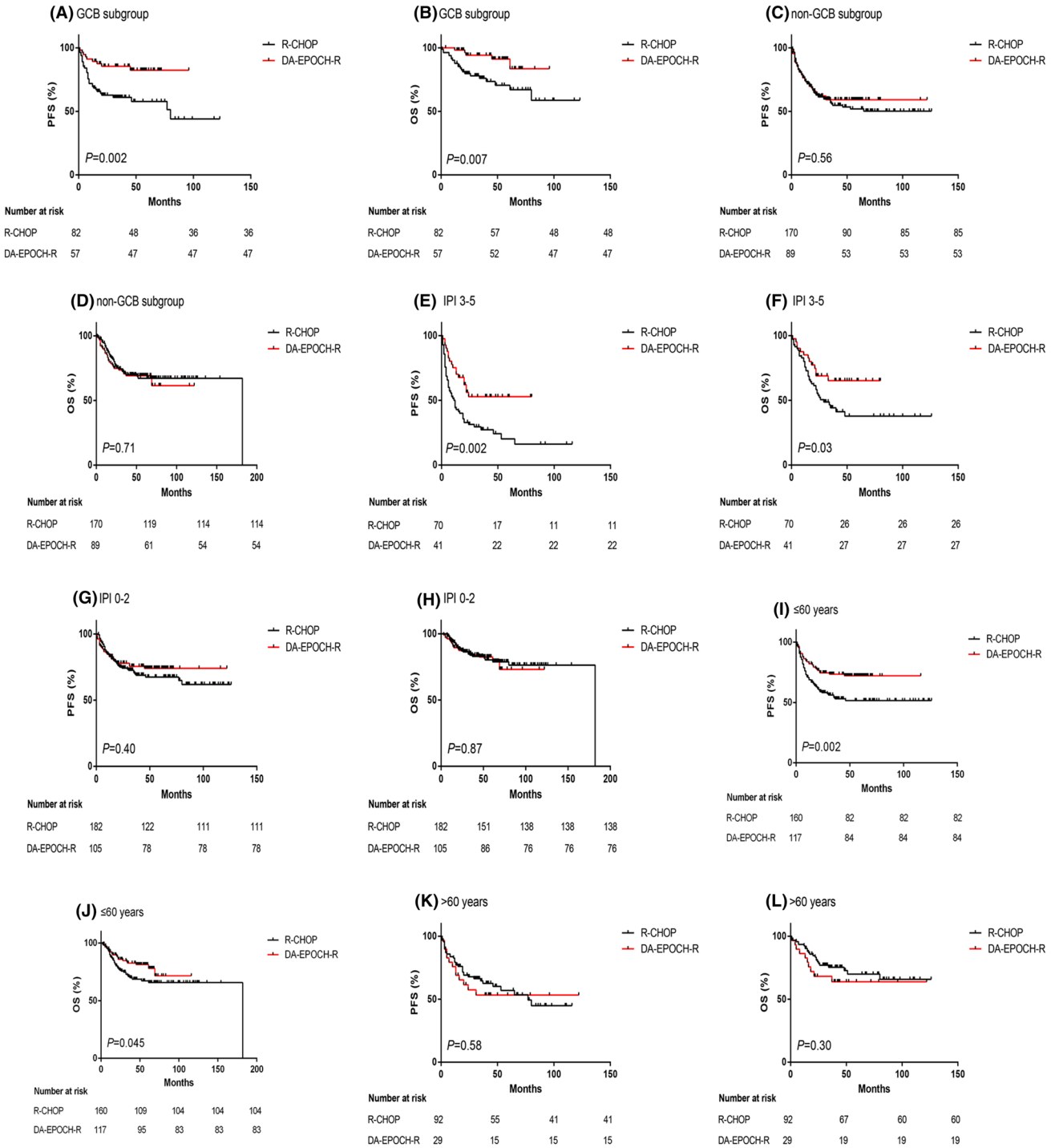

Fig. 2 Subgroup analysis of survival. **a** PFS of two regimens in patients with GCB phenotype. **b** OS of two regimens in patients with GCB phenotype. **c** PFS of two regimens in patients with non-GCB phenotype. **d** OS of two regimens in patients with non-GCB phenotype. **e** PFS of two regimens in high-risk patients (IPI 3–5). **f** OS of two regimens in high-risk patients (IPI 3–5). **g** PFS of two regimens in low-risk patients (IPI 0–2). **h** OS of two regimens in low-risk patients (IPI 0–2). **i** PFS of two regimens in patients below 60 years old. **j** OS of two regimens in patients below 60 years old. **k** PFS of two regimens in patients over 60 years old. **l** OS of two regimens in patients over 60 years old

($P=0.002$ for PFS, HR 0.52, 95% CI 0.341–0.759; $P=0.045$ for OS, HR 0.599, 95% CI 0.36–0.997, Fig. 2i, j). In contrast, the efficacy of R-CHOP and DA-EPOCH-R was comparable in patients over 60 years ($P=0.58$ for PFS, HR 1.193, 95% CI 0.634–2.246; $P=0.30$ for OS, HR 1.478, 95% CI 0.705–3.096, Fig. 2k, l).

Toxicity

Toxicity was assessed in 328 patients on study (Table 3). The most common grade 3/4 toxicities were anemia, neutropenia, thrombocytopenia, and fever with neutropenia. A low incidence of grade 3/4 hematologic toxicity was recorded in R-CHOP group compared with DA-EPOCH-R group, with at least one episode of anemia in 8.3% versus 17.4% of patients, neutropenia in 25% versus 55.3% of patients, thrombocytopenia in 6.4% versus 21.2% of patients and fever with neutropenia in 7.8% versus 31.1% of patients. There were three and two treatment-related deaths in R-CHOP and DA-EPOCH-R group, respectively. All five patients died from neutropenic sepsis. Mild peripheral neuropathy was present in seven patients of R-CHOP arm and ten patients in DA-EPOCH-R arm, respectively, but was moderate and controllable. Gastrointestinal toxicity such as nausea/vomiting, mucositis, constipation and diarrhea was generally mild. Other non-hematologic adverse events consisted of cardiac arrhythmia appeared in three and two patients in R-CHOP and DA-EPOCH-R group, respectively. Non-fatal venous thromboembolism happened in two patients who received DA-EPOCH-R. Liver toxicity was seen in 12 patients who received R-CHOP and 5 patients who received DA-EPOCH-R therapy, and one patient in DA-EPOCH-R group progress to liver failure. Two patients with HBV infection experienced the HBV reactivation when treated with R-CHOP. Two patients who received DA-EPOCH-R were diagnosed with secondary cancers, one of whom was diagnosed with myelodysplastic syndrome, and the other was acute lymphocytic leukemia.

Table 3 Toxicity stratified by treatment

Toxicity	R-CHOP ($n=204$)	DA-EPOCH-R ($n=132$)	P value
Hematological (grade 3–4)			
Neutropenia	51 (25.0)	73 (55.3)	**< 0.001**
Anemia	17 (8.3)	23 (17.4)	**0.015**
Thrombocytopenia	13 (6.4)	28 (21.2)	**< 0.001**
Fever with neutropenia	16 (7.8)	41 (31.1)	**< 0.001**
Peripheral neuropathy	7 (3.4)	10 (7.6)	0.125
Gastrointestinal	16 (7.8)	16 (12.1)	0.253
Cardiac arrhythmia	3 (1.5)	2 (1.5)	1.000
Venous thromboembolism	0 (0.0)	2 (1.5)	0.154
Liver toxicity	12 (5.9)	5 (3.8)	0.454
Treatment-related deaths	3 (1.5)	2 (1.5)	1.000
Secondary cancers	0 (0.0)	2 (1.5)	0.154

$P < 0.05$ are in bold

The prognosis of patients with DEL

A total of 189 patients in our cohort have immunohistochemical data of MYC and BCL2. Aberrant expression of MYC and BCL2 was detected in 74 patients (39.0%) and 106 patients (56.1%), respectively, using cut-off of 40% for MYC and 50% for BCL2. Among them, 53 patients (28.0%) were characterized as MYC and BCL2 double expression lymphoma (DEL). In DEL, 13 (24.5%) and 40 (75.5%) patients were GCB and non-GCB subtype, respectively.

Survival analysis showed that patients with DEL had significantly worse prognosis than non-DEL patients ($P<0.001$ for PFS, $P<0.001$ for OS, Fig. 3a, b). Median PFS and OS for DEL patients were 16 and 26 months, while median PFS and OS for non-DEL patients were both undefined.

The correlation between clinical characteristics and survival was analyzed by univariate and multivariate analyses shown in Tables 4 and 5. DEL, B symptom, BMI, advanced stage, ECOG PS ≥ 2, and elevated LDH, were associated with inferior PFS and OS. All factors in univariate analysis predictive of PFS and OS ($P<0.05$) were then entered into multivariate analysis. DEL was an independent prognostic factor for poor survival in patients with DLBCL.

Comparison of two therapies in patients with DEL

In DEL patients, no significant difference of PFS and OS was observed between R-CHOP and DA-EPOCH-R regimen ($P=0.47$ for PFS, $P=0.79$ for OS, Fig. 3c, d). Likewise, even though in DA-EPOCH-R group, the prognosis of patients with DEL was still significantly worse than non-DEL patients ($P=0.03$ for PFS, $P=0.002$ for OS, Fig. 3e, f). DA-EPOCH-R regimen may not overcome the poor prognosis.

Discussion

DLBCL is a heterogeneous disease following standard R-CHOP regimen. Only 60–70% patients can be cured, while one-third patients will have refractory disease or relapse eventually, and associated with rapid clinical progression and short survival. To improve the survival outcomes, many attempts have been made such as elevating dose intensity, adding non-crossing resistant cytotoxic agents and shorten regimen schedule. Nevertheless, less efficacy but more

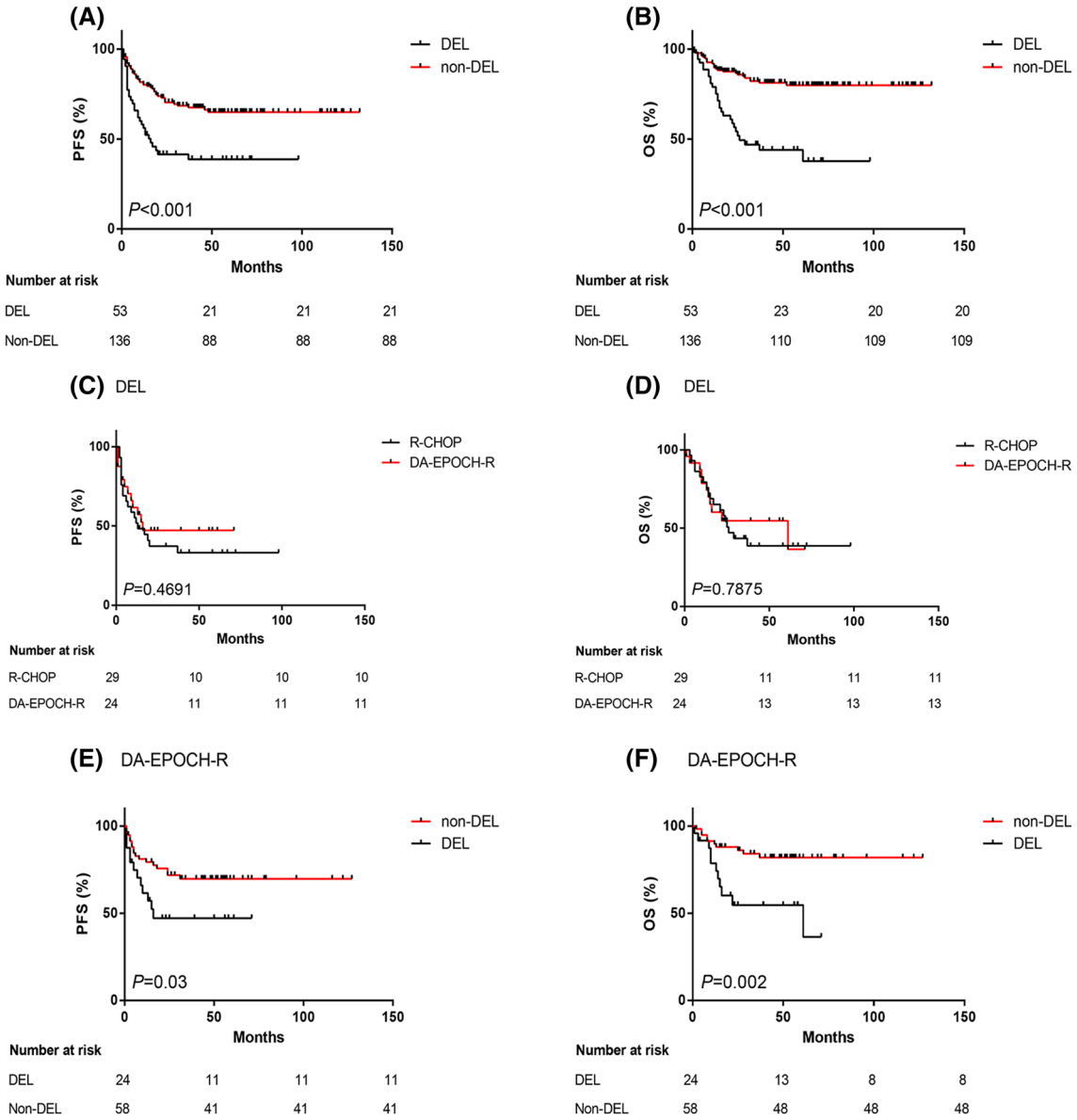

Fig. 3 Subgroup analysis of survival according to DEL and non-DEL. **a** PFS in patients with DEL and non-DEL. **b** OS in patients with DEL and non-DEL. **c** PFS of two regimens in patients with DEL. **d** OS of two regimens in patients with DEL. **e** PFS of DEL and non-DEL patients treated with R-DA-EPOCH. **f** OS of DEL and non-DEL patients treated with R-DA-EPOCH

toxic effects were found. In colon cancer, resistant tumor cell lines mediated by P-glycoprotein were more sensitive to continuous low-concentration drug exposure rather than high-concentration short-time exposure (Lai et al. 1991), and in consideration of the synergy and single-agent efficacy etoposide (Drewinko and Barlogie 1976; Hansen et al. 1980; Yalowich 1987), Wilson et al. (2002) designed the continuous intravenous infusion EPOCH therapy for 96 h. Due to the variation of drug clearance of individuals, they raised a dose-adjusted strategy according to hematopoietic nadir to compensate the plasma drug concentration for young patients (Wilson et al. 2002). The efficacy and well-tolerable toxicity were well-documented in relapsed and refractory as well as untreated DLBCL (Wilson et al. 1993, 2002, 2008, 2012).

A comparison between DA-EPOCH-R and standard R-CHOP as first-line immunochemotherapy was made in this study. However, as for all patients, no statistically superior OS of DA-EPOCH-R regimen over R-CHOP was observed. To further evaluate the effect of DA-EPOCH-R, we compared two regimens by subgroup analysis. Benefits occurred in GCB DLBCL, where the PFS and OS of DA-EPOCH-R were significantly better than R-CHOP. In contrast, non-GCB patients had similar PFS and OS in two

Table 4 Univariate and multivariate analysis of PFS

Variable	Univariate analysis			Multivariate analysis		
	P	HR	95% CI	*P*	HR	95% CI
Sex female	0.957	1.013	0.639–1.604	ND	ND	ND
Age > 60 years	0.294	1.278	0.803–2.035	ND	ND	ND
ECOG PS ≥ 2	**0.006**	2.039	1.211–3.435	0.393	1.273	0.732–2.214
B symptom (yes)	**0.003**	1.956	1.242–3.081	0.294	1.313	0.790–2.184
BMI (yes)	**< 0.001**	3.520	1.958–6.328	0.282	1.458	0.734–2.899
Extranodal site ≥ 2	0.100	1.526	0.914–2.548	ND	ND	ND
DEL (yes)	**< 0.001**	2.427	1.529–3.854	**0.028**	1.749	1.062–2.879
Stage (III–IV)	**< 0.001**	2.846	1.690–4.794	**0.011**	2.073	1.182–3.636
LDH > ULN	**< 0.001**	2.312	1.467–3.646	0.299	1.330	0.776–2.281

$P < 0.05$ are in bold

BMI bone marrow involvement, *DEL* double expressor lymphoma, *ECOG PS* Eastern Cooperative Oncology Group performance status, *IPI* International Prognostic Index, *LDH* lactate dehydrogenase, *ND* not done, *ULN* upper limit of normal

Table 5 Univariate and multivariate analysis of OS

Variable	Univariate analysis			Multivariate analysis		
	P	HR	95% CI	*P*	HR	95% CI
Sex female	0.479	0.817	0.466–1.433	ND	ND	ND
Age > 60 years	0.430	1.249	0.717–2.177	ND	ND	ND
ECOG PS ≥ 2	**0.017**	2.068	1.122–3.812	0.405	1.314	0.691–2.498
B symptom (yes)	**0.025**	1.829	1.067–3.136	0.521	1.217	0.669–2.213
BMI (yes)	**0.001**	2.985	1.497–5.956	0.96	1.020	0.469–2.220
Extranodal site ≥ 2	0.208	1.476	0.800–2.721	ND	ND	ND
DEL (yes)	**< 0.001**	3.808	2.211–6.559	**< 0.001**	3.022	1.711–5.338
Stage (III–IV)	**0.003**	2.433	1.321–4.482	0.145	1.626	0.846–3.123
LDH > ULN	**< 0.001**	2.887	1.668–4.998	**0.050**	1.884	1.000–3.549

$P < 0.05$ are in bold

BMI bone marrow involvement, *DEL* double expressor lymphoma, *ECOG PS* Eastern Cooperative Oncology Group performance status, *IPI* International Prognostic Index, *LDH* lactate dehydrogenase, *ND* not done, *ULN* upper limit of normal

groups. The mechanism of cell of origin as predictive marker for improved outcome after DA-EPOCH-R to DLBCL patients is poorly investigated. GCB DLBCL arises from germinal center B cell characterized by high-expression markers of germinal center differentiation such as CD10 and BCL6, while non-GCB DLBCL arises from post-germinal center B cells that are blocked during plasmacytic differentiation. The expression of CD10 and BCL6 was associated with increased proliferation in lymphoid malignancies (Bai et al. 2003; Shaffer et al. 2000), and the proliferation index was higher in GCB than non-GCB DLBCL (Chiu et al. 2003; Hasselblom et al. 2008; Şen Türk et al. 2011; Snak et al. 2018). However, the expression of BCL2 was significantly higher in non-GCB than GCB lymphoma, and the overexpression of BCL2 was associated with treatment failure of DA-EPOCH (Wilson et al. 2002). Thus, GCB DLBCL is more likely maintained by high tumor-proliferation response, while non-GCB is caused by high anti-apoptotic protein expression. Wilson et al. (2002) found that patients with high proliferation rate had higher rate of PFS and OS than those with lower proliferation rate when treated with DA-EPOCH, but CHOP-based regimen failed to benefit patients with high proliferation (Miller et al. 1994). DA-EPOCH-R was also active in Burkitt's lymphoma, another germinal B cell lymphoma with high proliferation (Dunleavy et al. 2013). Longer drug exposure may rely on increased sensitivity of cycling cells. The antiapoptotic nuclear factor kappa B (NF-κB) is constitutively activated in ABC (active B cell) DLBCL cases, and the activation of NF-κB may block the apoptotic response to chemotherapy, which may partially explain the poor response after doxorubicin-containing therapy including R-CHOP and DA-EPOCH-R (Davis et al. 2001; Lam et al. 2005). ABC DLBCL may be more sensitive to the addition of NF-κB inhibition. Dunleavy

et al. (2009) found that bortezomib can enhance the activity of DA-EPOCH in ABC patients. Bortezomib combination with DA-EPOCH (DA-EPOCH-B) achieved 41.5% CR and significantly longer survival time in ABC group, but DA-EPOCH-B was not helpful in GCB DLBCL. However, in a two phase study, the addition of bortezomib to rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) had no significant difference in CR rate, OR rate, PFS and OS compared to R-CHOP in non-GCB patients (Offner et al. 2015). These two studies suggest that mere bortezomib is not active sufficiently for non-GCB patients, it may also need the synergistic effect of DA-EPOCH. As for GCB DLBCL, the deletion of tumor repressor phosphatase and tensin homolog (PTEN) is a common, which results in the activation of PI3K/AKT pathway. PI3K inhibition has selective toxicity to PTEN-deficient GCB DLBCL models (Pfeifer et al. 2013), suggesting PI3K/AKT inhibition can be combined with chemotherapy for GCB DLBCL.

DLBCL is the most common subtype in non-Hodgkin lymphoma (NHL), and the median age at diagnosis is nearly 70 years (Chihara et al. 2016). Our subgroup analysis according to age showed the prognosis of patients treated with DA-EPOCH-R was significantly better than those with R-CHOP in patients younger than 60 years, but not in patients over 60 years. Hypofunction of bone marrow and comorbidities accompanied with older patients limit the choice of high dose and high-intense chemotherapy regimen which will increase the toxicity, treatment-related complications and mortality rate. DA-EPOCH-R regimen may not be well tolerated in the elderly. Likewise, in subgroup analysis according to IPI, DA-EPOCH-R regimen was more active than R-CHOP regimen in high-risk IPI group with significantly better PFS and OS, but not in low-risk IPI, which indicates high-intensity chemotherapy may not be necessary in patients with low risk. Dunleavy et al. (2013) investigated standard dose DA-EPOCH-R regimen and a short course regimen with a double dose rituximab (SC-EPOCH-RR) in Burkitt's lymphoma patients. Though 47% and 57% lower median cumulative doses of doxorubicin–etoposide and cyclophosphamide were used in the SC-EPOCH-RR group than standard DA-EPOCH-R, PFS and OS were similar in two groups, and SC-EPOCH-RR patients experienced less adverse effect. This investigation further proves that not intensity but length of exposure time above an effective threshold concentration is more important therapeutic principle. Therefore, the short course regimen may be more suitable for the elderly and patients with no high-risk factors.

Recent studies focus on the unfavorable prognostic value of MYC gene rearrangement and protein overexpression. Our results indicated that DEL was an independent adverse prognostic factor in DLBCL patients. The survival of patients with DEL was significantly worse than those without DEL in keeping with previous studies (Hu et al. 2013; Johnson et al. 2012). Little is known about the optimal therapy for these patients. A large retrospective analysis compared four regimens including R-CHOP, DA-EPOCH-R, R-Hyper-CVAD, R-CODOX-M/IVAC in patients with DHL, DA-EPOCH-R performed excitingly with high CR rate and better PFS and OS (Petrich et al. 2014). M.D. Anderson group also proved that patients with DHL can benefit from DA-EPOCH-R therapy (Oki et al. 2014). However, there is no consensus on the role of DA-EPOCH-R in patients with DEL. In our study, no significant difference was observed in patients with DEL treated with R-CHOP and DA-EPOCH-R. Unlike DHL patients, DEL patients are mostly non-GCB origin (Johnson et al. 2012) which may weaken the effect of DA-EPOCH-R. The comparison of combination DA-EPOCH-R or R-CHOP with ASCT as first-line therapy for high-risk DLBCL is still lacking, but DHL patients may not benefit from DA-EPOCH-R followed by ASCT (Chen et al. 2017). In a multi-center retrospective study (Herrera et al. 2017), DHL and DEL were also associated with poor prognosis even after ASCT, but some patients with isolated DEL without DHL can have durable remission after ASCT which indicates that DEL alone should not be the contraindication to ASCT. However, patients with DEL still can not be cured even after allogeneic transplantation (Kawashima et al. 2018). Innovative strategies are needed to improve DEL patients' outcomes. Many promising agents are under development for this disease including inhibitor targeting MYC and BCL2. ABT-199, a BCL2 inhibitor, showed strong synergistic activity with other drug in DHL cell line (Johnson-Farley et al. 2015). GSK525762, an inhibitor of BET family which prevent MYC transcriptional response is investigated in a phase I clinical trials for NHL patients including DHL (Borthakur et al. 2016), we are waiting for their results.

Because of the retrospective and non-randomized nature of our study, the selection bias exists indeed. Due to physician discretion in selecting treatment regimens and dose, more patients older than 60 years received R-CHOP regimen because of severe comorbidity. And the DA-EPOCH-R population had less non-GCB phenotype, more elevated LDH, and more ASCT consolidation therapy, despite no statistical significance. Hence, to remove these interferences as much as possible, we carried out a Cox multivariate analysis on the impact of treatment regimen. This multivariate analysis confirmed that treatment regimen was a predictor of PFS and OS, and the difference in the age distribution between two groups was not of importance. Further studies are also urgently needed to compare the efficacy of two regimens.

In summary, continuous-infusion DA-EPOCH-R regimen may improve the survival of patients younger than 60 years, GCB phenotype, and those with high-risk IPI. No survival benefit was observed in patients with DEL treated with DA-EPOCH-R compared to R-CHOP regimen. It is important

to recognize patients who can benefit from high dose and high-intense regimen after weighting pros and cons.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed coansent was obtained from all individual participants included in the study.

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