

Efficacy of dose-adjusted EPOCH plus rituximab/R-CHOP regimens and the prognosis analysis in patients with *MYC*, *BCL2/BCL6* gene copy number gain lymphoma and double-hit lymphoma: results from a single institution retrospective clinical study

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Purpose: To compare the efficacy of rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-DA-EPOCH) with traditional rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimens in double-hit lymphoma (DHL) and gene copy number gain (CNG) lymphoma and to contrast the prognosis of these two disease types.

Methods: We retrospectively examined 127 cases of newly diagnosed diffuse large B-cell lymphoma (DLBCL), and used fluorescence in situ hybridization (FISH) to detect genetic abnormalities in *MYC*, *BCL2*, and *BCL6*.

Results: In the two schemes, the 2-year progression-free survival (PFS) was higher for R-DA-EPOCH group than for R-CHOP (79.8% vs 57.5%, $P=0.002$), this advantage was also reflected in 2-year overall survival (OS) (81.6% vs 58.5%, $P=0.002$). In double CNG patients, R-DA-EPOCH regimen was significantly better than R-CHOP ($P=0.007$ for PFS, $P=0.010$ for OS), and R-DA-EPOCH has the same advantage in DHL patients ($P=0.001$ for PFS, $P=0.047$ for OS). For the two disease types, the PFS for DHL was inferior to that for double CNG (52.9% vs 72.4%, $P=0.008$), while the OS was not significantly different ($P=0.050$). Subgroup analysis showed that the PFS for double CNG with *MYC* and *BCL2* was superior to that for DHL with *MYC* and *BCL2* ($P=0.043$), this trend is also seen in double CNG and DHL with *MYC* and *BCL6* ($P=0.036$). However, the OS was not significantly different between the two subgroups. Multivariate analyses showed that in DLBCL patients with genetic abnormality detected by FISH, the treatment and disease types were independent prognostic factors. The adverse reaction rates were similar in R-DA-EPOCH and R-CHOP ($P>0.05$).

Conclusion: Our retrospective study shows that DHL has a poorer prognosis than double CNG. Based on its improved lifetime and good tolerance, R-DA-EPOCH is a promising regimen for DHL or double CNG, which is expected to become the first-line treatment for high-risk DLBCL types based on more clinical research.

Keywords: R-DA-EPOCH, R-CHOP, DHL, double CNG, efficacy and prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is highly invasive but curable. It accounts for 30%–40% of non-Hodgkin's lymphoma cases,^{1–3} which shows significant heterogeneity

in terms of age of onset, morphological characteristics, immunohistochemical phenotype, sensitivity to chemotherapy, and survival rate.⁴ With the advent of rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen has greatly improved the disease remission rates of patients with DLBCL, curing more than 80%–85% of DLBCL patients.³ However, there are still some patients with high-risk DLBCL who show poor prognosis after receiving standard R-CHOP, with a 5-year survival rate well <50%.^{3,5} The 2016 WHO classification of the lymphoid hematopoietic system⁶ clearly defined the concurrent translocation of the *MYC* and *BCL2/BCL6* genes as double-hit lymphoma (DHL),⁷ and expression of the *MYC* and *BCL2/BCL6* proteins by immunohistochemistry is known as double-expression lymphoma (DEL).^{8,9} Another molecular factor that affects the prognosis of DLBCL is the double gene copy number gain (double CNG), which is defined as simultaneous increase in *MYC* and *BCL2/BCL6* gene copy number detected by fluorescence in situ hybridization (FISH). Several studies have shown that an increased copy number of the *MYC/BCL2* genes can lead to poor prognosis.^{10–13} Previous studies have focused on comparing the prognosis of DHL with that of DEL at the protein level, while few studies have compared DHL with double CNG at the gene level. In this study, we used FISH to detect abnormalities in *MYC* and *BCL2/BCL6* and compared the prognostic difference of DHL and double CNG.

Due to a high-risk international prognostic index (IPI) score, advanced Ann Arbor stage, and elevated lactate dehydrogenase (LDH) levels, DLBCL patients have rapid disease progression (PD) and short median survival times.^{14,15} In the era of rituximab, the traditional R-CHOP does not effectively improve the survival of patients with high-risk DLBCL, and the optimal treatment remains to be established. In response to these high-risk patients, several studies have attempted to increase their long-term survival using dose- or density-enhanced immunochemotherapy regimens,^{15–23} such as R-DA-EPOCH (rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), R-Hyper CVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, and cytarabine), R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), and R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, and cytarabine). However, these studies did not compare the efficacy of R-DA-EPOCH and R-CHOP regimens in patients with DHL and double CNG. It is also worth noting that the

highly invasive nature of these disease types confers a higher recurrence rate. Whether consolidation therapy, such as hematopoietic stem cell transplantation, is needed after complete remission (CR) remains controversial.^{24–26} We aimed to compare the efficacy and adverse effects of R-DA-EPOCH with R-CHOP in patients with DHL and double CNG.

Methods

Clinical characteristics and regimens

We collected 474 cases of newly diagnosed DLBCL patients who underwent FISH detection from January 2015 to June 2018 in the First Affiliated Hospital of Zhengzhou University, 127 patients of which conformed to the criteria of DHL and double CNG (26 cases of DHL and 101 cases of double CNG). Patients' pathological section was reread by two senior lymphoma pathologists. Patient baseline clinical characteristics included age, gender, Ann Arbor stage, IPI score, serum LDH level, eastern cooperative oncology group score, extranodal lymph node involvement, Ki-67 level, and the presence or absence of a large mass. The genetic abnormality of *MYC* and *BCL2/BCL6* was detected by FISH. Double CNG was defined as simultaneous increase in *MYC* and *BCL2/BCL6* gene copy number, while DHL was defined as the concurrent translocation of *MYC* and *BCL2/BCL6* genes. The Hans classification²⁷ was used to analyze the cell of origin subtype, all patients were treated with R-CHOP or R-DA-EPOCH regimen. The chemotherapy regimens were as follows:

The R-CHOP regimen consisted of rituximab (375 mg/m²) on day 1, followed by CHOP, which consisted of cyclophosphamide 750 mg/m² as an intravenous infusion on day 1, vincristine 1.4 mg/m² (the maximum dose 2 mg) as an intravenous infusion on day 1, doxorubicin 50 mg/m² as an intravenous infusion on day 1, and prednisone 100 mg/m² orally on days 1–5.

The R-DA-EPOCH regimen consisted of rituximab (375 mg/m²) on day 1, followed by DA-EPOCH. The starting dose level of the DA-EPOCH consisted of etoposide 50 mg/m² as a continuous intravenous infusion on days 1–4, vincristine 0.4 mg/m² as a continuous intravenous infusion on days 1–4, doxorubicin 10 mg/m² as a continuous intravenous infusion on days 1–4, cyclophosphamide 750 mg/m² intravenous on day 5, and prednisone 60 mg/m² orally on days 1–5.

For the R-DA-EPOCH regimen, when grade 4 myelosuppression was not reached at the end of the previous cycle of treatment, 20% of the original dose was increased in subsequent cycles until the patient reached grade 4 myelosuppression. The cycle of two regimens was 21 days. All patients were inserted peripheral central line before

treatment. Chemotherapy-related adverse reactions were graded according to the WHO criteria for cancer treatment results,²⁸ specifically, granulocyte colony-stimulating factor (G-CSF) was given when patients suffered leukopenia or neutropenia, recombinant human thrombopoietin (TPO) was used for thrombocytopenia. If necessary, the infusion of blood components can be implemented. Symptomatic supportive care was given for non-hematological toxicities. This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. Informed consent for the collection of medical information was obtained from all patients. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee. The patient consent was written informed consent, and that this study was conducted in accordance with the Declaration of Helsinki.

Observation of efficacy and follow-up

According to the International Working Group's efficacy evaluation criteria,^{29,30} the efficacy is divided into CR, CR unconfirmed (CRu), partial remission (PR), disease stabilization (SD), and PD. An 18F-FDG PET-CT scan was used to evaluate the standard uptake value of the lesion before treatment, while a CT scan was used to evaluate the efficacy every 2 cycles. The lesion was evaluated by PET-CT again after 4 cycles, and the final evaluation was performed after 6–8 cycles. Evaluation of adverse reactions was implemented after every cycle. The primary study endpoints were progression-free survival (PFS), which refers to the time from the start of the study to PD or death from any cause, and overall survival (OS), which refers to the time from the start of the study to death from any cause or the end of the study. The secondary study endpoints were the objective response rate (ORR), defined as the proportion of patients with tumor shrinkage reaching a certain level and maintained for a certain period of time, including the proportion of CR, CRu, and PR. During the first 2 years after treatment, patients were followed up every 3 months during the first year and every 6 months during the second year. The follow-up deadline was September 30, 2018.

Statistical analysis

All data were analyzed using SPSS 22.0. The chi-squared test and Fisher's exact test were used to compare categorical variables. The survival rate of each group was estimated by the Kaplan–Meier method, and the survival rate between two groups was compared by a log-rank test. Prognostic factors were analyzed using COX proportional hazards regression model. All *P*-values were two-sided with a significance level of 0.05.

Results

Patient characteristics

Among the 474 patients who underwent the FISH detection, 127 patients conformed to the criteria of DHL and double CNG, 26 (20.5%) with DHL and 101 (79.5%) with double CNG lymphoma, of which 56 (44.1%) were treated with the R-DA-EPOCH regimen and 71 (55.9%) with R-CHOP. The median age was 55 years (18–85 years), and 74 (58.3%) of the patients had a grade 3/4 Ann Arbor stage. Patients with an IPI score of 3–5 accounted for 31.5%. Of the 127 patients, 4 of whom (3.1%) received transplantation, 1 patient received chimeric antigen receptor T-cell immunotherapy after disease relapse. Patient's characteristics are listed in Table 1, and the composition of DHL and double CNG is shown in Table 2.

Short-term efficacy

The median number of chemotherapy cycles was 6 (range: 4–8), and all 127 patients enrolled could be evaluated for efficacy, including CR (65 cases, 51.2%), CRu (18 cases, 14.1%), PR (10 cases, 7.9%), SD (15 cases, 11.8%), and PD (19 cases, 15.0%). The ORR was 73.2%. The chi-squared test was used to compare ORR between two groups, the results showed that the ORR in patients treated with R-DA-EPOCH was significantly higher than in R-CHOP group (85.7% vs 63.4%, *P*=0.005), while the difference in ORR between two disease types was not significant (*P*=0.131).

Long-term efficacy

The median follow-up time was 12 months (range: 1–33 months); until the end of follow-up, 28 patients died (9 [16.1%] patients were treated with R-DA-EPOCH regimen and 19 [26.7%] cases were treated with R-CHOP). We found that in the two regimens, the 2-year survival rate of R-DA-EPOCH group was significantly superior than that of R-CHOP (79.8% vs 57.5%, *P*=0.002 for PFS; 81.6% vs 58.5%, *P*=0.002 for OS) (Figure 1). We analyzed the survival rates of different regimens in patients with double CNG and DHL, and the results showed that in patients with double CNG, the PFS and OS for the R-DA-EPOCH regimen were significantly better than those for R-CHOP (82.8% vs 63.2% for PFS, *P*=0.007; 85.3% vs 65.0% for OS, *P*=0.010) (Figure 2), similarly, in DHL patients, the PFS and OS for R-DA-EPOCH regimen were higher than those for R-CHOP (73.0% vs 28.1%, *P*=0.001 for PFS, 68.4% vs 38.2%, *P*=0.047 for OS) (Figure 3).

For the two disease types, the PFS of DHL group was significantly worse than that of double CNG (52.9% vs 72.4%, *P*=0.008) (Figure 4), while no significant differences were

Table 1 Baseline clinical characteristics of patients with diffuse large B-cell lymphoma

	Number of patients (%)					
	R-CHOP (n=71)	R-DA-EPOCH (n=56)	P-value	Double CNG (n=101)	DHL (n=26)	P-value
Age (years)			0.002			0.269
>60	34 (47.9)	12 (21.4)		39 (38.4)	7 (26.9)	
≤60	37 (52.1)	44 (78.6)		62 (61.4)	19 (73.1)	
Sex			0.937			0.964
Male	35 (49.3)	28 (50.0)		50 (49.5)	13 (50.0)	
Female	36 (50.7)	28 (50.0)		51 (50.5)	13 (50.0)	
Ann Arbor stage			<0.001			0.705
I/II	40 (56.3)	13 (23.2)		43 (42.6)	10 (38.5)	
III/IV	31 (43.7)	43 (76.8)		58 (57.4)	16 (61.5)	
LDH			0.061			0.028
Elevate	25 (35.2)	29 (51.8)		38 (37.6)	16 (61.5)	
Normal	46 (64.8)	27 (48.2)		63 (62.4)	10 (38.5)	
ECOG PS			0.371			0.961
0–2	61 (85.9)	51 (91.1)		89 (88.1)	23 (88.5)	
3–5	10 (14.1)	5 (8.90)		12 (11.9)	3 (11.5)	
Extranodal involvement			0.023			0.595
Yes	38 (53.5)	41 (73.2)		64 (63.4)	15 (57.7)	
No	33 (46.5)	15 (26.8)		37 (36.6)	11 (42.3)	
Ki-67 (%)			0.341			0.947
>80	27 (38.0)	26 (46.4)		42 (41.6)	11 (42.3)	
≤80	44 (62.0)	30 (53.6)		59 (58.4)	15 (57.7)	
Bulky disease (cm)			0.042			0.808
>7.5	1 (1.4)	5 (8.9)		5 (5.0)	1 (3.8)	
≤7.5	70 (98.6)	51 (91.1)		96 (95)	25 (96.2)	
COO subtype			0.093			0.160
GCB	25 (35.2)	28 (50.0)		39 (38.6)	14 (53.8)	
Non-GCB	46 (64.8)	28 (50.0)		62 (61.4)	12 (46.2)	
IPI			0.363			0.701
0–2	51 (71.8)	36 (64.3)		70 (69.3)	17 (65.4)	
3–5	20 (28.2)	20 (35.7)		31 (30.7)	9 (34.6)	

Abbreviations: CNG, copy number gain; COO subtype, cell of origin subtype; DHL, double-hit lymphoma; ECOG PS, eastern cooperative oncology group performance status; GCB, germinal center; IPI, international prognostic index; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

Table 2 The composition of DHL and double CNG in two regimens

	Number of patients (%)		
	R-CHOP (n=71)	R-DA-EPOCH (n=56)	P-value
<i>MYC</i> and <i>BCL2</i> translocation	7 (9.9)	7 (12.5)	0.204
<i>MYC</i> and <i>BCL6</i> translocation	4 (5.6)	8 (14.3)	
<i>MYC</i> and <i>BCL2</i> CNG	27 (38.0)	26 (46.4)	0.058
<i>MYC</i> and <i>BCL6</i> CNG	33 (46.5)	15 (26.8)	

Abbreviations: CNG, copy number gain; DHL, double-hit lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

observed in OS (52.9% vs 75.2%, $P=0.050$). We performed subgroup analyses on the two disease types, the results showed that the PFS for double CNG with *MYC* and *BCL2*

was superior to that for DHL with *MYC* and *BCL2* (MB2) (73.3% vs 48.2%, $P=0.043$) (Figure 5), this trend is also seen in double CNG and DHL with *MYC* and *BCL6* (MB6) (73.2% vs 51.4%, $P=0.036$) (Figure 6). However, the OS was not significantly different between the two subgroups ($P=0.161$ for MB2; $P=0.166$ for MB6).

Univariate and multivariate analysis

Both univariate and multivariate analyses showed that in DLBCL patients with genetic abnormality detected by FISH, the treatment regimen and disease types were independent prognostic factors while the other factors were not (Table 3). Patients treated with R-DA-EPOCH regimen had a lower risk of death than traditional R-CHOP (PFS: R-DA-EPOCH: HR 0.173; 95% CI: 0.064–0.466; $P=0.001$; OS: R-DA-EPOCH: HR 0.248; 95% CI: 0.104–0.589; $P=0.002$),

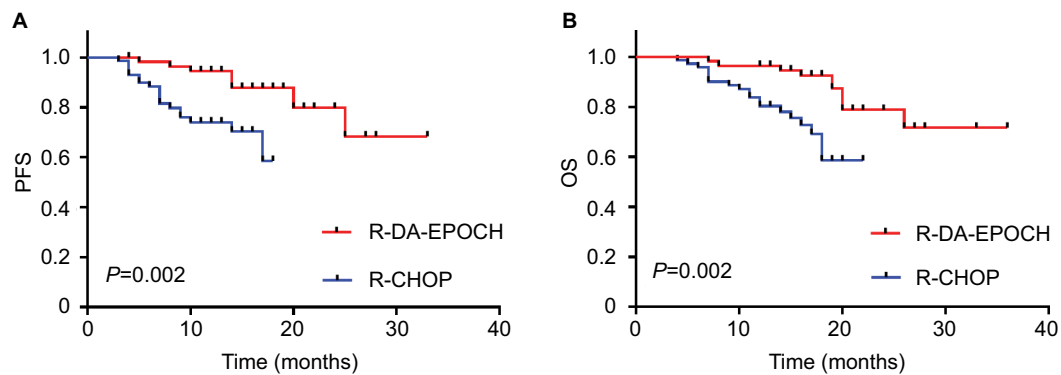


Figure 1 PFS (A) and OS (B) for 127 patients treated with R-DA-EPOCH or R-CHOP regimen.

Abbreviations: OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

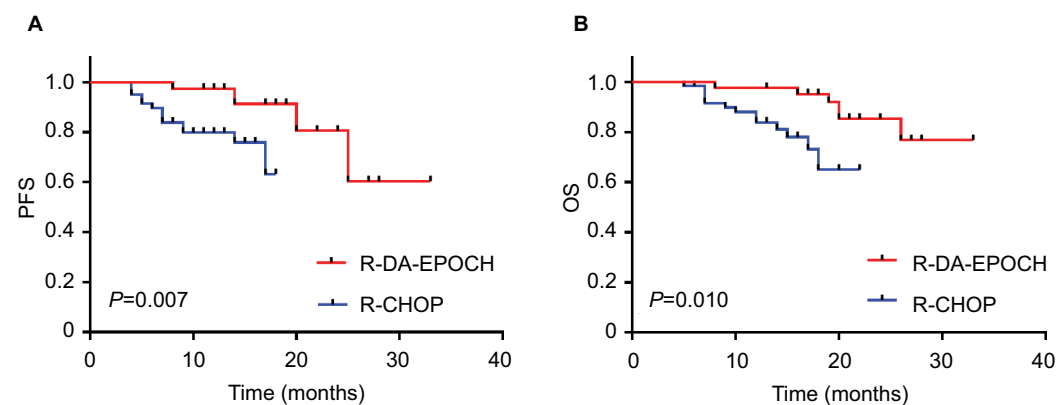


Figure 2 PFS (A) and OS (B) comparing R-DA-EPOCH and R-CHOP regimen in 101 cases double CNG patients.

Abbreviations: CNG, copy number gain; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

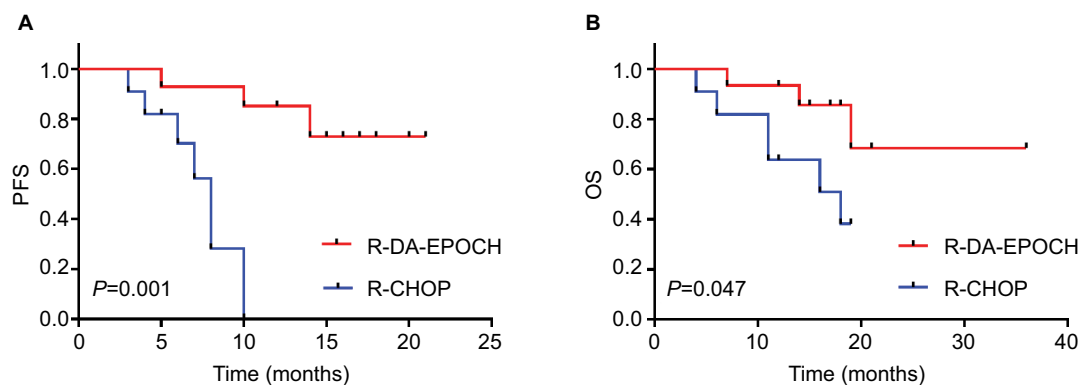


Figure 3 PFS (A) and OS (B) comparing R-DA-EPOCH and R-CHOP regimen in 26 cases of DHL patients.

Abbreviations: DHL, double-hit lymphoma; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

while patients with DHL had a higher risk of death than patients with double CNG (PFS: DHL: HR 4.549; 95% CI: 1.926–10.746; $P=0.001$; OS: DHL: HR 2.506; 95% CI: 1.120–5.606; $P=0.025$).

Adverse effects

Adverse events (AEs) were evaluated in all 127 patients, the main AE in our cohort was hematologic. The incidence of grade 3/4 leukopenia was 41.7%, grade 3/4 neutropenia

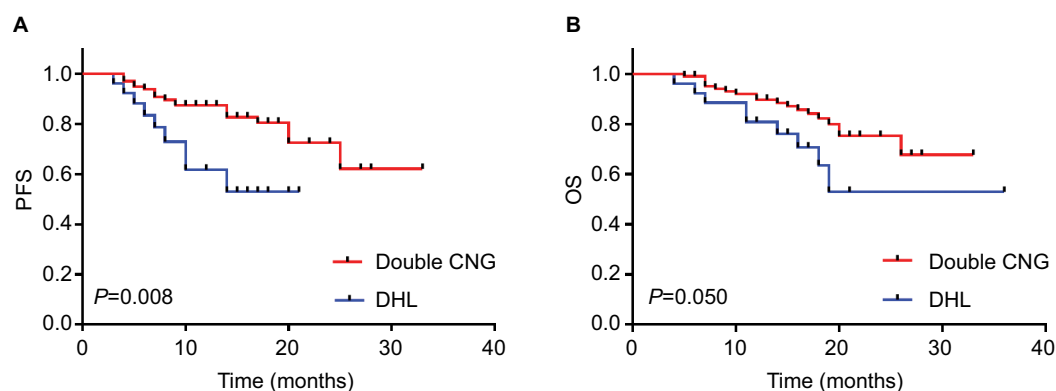


Figure 4 PFS (A) and OS (B) in double CNG and DHL patients.

Abbreviations: CNG, copy number gain; DHL, double-hit lymphoma; OS, overall survival; PFS, progression-free survival.

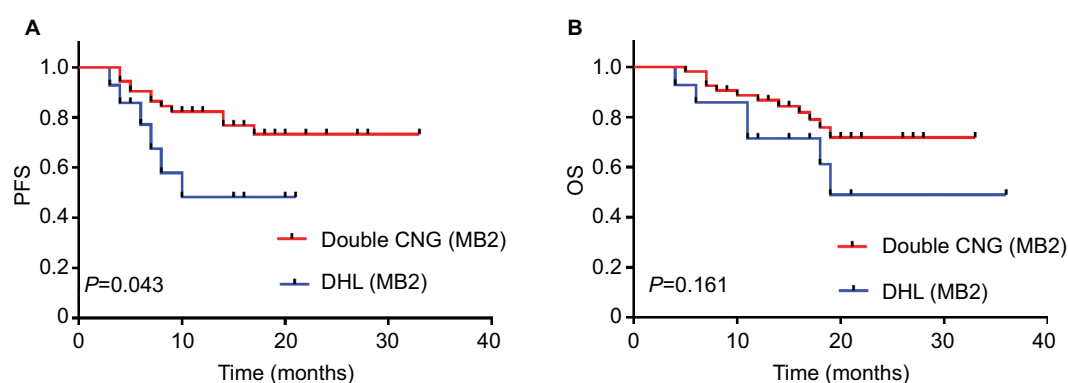


Figure 5 PFS (A) and OS (B) in double CNG (MB2) and DHL (MB2).

Notes: Double CNG (MB2) represented as double CNG of MYC and BCL2. DHL (MB2) represented as DHL of MYC and BCL2.

Abbreviations: CNG, copy number gain; DHL, double-hit lymphoma; OS, overall survival; PFS, progression-free survival.

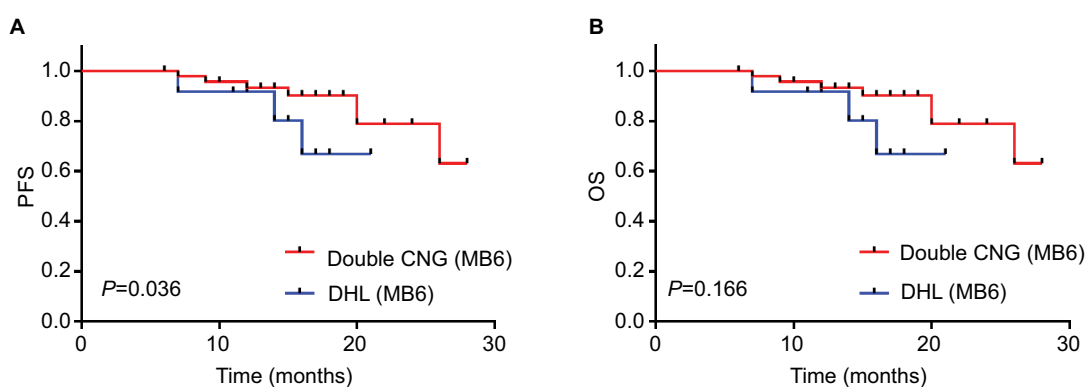


Figure 6 PFS (A) and OS (B) in double CNG (MB6) and DHL (MB6).

Notes: Double CNG (MB6) represented as double CNG of MYC and BCL6. DHL (MB6) represented as DHL of MYC and BCL6.

Abbreviations: CNG, copy number gain; DHL, double-hit lymphoma; OS, overall survival; PFS, progression-free survival.

accounted for 27.6% of all patients, the incidence of grade 3/4 thrombocytopenia was 8.7%, and grade 3/4 anemia occurred in 14.2% patients. The non-hematological toxicity were mild, 10.2% of patients had grade 3/4 elevated alanine aminotransferase/aspartate transaminase levels; 6.3% had

pulmonary infection caused by neutropenia; the incidence of nausea/vomiting was 40.9%, but mainly 1/2 grade AEs; only 7.9% of patients had grade 3/4 of gastrointestinal reactions and 3 (2.4%) had allergic reaction. No serious cardiotoxicity, chemotherapy-related deaths, or secondary

Table 3 Univariate and multivariate analysis for predicting prognosis of diffuse large B-cell lymphoma

	Univariate analysis		Multivariate analysis			
	P-value		PFS		OS	
	PFS	OS	HR (95.0% CI)	P-value	HR (95.0% CI)	P-value
Sex	0.604	0.593	–	–	–	–
Age	0.215	0.084	–	–	–	0.083
Ann Arbor stage	0.668	0.716	–	–	–	–
IPI	0.380	0.408	–	–	–	–
COO subtype	0.993	0.914	–	–	–	–
LDH	0.945	0.839	–	–	–	–
Ki-67	0.457	0.475	–	–	–	–
Extranodal involvement	0.361	0.570	–	–	–	–
ECOG PS	0.633	0.666	–	–	–	–
Bulky disease	0.862	0.847	–	–	–	–
First-time effect	0.035	0.130	–	0.078	–	0.183
Therapeutic regimen	0.002	0.002	0.173 (0.064–0.466)	0.001	0.248 (0.104–0.589)	0.002
Disease types	0.011	0.052	4.549 (1.926–10.746)	0.001	2.506 (1.120–5.606)	0.025

Abbreviations: COO subtype, cell of origin subtype; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, international prognostic index; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

tumors were observed. The grade 3/4 myelosuppression in R-DA-EPOCH was heavier than in R-CHOP, but there was no statistical difference ($P>0.05$), and other AEs were similar (Table 4).

Discussion

Due to the lack of evidence for the optimal treatment of DHL and double CNG in the era of rituximab, physicians can only choose treatments ranging from R-CHOP to R-CHOP-like regimens. The innovation of our research is that we compared the prognosis of DHL and double CNG, and contrast the efficacy of the R-DA-EPOCH and R-CHOP regimens in these two disease types. As far as we know, this is the first report comparing the efficacy of two regimens in this two disease types.

DHL is a subtype of DLBCL with both MYC and BCL2/BCL6 translocations. Studies showed that this type has invasive clinical manifestations and a poor response to R-CHOP, with a mean OS fluctuating between 5 months and 2 years.^{14,31–34} DHL patients are prone to happen central invasion (13%), while after given the prevention treatment such as preventive intrathecal injection, the central recurrence rate is reduced from 15% to 3%.^{35,36} In addition, studies have shown that patients with CNG of MYC/BCL2 have poor prognosis.^{10–13} Yoon et al¹¹ studied 145 patients with DLBCL, 17 (12%) of whom exhibited increased BCL2 copy number and had poor prognosis. Collectively, these studies show that MYC or BCL2 CNG confers inferior survival rates. However, these studies only examined MYC or BCL2 CNG individually, not in combination. Our study analyzed the prognostic difference

between DHL and double CNG, and the results showed that DHL had a shorter 2-year PFS than double CNG ($P=0.008$), while the OS was not significantly different ($P=0.050$). Sub-group analysis showed that patients with double CNG (MB2) had a higher PFS to patients with DHL (MB2) ($P=0.043$), similarly, patients with double CNG (MB6) had a superior PFS to patients with DHL (MB6) ($P=0.036$), while the OS in two subgroups was not significantly different. The aforementioned results suggested that DHL has a poorer prognosis than double CNG. Considering the short observation period and small sample size of DHL patients, some bias may exist in analysis of small subgroups, and further clinical studies are needed to confirm these findings.

At present, there is no international consensus on the standardized treatment for DHL/double CNG. Some investigators have analyzed prognosis by increasing the dose or density of chemotherapy and observed better therapeutic effects.^{15–23,26} In recent years, two large-scale retrospective clinical analyses^{17,36} have shown that the application of R-DA-EPOCH regimen significantly increased the PFS compared with other regimens in DHL. Petrich et al¹⁷ investigated 311 patients in a multicenter retrospective analysis, and results showed that each enhancement protocol significantly improved the PFS rate (R-DA-EPOCH compared with R-CHOP, $P=0.0463$; R-Hyper CVAD, $P=0.001$; R-CODOX-M/IVAC, $P=0.036$), while no significant difference was observed in OS ($P=0.119$). Howlett et al³⁶ investigated 394 patients from 11 studies, and this meta-analysis showed that the median PFS of R-CHOP, R-EPOCH, and dose intensity groups (refers to R-Hyper-

Table 4 Treatment-related adverse events between R-CHOP and R-DA-EPOCH regimen^a

Adverse events	Grade 1/2, n (%)		Grade 3/4, n (%)		P-value
	R-CHOP	R-DA-EPOCH	R-CHOP	R-DA-EPOCH	
Hematologic					
Leukopenia	33 (46.5)	28 (50.0)	29 (40.8)	24 (42.9)	0.819
Neutropenia	30 (42.3)	27 (48.2)	18 (25.4)	17 (30.4)	0.655
Thrombocytopenia	11 (19.6)	14 (25.0)	6 (8.5)	5 (8.9)	0.546
Anemia	18 (25.4)	15 (26.8)	10 (14.1)	8 (14.3)	0.974
Non-hematologic					
Pulmonary infection	1 (1.4)	2 (3.6)	2 (2.8)	3 (5.4)	
ALT/AST elevation	29 (40.8)	23 (41.1)	7 (9.9)	6 (10.7)	
Nausea/vomit	23 (32.4)	19 (33.9)	6 (8.5)	4 (7.1)	
Cardiotoxicity	0 (0)	0 (0)	0 (0)	0 (0)	
Anaphylactic reaction	1 (1.4)	2 (1.6)	0 (0)	0 (0)	

Note: ^aWHO grade of adverse reaction.

Abbreviations: ALT/AST, alanine aminotransferase/aspartate transaminase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

CVAD, R-M/A, R-CODOX-M/IVAC) were 12.1, 22.2, and 18.9 months, respectively. Furthermore, the PD risk of R-DA-EPOCH was reduced by 34% compared with that of R-CHOP ($P=0.032$). However, there was no significant difference in the OS between different regimens. Récher³⁷ compared the efficacy of the R-ACVBP and R-CHOP regimens in an open-label randomized trial, and observed a superior 3-year event-free survival (EFS), PFS, and OS in the R-ACVBP group compared with the R-CHOP group after a median follow-up of 44 months (81% vs 67%, $P=0.0035$ for EFS; 87% vs 73%, $P=0.0015$ for PFS; 92% vs 84%, $P=0.0071$ for OS). However, hematological toxicity in R-ACVBP group was significantly increased. H. Sun³⁸ studied 32 patients with DHL in a retrospective analysis, and the results showed that R-CODOX-M/IVAC combined with transplantation increased the PFS and OS to 41% and 53%, respectively. Taken together, these studies have shown that although a stronger chemotherapy regimen can improve the survival of patients with high-risk DLBCL, the toxicity of intensive regimens is increased compared with that of R-CHOP regimen.³⁷ Our study showed that the ORR of the R-DA-EPOCH group was higher than that of R-CHOP group ($P=0.005$). For 2-year PFS and OS, R-DA-EPOCH also showed significant advantages over R-CHOP (79.8% vs 57.5%, $P=0.002$ for PFS; 81.6% vs 58.5%, $P=0.002$ for OS). Separately analyzing the survival of patients with DHL and double CNG, we found that for double CNG patients, the R-DA-EPOCH regimen achieved a higher 2-year PFS and OS than traditional R-CHOP (82.8% vs 63.2%, $P=0.007$ for PFS; 85.3% vs 65.0%,

$P=0.010$ for OS), similarly, in DHL patients, the PFS and OS for R-DA-EPOCH regimen were higher than those for R-CHOP (73.0% vs 28.1%, $P=0.001$ for PFS; 68.4% vs 38.2%, $P=0.047$ for OS). These results are consistent with those of studies by Petrich et al¹⁷ and Howlett et al³⁶, which indicate that the R-DA-EPOCH demonstrates therapeutic advantages both in DHL and double CNG.

Since the administration of the R-DA-EPOCH regimen is continuous intravenous infusion, the adverse reactions increase simultaneously. The results showed that the grade of 3/4 myelosuppression in R-DA-EPOCH was heavier than in R-CHOP (Table 4), while there was no statistical difference ($P>0.05$). In addition, these AEs can be returned to normal within a short period of time after given symptomatic treatment, no chemotherapy-related deaths or secondary tumors occurred, indicating that R-DA-EPOCH regimen is relatively safe.

Conclusion

In summary, our retrospective study showed that DHL has a poorer prognosis than double CNG. Compared with traditional R-CHOP, R-DA-EPOCH is a more effective and well-tolerated regimen for both DHL and double CNG, and is expected to become the first-line treatment for these two disease types. However, due to the potential limitations of single center, small sample, retrospective analysis, further prospective, multicenter, and large-scale studies are needed to establish the status of R-DA-EPOCH regimen and the first-line therapy for these high-risk DLBCL patients.

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Disclosure

The authors report no conflicts of interest in this work.

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