

DA-EPOCH-R is more effective and less toxic than modified CODOX-M/IVAC-R for treating Chinese HIV-infected patients with Burkitt lymphoma: an uncontrolled retrospective clinical trial

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Abstract

BACKGROUND Burkitt lymphoma (BL), commonly associated with human immuno-deficiency virus (HIV) in China, is an aggressive B-cell lymphoma with a poor prognosis. Current treatments are insufficient and have severe side effects in adult patients with immunodeficiency.

METHODS We retrospectively studied HIV-positive patients with untreated BL from December 2011 to June 2019. We compared a low-intensity treatment regimen comprising infused etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (dose-adjusted EPOCH-R, study group) and a dose-intensive regimen comprising cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine, and rituximab (CODOX-M/IVAC-R, control group). Differences in survival outcomes, toxicity, and survival-associated factors were analyzed.

RESULTS Twenty-eight consecutive patients were enrolled with integrated clinical data, with 18 patients in the DA-EPOCH-R group and 10 in the modified CODOX-M/IVAC-R group. The median age of patients was 40 years (range: 21–60 years). The median baseline absolute CD4+ cell count was 243.5 cells/ μ L. All patients had high-risk diseases. Overall, grade 3–4 toxicity was observed at least once in 22 patients. The principal grade 3–4 toxic events, namely leukopenia (100% vs. 50%), febrile neutropenia (90% vs. 22.2%), and thrombocytopenia (80% vs. 16.7%), were significantly higher in the control group than in the study group. One patient in the control group died of septic shock induced by pneumonia. The median follow-up time was 19 months, and the median overall survival (OS) was significantly improved in the study group compared with that in the control group [18.0 months (95% confidence interval [CI], 14.0–22.0 months) vs. 7.9 months (95% CI, 4.8–11.0 months), respectively; $P = 0.032$]. Treatment with DA-R-EPOCH was a favorable prognostic factor for OS (HR: 0.19 [95% CI: 0.05–0.68]; $P = 0.011$).

CONCLUSIONS DA-EPOCH-R may be an alternative to modified CODOX-M/IVAC-R, with better efficacy and lower toxicity, for treating Chinese patients with high-risk HIV-associated BL.

Background

With the introduction of combination antiretroviral therapy (cART), the survival of patients with acquired immunodeficiency syndrome (AIDS)-associated lymphoma has increased three-fold since the era of highly active antiretroviral therapy (HAART) [1]. However, human immuno-deficiency virus (HIV)-positive patients with Burkitt lymphoma (BL), continue to have a very poor prognosis [2–9]. BL cases are rare among the general population, but they comprised 10–37.2% of HIV-associated NHL cases in the era of HAART [9–11]. HIV-positive patients with BL closely resemble the general BL population in terms of stage, marrow involvement (33–35%), central nervous system (CNS) involvement (17–19%) [12], and histology [13]. BL is an aggressive type of non-Hodgkin lymphoma (NHL) characterized by obligate *MYC* expression, which drives a nearly 100% growth phase fraction. The prognosis of BL is significantly worse compared with that of diffuse large B-cell lymphoma (DLBCL), according to limited data on Chinese HIV-related NHL cases [8, 9].

Improved immune function in the HAART era has led to a reevaluation of full-dose, high-intensity chemotherapy. Moreover, HIV-positive patients with BL and preserved immune function may benefit from more aggressive chemotherapeutic regimens with strong toxicities, such as the modified cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine, and rituximab (CODOX-M/IVAC-R) regimen [4–7], which is preferentially recommended under current National Comprehensive Cancer Network (NCCN) guidelines. The AIDS Malignancy Consortium 048 trial further prospectively evaluated modification of the CODOX-M/IVAC regimen in 34 patients with HIV-associated BL. This trial demonstrated a grade 3–4 toxicity rate of 79%, with a 68% protocol completion rate [5]. The one-year progression-free survival (PFS) rate was 69%, and the overall survival (OS) rate was 72%; the two-year OS rate was 69% [5]. The severe toxicity of CODOX-M/IVAC ± R has gained attention. Chinese patients with HIV-associated BL in the retrospective case series evaluated by Xiao et al. also experienced a 33.3% rate of grade 3–4 infectious complications, with a 13.3% rate of septic shock, when treated with a regimen of CODOX-M/IVAC ± R [8]. An optimal treatment regimen has not been established for HIV-associated BL in China.

Therefore, because of the perceived risk of increased hematologic and infectious complications, HIV-associated BL cases tend to be treated with low-intensity therapy. During the HAART era, dose-adjusted infusional etoposide, infusional doxorubicin, and cyclophosphamide with infusional vincristine, prednisone, and rituximab (DA-R-EPOCH) is another preferred regimen for treating HIV-associated DLBCL under current NCCN guidelines based on the results of multiple phase II clinical trials and retrospective studies [10, 14–16]. Moreover, because of severe side effects and inferior outcomes of CODOX-M/IVAC-R in immunodeficiency patients, the DA-R-EPOCH regimen was tested as an alternative to improve the toxicity profile and effectively treat BL [17]. Dunleavy et al. investigated DA-EPOCH-R and a short course regimen with a double dose of rituximab (SC-EPOCH-RR) in 30 untreated patients with BL [17]. In this trial, 11 patients with HIV-associated BL were enrolled in the SC-EPOCH-RR group. The median follow-up period was 73 months in the SC-EPOCH-RR group, and the PFS and OS rates were 100% and 90%, respectively [17]. Despite these advancements, the median OS of Chinese HIV-associated BL patients was approximately 1 year [8, 9], treatment of those remains challenging. Additionally, no studies have evaluated the efficacy and tolerability of the DA-EPOCH-R versus modified CODOX-M/IVAC-R regimens.

Thus, in the present retrospective study, we compared the safety and clinical outcomes of DA-R-EPOCH versus modified CODOX-M/IVAC-R combined with cART in Chinese patients with BL.

Patients And Methods

This prospective study was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University, Beijing, China. All patients provided written informed consent.

Patients

Twenty-eight patients were consecutively enrolled between December 2011 and June 2019 from a top-tier comprehensive hospital. All patients had documented HIV infection and were newly diagnosed with

untreated BL according to the World Health Organization (WHO) criteria [18]. Fluorescence *in situ* hybridization for *MYC* using a break-apart probe was performed for patients in whom the immunophenotype and morphology were not obvious for a BL diagnosis.

All patients underwent diagnostic procedures, molecular evaluations, and treatment with DA-R-EPOCH or modified CODOX-M/IVAC-R. Pre-treatment evaluations included patients' demographic characteristics, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), complete blood count, blood chemistry, and computed tomography or magnetic resonance imaging scans of the abdomen and pelvis. All patients were staged according to the Ann Arbor staging system. The disease risk was evaluated according to NCCN guidelines. Patients were regarded as high-risk based on the following features: stage I and abdominal mass or extra-abdominal mass > 10 cm or Ann Arbor stage II–IV. Patients not meeting these criteria were regarded as low-risk [19].

The eligibility criteria were as follows: adequate cardiac function (ejection fraction $\geq 50\%$), ECOG PS of 0–3; and renal (serum creatinine of ≥ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min) and hepatic function (aspartate aminotransferase and alanine aminotransferase $\leq 3 \times$ the upper limit of normal and direct bilirubin level of ≥ 2.0 mg/dL) unless they were secondary to antiretroviral therapy. In this case, the total bilirubin cutoff was ≥ 3.5 mg/dL, provided that the direct bilirubin was normal. Additionally, absolute neutrophil count $\geq 1.5 \times 10^9/L$ and platelet count $\geq 50 \times 10^9/L$ were necessary unless they were disease-related. Cases of primary CNS BL or atypical BL were excluded. Prior malignancies were excluded unless the patient had been disease-free more than 5 years other than having curatively treated cutaneous basal cell or squamous cell carcinoma, *in situ* cervical carcinoma, or cutaneous Kaposi sarcoma. Non-measurable diseases (e.g., isolated bone marrow involvement) were allowed. Patients lost to follow-up or who refused systemic treatment were excluded.

Treatment administration

DA-EPOCH-R was administered through a central line on days 1–5 as a 96-h continuous infusion of etoposide (50 mg/m²/d), doxorubicin (10 mg/m²/d), and vincristine (0.4 mg/m²/d; no cap) and oral prednisone (60 mg/m²/d) with cyclophosphamide (750 mg/m²) on day 5 as previously described [13]. Rituximab (375 mg/m²) was administered on day 1 (before continuous infusion began). For subsequent cycles, cyclophosphamide was dose-adjusted according to specified guidelines based on nadir counts. Eighteen patients were scheduled to be administered DA-EPOCH-R for a total of eight cycles. These patients were administered prophylactic granulocyte colony-stimulating factor with filgrastim or pegfilgrastim. Cycles were repeated every 21 days. Treatment and supportive care options are summarized in **Table S1**.

Ten patients were considered as high-risk and planned to be administered modified CODOX-M/IVAC-R in an R-CODOX-M/IVAC/R-CODOX-M/IVAC sequence for a total of 4 cycles [5]. R-CODOX-M cycles were to span between 21 and 28 days. Treatment and supportive care options are summarized in **Table S2**.

Patients were administered 10 mg of intrathecal methotrexate on days 1 and 5 of cycle 3; this regimen was repeated every three weeks for a total of six doses (i.e., cycles 3–5) regardless of when DA-EPOCH or CODOX-M/IVAC treatment was stopped. Patients with positive flow cytometry or cytology of cerebrospinal fluid test results were administered intrathecal or intraventricular methotrexate twice weekly for two weeks beyond negative flow cytometry for a minimum of four weeks, with consolidation weekly for six weeks and maintenance monthly for six months.

Drug combinations for HIV

All patients were administered cART before initiation of chemotherapy. The preferred regimen was tenofovir and lamivudine, plus efavirenz, as recommended by the Chinese guidelines for diagnosis and treatment of HIV/AIDS (2018) [20]. In this study, patients who did not start cART until diagnosis of lymphoma initiated treatment with tenofovir and lamivudine, plus efavirenz, whereas those administered cART regimens such as zidovudine and lamivudine, plus nevirapine or efavirenz, were switched to the above regimen prior to chemotherapy to reduce the risk of zidovudine-associated myelosuppression and nevirapine-induced liver injury. All patients were administered cART until their death. Patients were also administered prophylactic treatment for pneumocystis pneumonia if CD4 + cell counts were below 200 cells/ μ L [20]. Trimethoprim-sulfamethoxazole is the recommended prophylactic agent, and one double-strength tablet daily is the preferred regimen. Patients with a CD4 count < 50 cells/ μ L were administered azithromycin 1200 mg once weekly against disseminated *Mycobacterium avium* complex disease [20].

Endpoints and follow-up

The primary endpoint was OS. The secondary endpoints included PFS, clinical tumor response, and adverse events (AEs). OS was calculated from the date of study enrollment until death or the last follow-up visit. PFS was calculated from the date of study enrollment until the date of progression or the last follow-up visit. The tumor response was assessed by standard whole-body computerized tomographic scanning criteria [21] after cycle 3, and post-treatment (4–8 weeks, and months 6, 12, 18, and 24). AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 [22]. Patients were followed every three months for two years post-treatment, and then every six months for years 3–5.

Statistical analysis

Survival curves were constructed using the Kaplan-Meier method, and statistical significance was determined using the log-rank test. For PFS, deaths unrelated to acute treatment or lymphoma were censored. Between-group comparisons were performed using the Student *t*-test for continuous data and Chi-square (χ^2) test for categorical data. Furthermore, an exploratory Cox proportional hazard analysis was conducted to assess the influence of baseline characteristics on OS. For univariate analysis, the following variables were included to calculate the independent predictors of PFS and OS: age, ECOG PS, B symptom, primary tumor site, treatment regimen, disease risk classification, Ann Arbor stage, baseline absolute CD4 + cell count, baseline lactate dehydrogenase elevation, and Epstein-Barr virus (EBV) expression. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a non-parametric log-rank test, (i.e., Cox proportional hazards model). All reported *P*-values are two-tailed and

presented without adjustment for multiple comparisons. $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS software (version 17.0, SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

Between December 2011 and June 2019, 41 patients were initially included, of whom 28 were treated with chemotherapy plus rituximab (Fig. 1). Ten patients were administered modified CODOX-M/IVAC-R (control group), and 18 patients received the DA-R-EPOCH regimen (study group). All patients were male and administered cART before chemotherapy.

The baseline patients and disease characteristics were listed in Table 1. The median patient age was 40 years (range: 21–60 years). The median baseline absolute CD4 + cell count was 243.5 cells/ μ L (range: 11–782 cells/ μ L). All patients were classified as high-risk diseases. All evaluable patients were CD20 + CD10 + and had a Ki-67 of > 95%. Most patients (82.1%, 23) presented with bulky disease. Baseline median CD4 + cell counts were comparable between the two groups (198 vs. 188 cells/ μ L; $P = 0.28$). Two patients (20.0%) in the control group were on cART at baseline, whereas five patients (27.8%) in the study group were on cART at baseline. The two groups were well-balanced regarding baseline median CD4 + cell count, age, previous cART, HIV viral load, EBV expression, demographic and disease characteristics (Table 1).

Table 1
Baseline Demographics and Characteristics of Patients

characteristic	CODOX-M/IVAC-R (control group: n = 10)	DA-R-EPOCH (study groupn = 18)	P-value
Age (years) Median (range)	43(29–60)	37(21–58)	0.319(-1.016)
Baseline absolute CD4 + cell count, cells/ul	238(11–415)	244(40–782)	0.439(0.787)
HIV viral load, copies/ml Undetectable (n, %) Positive (n, %) Median (range)	0 10 (100.0%) 46293(3278-1603243)	4 (22.2%) 14 (67.8%) 19414(0-1373237)	0.265 0.361(-0.929)
Having received cART at baseline (n, %)	2 (20.0%)	5 (27.8%)	0.649
Ann Arbor stage I- II (n, %) III-IV (n, %)	3 (30.0%) 7 (70.0%)	6 (33.3%) 12 (66.7%)	1.000
Bulky disease(tumors > 10 cm) (n, %)	9 (90%)	14 (77.8%)	0.418
Primary tumor site Lymph node (n,%) Extra lymphnode organ (n,%)	8 (80.0%) 2 (20.0%)	14 (67.8%) 4 (22.2%)	1.000
ECOG PS 1 (n,%) 2–3 (n,%)	5 (50.0%) 5 (50.0%)	13 (72.2%) 5 (27.8%)	0.412
risk classification Low (n,%) high (n,%)	0 10 (100.0%)	0 17 (100.0%)	1.000

BL: Burkitt lymphoma; ECOG PS:Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; EBV:Epstein-Barr virus; cART, combination antiretroviral therapy

characteristic	CODOX-M/IVAC-R (control group: n = 10)	DA-R-EPOCH (study groupn = 18)	P-value
LDH elevation	9 (90.0%)	12 (66.7%)	0.364
Yes (n,%)	565.5(242.6-1950.7)	369(188-7345.5)	0.769(0.297)
Median(range)	1 (10.0%)	6 (33.3%)	
No (n,%)			
EBV expression	0	4 (22.2%)	0.265
Positive (n,%)	10 (100.0%)	14 (67.8%)	
Negative (n,%)			
Number of cycles	2.5 (2–4)	6 (3–8)	–
Median (range)			
BL: Burkitt lymphoma; ECOG PS:Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; EBV:Epstein-Barr virus; cART, combination antiretroviral therapy			

Treatment Efficacy

The median follow-up time for survivors was 19 months (range, 13.3–20.7 months). Overall, the one-year PFS rate was 47.5%, and 18-month PFS rate was 29.6%. The one-year OS rate was 52.1%, and two-year OS rate was 26.1%. The overall response rates in the study group (DA-R-EPOCH group) and control group (modified CODOX-M/IVAC-R group) were 90% (CR and PR rates of 20% and 70%, respectively) and 94.4% (CR and PR rates of 44.4% and 50%, respectively). The study group had a longer PFS (14.0 months [95% CI, 4.7–23.3 months]) compared with the control group (4.6 months [95% CI, 2.1–7.1 months]; $P = 0.078$) (Fig. 2A). The median OS was significantly prolonged in the study group (18.0 months [95% CI, 14.0–22.0 months]) compared with that in the control group (7.9 months [95% CI, 4.8–11.0 months]; $P = 0.032$) (Fig. 2B). Overall, 11 patients died during the study. One patient died of treatment-related toxicity characterized by septic shock with pneumonia. During the follow-up period, 10 patients died of systemic disease progression, including one patient who died from CNS disease that was not present at baseline.

Treatment-related Adverse Events

The details of toxicities are shown in Table 2. Overall, grade 3–4 toxicity occurred at least once in 22 patients. The occurrence rates of leukopenia (100% vs. 50%), febrile neutropenia (90% vs. 22.2%), and thrombocytopenia (80% vs. 16.7%) were significantly higher in the control group than in the study group. As a result, grade 4 transfusion level anemia occurred in two patients (11.1%), and thrombocytopenia occurred in three patients (16.7%) in the study group. Additionally, grade 4 transfusion level anemia developed in two patients (20%), and thrombocytopenia developed in four patients (40%) in the control group. Because of severe bone marrow suppression, eight patients (80%) acquired grade 3–4 infection in

the control group compared with one (5.6%) in the study group ($P = 0.001$). Furthermore, one patient died of septic shock induced by pneumonia. Five patients had non-hematologic related grade 3–4 toxicities, including three grade 3–4 elevation of serum transaminase, one grade 3–4 elevation of transaminase combined with grade 3 renal toxicity, and one grade 3 gastrointestinal bleeding.

Table 2
AEs between the two regimens

AEs	CODOX-M/IVAC-R (control group: n = 10)			DA-R-EPOCH (study group: n = 18)			P-value
	1/2	3/4	5	1/2	3/4	5	
Neutropenia (n,%)	0	10	0	6	12	0	0.062
Leukopenia	0	10	0	9	9	0	0.010
Anemia	4	6	0	14	3	0	0.057
Thrombocytopenia	2	8	0	4	3	0	0.002
Febrile neutropenia	0	9	0	0	4	0	0.001
Infection necessitating hospital admission	0	8	1	0	3	0	0.001
Weight loss	7	0	0	6	0	0	0.114
Fatigue	4	6	0	7	2	0	0.011
Nausea	9	1	0	12	0	0	0.061
Vomiting	9	0	0	9	0	0	0.048
Anorexia	8	1	0	10	0	0	0.092
Neurologic	10	0	0	11	0	0	0.030
Cardiac	1	0	0	0	0	0	0.357
Decrease of Albumin	8	0	0	5	0	0	0.016
Elevation of transaminase	5	2	0	4	2	0	0.173
Elevation of Total Bilirubin	3	0	0	2	0	0	0.315
Renal	1	1	0	1	0	0	0.345
Dermatologic	2	0	0	2	0	0	0.601
Blood transfusion	6			4			0.097
gastrointestinal bleeding	0			1			1.000
AE: adverse event.							

Table 3 outlines the treatment completion status. Only one patient in the control group completed the treatment scheme. Early termination of therapy in the control group occurred due to disease progression

and AEs in 40% and 50% of patients, respectively. AEs leading to early termination were hematologic ($n = 2$) or infectious ($n = 3$). Further, 35.3% (6 out of 17) high-risk patients in the study group completed the treatment scheme. Early termination of therapy by high-risk patients in the study group occurred because of disease progression, patient withdrawal, and AEs in 29.4% ($n = 5$), 23.5% ($n = 4$), and 11.8% ($n = 2$) of patients, respectively. AEs leading to early termination were hematologic ($n = 1$) or infectious ($n = 1$).

Table 3
Treatment completion status

Status (% <i>n</i>)	CODOX-M/IVAC -R (control group: $n = 10$)		DA-R-EPOCH (study group: $n = 18$)	
	Low-risk	High-risk	Low-risk	High-risk
	Treatment completed per protocol (% <i>n</i>)	0	10% (1)	100% (1)
Disease progression (% <i>n</i>)		40% (4)		29.4% (5)
Early termination (% <i>n</i>)		50% (5)		35.3% (6)
AE (% <i>n</i>)		50% (5)		11.8% (2)
Patient withdrawal (% <i>n</i>)		0		23.5% (4)
AE: adverse events				

Multivariable Analyses

The multivariable Cox proportional hazards model for PFS identified BL with primary extra-nodal organs (HR: 5.43 [95% CI: 1.30–22.80]; $P = 0.021$) and B symptoms (HR: 5.49 [95% CI: 1.62–18.59]; $P = 0.006$) as significant adverse prognostic factors. Patients with primary extra-nodal organs (HR: 28.78 [95% CI: 4.00–207.08]; $P = 0.001$) or B symptoms had significantly worse OS (HR: 7.32 [95% CI: 1.61–33.20]; $P = 0.01$) (Table 4). Treatment with DA-R-EPOCH was a significant favorable prognostic factor for OS (HR: 0.19 [95% CI: 0.05–0.68]; $P = 0.011$) (Table 4), but it was not associated with PFS (HR: 0.52 [95% CI: 0.18–1.49]; $P = 0.22$). Additionally, patients showing an objective response had significant favorable OS (HR: 0.12 [95% CI: 0.018–0.84]; $P = 0.033$).

Table 4
Multivariable Cox proportional hazard model for PFS and OS

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI, P)		HR (95%CI, P)	
	PFS	OS	PFS	OS
Treatment group	0.43	0.37	0.52	0.19
DA-R-EPOCH vs CODOX-M/IVAC-R (reference)	(0.17–1.14, 0.09)	(0.14– 0.96,0.041)	(0.18–1.49, 0.22)	(0.05–0.68, 0.011)
Bulky disease	1.46	1.96	–	2.67
> 10 cm vs ≤ 10 cm (reference)	(0.42–5.12, 0.55)	(0.14– 0.96,0.041)		(0.36–19.84, 0.34)
Baseline cART	0.75	0.75	–	–
Yes vs no (reference)	(0.24–2.33, 0.62)	(0.24– 2.33,0.61)		
ECOG	1.72	2.41	–	0.76
3 vs 1 or 2 (reference)	(0.88–3.36, 0.12)	(1.10– 4.17,0.025)		(0.31–1.89, 0.56)
Primary tumor site	8.05	13.15	5.43	28.78
Extra-nodal organ vs lymph node (reference)	(2.02–3.07, 0.003)	(3.51–49.31, <0.001)	(1.30–22.80, 0.021)	(4.00–207.08, 0.001)
Arbor stage	0.59	0.73	–	–
I/II vs III/IV (reference)	(0.19–1.81, 0.36)	(0.24–2.26, 0.59)		
B symptom	7.77	7.92	5.49	7.32
Yes vs no (reference)	(2.40–25.17, 0.001)	(2.25–27.83, 0.001)	(1.62–18.59, 0.006)	(1.61–33.20, 0.01)
Baseline LDH elevation	1.78	0.86	–	
Yes vs no (reference)	(0.40–8.01, 0.45)	(0.24–3.17, 0.82)		
Note.-Numbers in parentheses are the 95% confidence interval. Objective response is defined as achieving a complete or partial response based on the modified Response Evaluation Criteria for Solid Tumors. BL: Burkitt lymphoma. CR: complete response. PR: partial response. SD: stable disease. PD: progression of disease.				
cART, combination antiretroviral therapy				

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI, P)		HR (95%CI, P)	
	PFS	OS	PFS	OS
Baseline CD4 + cell counts(cells/ul) < 100 vs ≥ 100 (reference)	1.33 (0.38–4.66, 0.66)	0.81 (0.26–2.50, 0.71)	–	
Baseline HIV viral load Undetectable vs detectable (reference)	0.24 (0.031–1.81, 0.17)	0.23 (0.03–1.74, 0.15)	–	
EBV expression Yes vs no (reference)	0.034 (0.00-6.65, 0.21)	0.037 (0.00-13.10, 0.27)	–	–
Efficacy CR or PR vs SD or PD (reference)	–	0.24 (0.051–1.11, 0.068)	–	0.12 (0.018–0.84, 0.033)
Note.-Numbers in parentheses are the 95% confidence interval. Objective response is defined as achieving a complete or partial response based on the modified Response Evaluation Criteria for Solid Tumors.BL: Burkitt lymphoma. CR: complete response. PR: partial response. SD: stable disease. PD: progression of disease.				
cART, combination antiretroviral therapy				

Discussion

Although the clinical outcomes of HIV-positive patients with NHL have improved since the advent of cART, management remains challenging in those with BL. Because of the rarity of this disease, no comparative study of modified CODOX-M/IVAC-R versus DA-R-EPOCH has been performed. This prospective study was designed to compare these regimens, which are recommended by the present NCCN guidelines, in Chinese patients with HIV-associated BL. DA-R-EPOCH may be an alternative to the modified CODOX-M/IVAC-R regimen for treating Chinese patients with HIV-associated BL, with better efficacy as demonstrated by the median OS of 18.0 (95% CI, 14.0–22.0 months) versus 7.9 months (95% CI, 4.8–11.0 months; $P = 0.032$). Particularly, no treatment-related deaths were reported in the DA-R-EPOCH group; however, one patient died of septic shock in the modified CODOX-M/IVAC-R group. Hematologic toxicities were manageable in the DA-R-EPOCH group, and the incidence of febrile neutropenia was much more frequent in the modified CODOX-M/IVAC-R group than in the DA-R-EPOCH group (90% [$n = 9$] vs 22.2% [$n = 4$]; $P = 0.001$).

We found a one-year PFS rate of 47.5% (95% CI, 51–82%), one-year OS rate (primary endpoint) of 52.1% (95% CI, 53–85%), and two-year OS rate of 26.1% (95% CI, 50–82%) in 28 Chinese patients with HIV-associated BL. The survival rates with the CODOX-M/IVAC ± R treatment regimen were contradictory for HIV-associated BL. In one retrospective study of CODOX-M/IVAC with or without rituximab in 80 HIV-positive patients with BL, the 3-year PFS and 3-year OS rates were 68% and 68%, respectively [6]. Another retrospective study of 42 patients with HIV-associated BL treated with CODOX-M/IVAC-R showed a two-year OS rate of 72% and event-free survival (EFS) rate of 81% [7]. Additionally, one study of 34 patients with HIV-associated BL treated with CODOX-M/IVAC-R reported a one-year PFS rate of 69% and one-year OS rate of 72% [5]. However, a study of 35 patients with HIV-associated BL and BL/DLBCL in a South African public hospital reported a two-year OS rate of 38% and two-year EFS rate of 23% [2]. Similarly, our results were very inferior to those of a previous study by Dunleavy, which showed 100% EFS and 90% OS rates in 11 patients with HIV-associated BL treated with SC-EPOCH-RR [17]. Despite the potential differences in the underlying patient populations, the average age (40 years) and median CD4 + cell count (243.5 cells/ μ L) are similar to those of international studies of HIV-associated BL [2–7, 17, 21]. It appears that the prognosis for Chinese patients with HIV-associated BL was worse than that found in previous studies. The reason is unclear, but the ratio of bulky disease was higher than that in previous studies [2–7, 17, 21]. The tumors in Chinese patients with HIV-associated BL may be less differentiated and much more invasive. Therefore, a clinical trial of a more efficacious regimen for Chinese patients with HIV-associated BL is needed.

The present prospective study showed that DA-R-EPOCH significantly prolonged the median OS compared with modified CODOX-M/IVAC-R (18.0 vs. 7.9 months; $P = 0.032$). DA-R-EPOCH yielded a longer median PFS, but this increase was not significant (14.0 vs. 4.6 months; $P = 0.078$). However, the objective response rate (ORR) was similar between the two groups (94.4% for DA-R-EPOCH and 90.0% for modified CODOX-M/IVAC-R). These results are similar to those of a study by Tan et al. on DA-R-EPOCH in 106 cases of HIV-related lymphoma, which showed that the ORR was 78.3% [14]. The results were also consistent with the ORR of SC-RR-EPOCH, which was 100%, as reported by Dunleavy et al., in 11 patients with HIV-related BL [17]. There was no difference between SC-RR-EPOCH and DA-R-EPOCH according to Dunleavy et al., and their ORR was higher than that of 49% in the report by Sissolak et al. on HIV-associated BL treated with mainly intensive chemotherapy regimens: cyto reduction with low-dose cyclophosphamide, vincristine, and prednisone followed by induction with vincristine, methotrexate, cyclophosphamide, doxorubicin and prednisone (LMB-86); or cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone [2]. Additionally, SC-RR-EPOCH had a higher OS rate of 90% compared with OS rates of approximately 70% in studies by Noy et al. and Barnes et al. on CODOX-M/IVAC-R for HIV-associated BL [5, 6, 17]. One study of 30 patients with HIV-associated BL treated with CODOX-M/IVAC showed a three-year OS rate of 52% [22]. Thus, addition of rituximab to traditional chemotherapy is effective and significantly improves ORR and OS [7]. In addition to the stronger anti-tumor activity of DA-R-EPOCH, another potential reason for the improved efficacy of DA-R-EPOCH or SC-RR-EPOCH is the lower toxicity compared with that of the intensive chemotherapy CODOX-M/IVAC-R regimen, which caused grade 3–5 AEs in 80% of patients [5–7, 17].

Approximately 88% of the SC-EPOCH-RR/EPOCH-R cycles were administered to outpatients, whereas the modified CODOX-M/IVAC-R required hospitalization for both high-dose methotrexate and IVAC [5–7]. In our study, all patients were hospitalized. Neutropenic fever was significantly higher in the modified CODOX-M/IVAC-R group than in the DA-R-EPOCH group (90.0% vs. 22.2%; $P = 0.001$). The high toxicity was consistent with that reported previously. In a retrospective study, Xiao et al. found that, of 15 Chinese patients with HIV-associated BL, 12 (80.0%) developed neutropenia, and 7 (46.6%) died of treatment-related causes (septic shock [$n = 4$], hemorrhage [$n = 1$], severe arrhythmia [$n = 1$], and renal failure [$n = 1$]) [8]. Furthermore, in the AMC 048 trial, the frequency of neutropenic fever was 24% [5], and in a study by Dunleavy et al., the frequency was 22% after treatment with DA-R-EPOCH, which required hospitalization [17]. Because of the decreased hematologic toxicity, the rate of infection necessitating hospital admission was significantly decreased in the DA-R-EPOCH group compared with that in the modified CODOX-M/IVAC-R group (16.7 vs. 90%; $P = 0.001$). Additionally, thrombocytopenia of grades 3 and 4 was significantly decreased in the DA-R-EPOCH group compared with that in the modified CODOX-M/IVAC-R group (16.7% vs. 80%; $P = 0.002$). Particularly, we eliminated grades 3 and 4 mucositis toxicities. Compared with that of modified CODOX-M/IVAC-R, the toxicity of DA-R-EPOCH was tolerable and had less fatal treatment-related AEs.

Finally, for prognostic factors of Chinese patients with HIV-associated BL, the primary extra-nodal organ was identified as a significant adverse factor for OS (HR: 28.78 [95% CI: 4.00–207.08]; $P = 0.001$). This suggests that the tumor characteristic at the time of clinical presentation is an important determinant of clinical outcomes. Numerous studies have identified IPI and CD4 + cell counts as important predictors of HIV-associated BL outcomes in the post-cART era [3, 13, 14]. Unlike other studies, the present study found that no clinical disease prognostic characteristics, including IPI and CD4 + cell counts, were associated with PFS or OS. CD4 + cell count was not identified as an important predictor of HIV-associated BL outcome in a retrospective study by Sissolak et al. [2]. Treatment with R-EPOCH was a significant favorable prognostic factor for OS (HR: 0.19 [95% CI: 0.05–0.68]; $P = 0.011$). This finding may account for the potential superiority of DA-EPOCH over modified CODOX-M/IVAC-R among Chinese patients with HIV-associated high-risk BL, including the higher efficacy and lower toxicity. There are challenging questions regarding the role of HAART during treatment of cART [3]. The scientific consensus states that HAART is necessary to prevent uncontrolled HIV replication and loss of immune function during chemotherapy; therefore, 100% of patients were administered HAART before chemotherapy. This may explain why CD4 + cell counts were not associated with the clinical outcomes of chemotherapy plus rituximab.

Our study had some limitations. As this was a prospective single-center study, investigator bias and selection bias could not be avoided. The use of concurrent cART was not uniformly prescribed. Prior WHO guidelines recommended that cART should not be initiated if the CD4 + cell count was > 350 cells/ μL . However, based on Chinese guidelines for HIV [20], all patients were administered cART before chemotherapy regardless of the baseline CD4 + cell count. Finally, our analysis maybe underpowered and could not detect subtle differences in outcomes given the small number of patients in each group.

In summary, the data from our study suggest there is no longer a need for high-intensity, high-toxicity chemotherapy treatment for high-risk BL. We aggressively treated HIV-infected patients with BL and improved OS rates by using DA-R-EPOCH. This regimen minimized drug-related toxicity compared with modified CODOX-M/IVAC-R. Thus, given the severe toxicity associated with previous chemotherapy regimens for BL, the results of this uncontrolled retrospective clinical trial are particularly promising. Confirmatory prospective trials of patients with HIV and BL are warranted.

Abbreviations

cART, combination antiretroviral therapy; HAART, highly active antiretroviral therapy; BL, Burkitt lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; CNS, central nervous system; NCCN, National Comprehensive Cancer Network; PFS, progression-free survival; OS, overall survival; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AE, adverse event; HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response.

Declarations

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Availability of data and materials.

The data and materials are available in the main manuscript.

Authors' contributions

WL and JLC conceived and designed the study. XYD, WS, WL, JLC, YJS, XDG, XML and WDL perform the study, collected and entered the data. XYD and WS analyzed the data. XYD and WS wrote the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the independent ethics board. All patients provided informed consent for both treatment for lymphoma and HIV Author details Cancer Center, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China.

References

1. Meister A, Hentrich M, Wyen C, Hübel K. [Malignant lymphoma in the HIV-positive patient](#). *Eur J Haematol*. 2018;101:119-26.
2. Sissolak G, Seftel M, Uldrick TS, Esterhuizen TM, Mohamed N, Kotze D. Burkitt's lymphoma and B-cell lymphoma unclassifiable with features intermediate between diffuse large b-cell lymphoma and Burkitt's lymphoma in patients with HIV: outcomes in a South African public hospital. *J Glob Oncol*. 2017;3:218-26.
3. Galicier L, Fieschi C, Borie R, Meignin V, Daniel MT, Gérard L, et al. [Intensive chemotherapy regimen \(LMB86\) for St Jude stage IV AIDS-related Burkitt lymphoma/leukemia: a prospective study](#). 2007;110:2846-54.
4. Mead GM, Sydes MR, Walewski J, Grigg A, Hatton CS, Pescota N, et al. [An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study](#). *Ann Oncol*. 2002;13:1264-74.
5. Noy A, Lee JY, Cesarman E, Ambinder R, Baiocchi R, Reid E, et al. AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma. *Blood*. 2015;126:160-6.
6. Barnes JA, Lacasce AS, Feng Y, Toomey CE, Neuberg D, Michaelson JS, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. *Ann Oncol*. 2011;22:1859-64.
7. Alwan F, He A, Montoto S, Kassam S, Mee M, Burns, F, et al. Adding rituximab to CODOX-M/IVAC chemotherapy in the treatment of HIV-associated Burkitt lymphoma is safe when used with concurrent combination antiretroviral therapy. *AIDS*. 2015;29:903-10.
8. Xiao J, Du SX, Dai GR, Gao G, Yang D, Zhao H. Efficacy and tolerability of chemotherapy in Chinese patients with AIDS-related Burkitt lymphoma and diffuse large B-cell lymphoma: an observational study. *Sci Rep*. 2017;7:1905.
9. Shen Y, Zhang R, Liu L, Shen Y, Song W, Qi T, et al. Clinical and prognostic analysis of 78 patients with human immuno-deficiency virus-associated non-Hodgkin's lymphoma in Chinese population. [Infect Agent Cancer](#). 2017;12:7.
10. Barta SK, Xue X, Wang D, Tamari R, Lee JY, Mounier N, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. *Blood*. 2013;122:3251-62.
11. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. *AIDS*. 2014;28:2313-8.

12. Spina M, Tirelli U, Zagonel V, Gloghini A, Volpe R, Babare R, et al. Burkitt's lymphoma in adults with and without human immunodeficiency virus infection: a single institution clinicopathologic study of 75 patients. *Cancer*. 1998;82:766-74.
13. Davi F, Delecluse HJ, Guiet P, Gabarre J, Fayon A, Gentilhomme O, et al. Burkitt-like lymphomas in AIDS patients: characterization within a series of 103 human immunodeficiency virus-associated non-Hodgkin's lymphomas. Burkitt's Lymphoma Study Group. *J Clin Oncol*. 1998;16:3788-95.
14. tan CRC, Barta SK, Lee J, Rudek MA, Sparano JA, Noy A. Combination antiretroviral therapy accelerates immune recovery in patients with HIV-related lymphoma treated with EPOCH: a comparison within one prospective trial AMC034. *Leuk Lymphoma*. 2018;59:1851-60.
15. Little RF, Pittaluga S, Grant N, Steinberg SM, Kavlick MF, Mitsuya H, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood*. 2003;101:4653-9.
16. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood*. 2002;99:2685-93.
17. Dunleavy K, Pittaluga S, Shovlin M, Steinberg SM, Cole D, Grant C, et al. [Low-intensity therapy in adults with Burkitt's lymphoma](#). *N Engl J Med*. 2013; 369:1915-25.
18. Grimm KE, O'Malley Aggressive B cell lymphomas in the 2017 revised WHO classification of tumors of hematopoietic and lymphoid tissues. *Ann Diagn Pathol*. 2019;38:6-10.
19. Oosten LEM, Chamuleau MED, Thielen FW, de Wreede LC, Siemes C, Doorduijn JK, et al. Treatment of sporadic Burkitt lymphoma in adults, a retrospective comparison of four treatment regimens. *Ann Hematol*. 2018;97:255-66.
20. AIDS and Hepatitis C Professional Group, Society of Infectious Diseases, Chinese Medical Association, Chinese Center for Disease Control and Prevention. Chinese guidelines for diagnosis and treatment of HIV/AIDS (2018). *Chin J Intern Med*. 2018; 57:867-84. (in Chinese)
21. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579-86.
22. NCI. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). 2009. <http://ctep.cancer.gov/forms/CTCAE v4.0 pdf>. Accessed 14 June 2010.
23. Oriol A, Ribera JM, Bergua J, Giménez Mesa E, Grande C, Esteve J, et al. High-dose chemotherapy and immunotherapy in adult Burkitt lymphoma: Comparison of results in human immunodeficiency virus-infected and noninfected patients. *Cancer*. 2008;113:117-25.
24. Montoto S, Wilson J, Shaw K, Heath M, Wilson A, McNamara C, et al. Excellent immunological recovery following CODOX-M/IVAC, an effective intensive chemotherapy for HIV-associated Burkitt's lymphoma. *AIDS*. 2010;24:851-6.

Figures

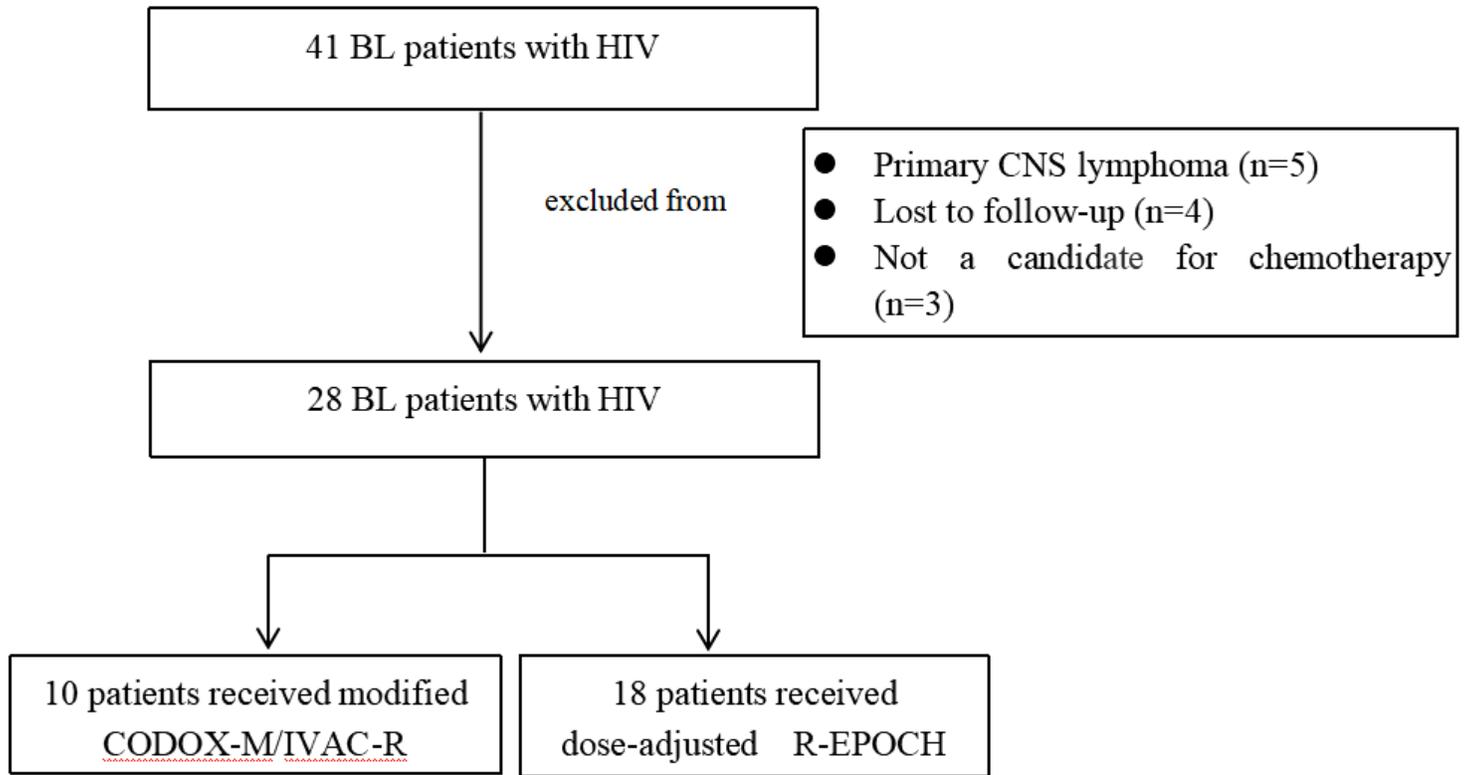


Figure 1

Trial flowchart of participant selection and diagram of treatment.

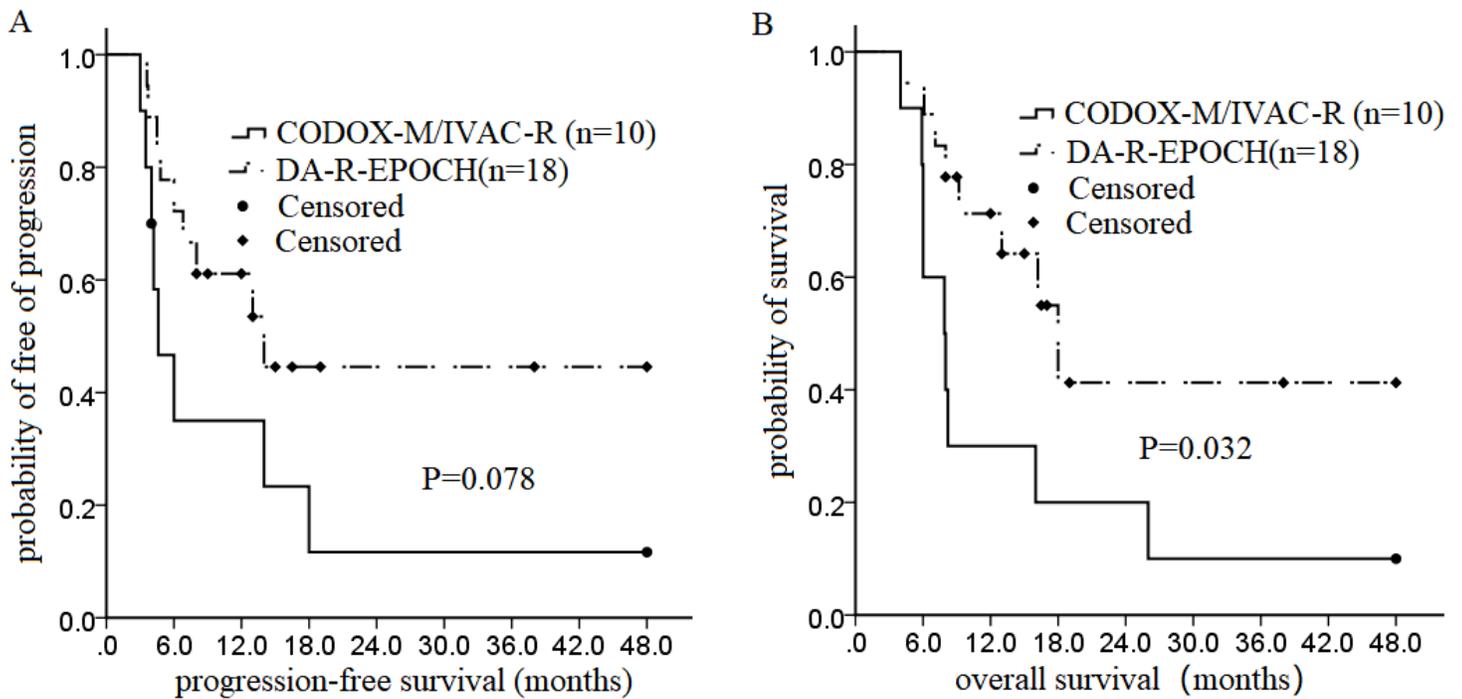


Figure 2

Kaplan-Meier curves showing progression-free survival (A) and overall survival (B) for the two different treatment regimens: DA-R-EPOCH (study group) and CODOX-M/IVAC-R group (control group).

Supplementary Files

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