Clinical characteristics and outcomes for HIV-associated Diffuse Large B-cell Lymphoma in China: A retrospective single-center study

Jiazhu Wu
Jiangsu Province Hospital
Yi Miao
Jiangsu Province Hospital
Xia Li
Yunnan AIDS care center
Jincheng Lou
Yunnan AIDS care center
Chuan Qian
Yunnan AIDS care center
Pengfei Tao
Yunnan AIDS care center
Xicheng Wang
Yunnan AIDS care center
Xingqi Dong
Yunnan AIDS care center
JingJing Guo
the second Hospital of Nanjing
Jinhua Liang
Jiangsu Province Hospital
Wei Xu
Jiangsu Province Hospital
Jianyong Li
Jiangsu Province Hospital
Haiyan Min (454755295@qq.com)
Yunnan AIDS care center https://orcid.org/0000-0002-5144-1776

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Abstract

Background: Human immunodeficiency virus (HIV) infection is associated with an increased risk of aggressive lymphoma, especially diffuse B cell lymphoma (DLBCL). We aimed to analyze characteristics and outcomes of DLBCL in HIV-associated patients. Methods: We retrospectively studied HIV-infected patients with DLBCL since 2011. Data on HIV infection and lymphoma characteristics, treatment and outcome were retrieved and analyzed. Results: In 53 patients with HIV-associated DLBCL, most patients had frequent bad performance status (PS) (74%), elevated LDH level (94%), B symptoms (69%), advanced Ann Arbor (75%), bulky tumor (72%) and extra-nodal involvement (68%) at diagnosis. The median CD4 T cell count was 175/μl, and 17 patients were already on cART treatment. Plasma EBV DNA was detectable in 18 patients (53%, 18/34). Of the patients evaluated at the end of treatment, 21 (64%) achieved CR, 1 (3%) achieved PR and 6 (18%) experienced progressive disease. The 2-year progression free survival (PFS) was 50% and overall survival (OS) rate was 60%. Factors associated with poor PFS in univariate analysis were unfavorable PS, high IPI score and detectable plasma EBV load. High IPI and detectable EBV load correlated with worse OS. However, only detectable plasma EBV load was the independent factor of poor prognosis for PFS (HR: 14.46, 95% CI [2.57-81.50]) and OS (HR: 7.47, 95% CI [1.48-37.59]) in a multivariate Cox regression model. Conclusions: In our population, HIV-associated DLBCL still presented aggressive characteristics and poor survival outcomes. Plasma EBV DNA could be used as a prognostic factor in HIV-infected DLBCL.

Introduction

Human immunodeficiency virus (HIV) infection is associated with an increased incidence of malignancy. HIV-associated diffuse large B cell lymphoma (DLBCL) and Burkitt's lymphoma (BL) are among the commonest cancers in HIV-positive patients [1–3]. Other non-Hodgkin's lymphomas (NHLs), including primary effusion lymphoma (PEL), plasmablastic lymphoma, KSHV-associated multicentric Castleman's disease, primary central nervous system (CNS) lymphoma and classic Hodgkin's lymphoma (cHL), are diagnosed in patients with HIV as well [1]. It has been previously studied that HIV strongly contributed to the NHL mortality, particular in acquired immunodeficiency syndrome (AIDS)-defining subtypes [4]. With the widespread administration of combination antiretroviral therapy (cART), the incidence of HIV-associated lymphoma has decreased and an improvement in the survival outcome has been observed [4, 5].

DLBCL is the most common subtype of lymphoid malignancy in adults. It represents approximately 30% of NHL cases without HIV infection and 45% of cases with HIV-related lymphoma [6–8]. In a Spanish study, compared with HIV-uninfected DLBCL patients, HIV-infected patients had more aggressive features with a poorer performance status, more frequent B symptoms and more advanced Ann Arbor stages [5]. In the above study, when treated with the standard-of-care regimen rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP), HIV-infected patients had a similar disease-free survival but a significantly worse overall survival (OS), compared to those without HIV infection [5]. In contrast, a French study revealed that HIV-infected patients with DLBCL showed survival outcomes similar to those of HIV-negative DLBCL patients [9].

Infections with Epstein-Barr virus (EBV), Hepatitis B virus (HBV), and/or Hepatitis C virus (HCV) have been reported previously in DLBCL, and the former two factors independently predicted poor prognosis [10–13]. In HIV-infected patients with DLBCL, it has been shown that elevated EBV load predicted inferior survival outcome; however, few data on HIV and HBV/HCV co-infected situation in patients with DLBCL were published [13].

The HIV epidemic appears to have obvious regional distribution in China, occurring frequently in Sichuan province and Yunnan province [14, 15]. So far, there are only few studies described the clinical features of Chinese AIDS patients with DLBCL [16, 17]. Herein, we retrospectively analyzed the characteristics and outcomes of Chinese HIV-infected DLBCL patients in Yunnan Provincial Infectious Diseases Hospital/Yunnan AIDS Care Center.

Methods

Patients

We retrospectively included 53 HIV-infected individuals with newly diagnosed DLBCL between 2011 and 2018 in Yunnan Provincial Infectious Diseases Hospital/Yunnan AIDS Care Center, which is the largest HIV/AIDS referral hospital in southwestern China. This study was approved by institutional review board and conducted according to the declaration of Helsinki. The diagnosis was established in accordance with 2008 WHO classification. DLBCL was classified by the Hans classification algorithm. The clinical data were collected from medical records. Data of patient's demographic characteristics (gender and age), HIV-related characteristics (HIV transmission route, years of HIV infection at DLBCL diagnosis, CD4 cell count at DLBCL diagnosis and date of cART initiation), lymphoma-related characteristics (cell-of-origin subtype, Eastern Cooperative Oncology Group (ECOG) performance status score, serum lactate dehydrogenase (LDH), B symptoms, extra-nodal sites, Ann Arbor stage, international prognostic index (IPI) score, bulky tumor, bone marrow involvement and CNS-IPI score) and other related characteristics (EBV load, HBV load, HCV load, comorbidities, time from first complain to diagnosis) were available.

In this study, cART regimen included two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. Patients after diagnosis of DLBCL initiated or were switched to the cART treatment with tenofovir, lamivudine, plus efavirenz or raltegravir potassium. Patients with a $CD4^+$ cell count below 200 cells/μl received trimethoprim/sulphamethoxazole against *Pneumocystis jiroveci* as prophylactic agent. HIV−1 RNA load was monitored during chemotherapy. For patients with positive hepatitis B surface Ag (HBsAg), prophylaxis was not used because both tenofovir and lamivudine have antiviral activity against HBV. HBV DNA (cutoff ≥ 5×10^2 copies/ml) and HCV RNA loads (cutoff ≥ 5×10^2 IU/ml) were assessed during chemotherapy as well. Laboratory monitoring of plasma EBV DNA (cutoff ≥ 5×10^3 copies/ml) load was performed in some patients.

Response assessment

Interim evaluation was performed after completion of three or four cycles of chemotherapy. After one month of the completion of all the treatment, the efficacy evaluation was conducted. Computed tomography (CT) or ^{18}F-fluorodexyglucose positron emission tomography (PET) was performed for radiological

evaluation. Brain Magnetic Resonance Imaging (MRI) was used for CNS involvement evaluation. The 2007 revised Cheson criteria were performed to define complete response (CR), partial response (PR), progressive disease (PD) and relapse.

Statistical analysis

All statistical data were analyzed using SPSS software, version 18 or GraphPad Prism 6. Continuous variables were presented as the median with the first quartile and third quartile, and categorical variables as numbers and percentages. PFS was defined as time from DLBCL diagnosis to progression, relapse or death from any cause. OS was defined as time from DLBCL diagnosis to last follow-up or death from any cause. Survival curves were plotted using the Kaplan-Meier method and the log-rank test was used for comparison. Cox proportional regression models were performed for univariate and multivariate analyses of outcomes. P value 0.05 was considered as statistically significant.

Results

Patient characteristics

The baseline clinical features of HIV-infected patients were summarized in Table 1. Of these patients, median age was 42 and 46 (87%) of them were male. The main HIV transmission group was heterosexuals. Among 53 patients, 20 patients had a HIV infection history more than 1 year at the time of DLBCL diagnosis, and in 24 patients, DLBCL and HIV infection were diagnosed concomitantly. The median CD4 T cell count at DLBCL diagnosis was 175/μl (range 26–551) in these 53 patients, of whom 4 patients had a CD4 T cell count less than 50/μl. At DLBCL diagnosis, 17 patients were already on cART treatment. The median time from patients' first complain to diagnosis was 2 months. Most patients (74%) had a bad performance status (PS) (ECOG PS 2–4), and elevated LDH at diagnosis were present in 94%. Five patients presented with 1 or 2 comorbidities (9%). Six-nine percent of patients had B symptoms, 75% had an advanced Ann Arbor stage (-) and 72% had bulky tumor at diagnosis. Thirty-six patients (68%) had extra-nodal involvement, of whom thirteen patients with more than 2 extra-nodal sites. The most frequent extra-nodal sites were the gut (n = 19), bone marrow (n = 7), stomach (n = 6), bone (n = 6), liver (n = 4) and/or kidney (n = 4). One-third of the patients had a higher central nervous system-IPI (CNS-IPI) at diagnosis. Among 34 cases with information on EBV status, EBV load was elevated (5×10^3 copies/ml) in 18 (53%). Of all patients, six patients (11%) presented with positive HBsAg and four (7.5%) presented with positive anti-HCV antibody.

DLBCL treatment

Forty-two (42/53) patients received CHOP±R regimen among which twenty-one patients received six to eight cycles CHOP±R regimen. Nine of these 42 patients received R-CHOP and seven received CHOP regimen, while five received CHOP followed by R-CHOP or vice versa depending on their financial situation at that time. A total of twelve patients stopped CHOP±R after a median cycle of 3 when symptoms improved without respect to our advices. One patient who received 4 cycles R-CMOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) was switched to R-GOD (gemcitabine, oxaliplatin and dexamethasone) plus oral lenalidomide due to PD. Six patients who received less than 6 cycles CHOP±R regimen died on therapy. Nine patients with high aaIPI or high-grade disease received R-EPOCH/R-DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) regimen. Two patients received first-line R-CHOP progressed in interval evaluation and one was changed to GemOx (gemcitabine and oxaliplatin) regimen and the other was switched to GDP (gemcitabine, dexamethasone and carboplatin) regimen. One patient received four cycles R-CHOP was in PR in interval evaluation; however it was switched to R-GDP regimen due to a high SUVmax of interval PET/CT evaluation. Thirty-eight out of 53 patients received intrathecal methotrexate and cytarabine for central nervous system prophylaxis. Radiotherapy with 40–50 Gy was given in ten patients with bulky tumor among which 4 patients received radiotherapy as consolidation after chemotherapy with CR and 6 patients were treated with concurrent chemoradiotherapy. Three patients were given autologous hematopoietic stem cell transplant (auto-SCT) following chemotherapy.

Treatment response and outcomes

Among forty-seven HIV-infected DLBCL patients who are evaluable in interim analysis, the overall response rate (ORR) was 88%, including 22 (47%) CR and 19 (41%) PRs. Three patients experienced PD and three patients died before the interval evaluation. One died from hemorrhage, one from severe pleural effusion due to *mycobacteriumtuberculosis* and one from rapid progression of disease. Of the 33 patients evaluated at the end of treatment, 21 (64%) achieved CR, 1 (3%) achieved PR and 6 (18%) experienced progressive disease (Table 2). The other 5 patients died during chemotherapy, before response could be evaluated, from sepsis (n = 4), or heart failure (n = 1). No one included in our cohort had baseline CNS involvement. With over 70% patients received CNS prophylaxis, one patient had a CNS relapse 4 months after reaching CR, died quickly.

The median PFS for HIV-infected DLBCL patients in our study was 24 months and median OS was not reached. The overall 2-year PFS and OS rates were 50% (95% CI [33%–65%]) and 60% (95% CI [42%–74%]), respectively (Fig. 1A and 1B). ECOG performance status score at least 2 (HR: 4.73, 95% CI [1.10–20.26]), IPI ≥3 (HR: 3.65, 95% CI [1.08–12.34]) and elevated plasma EBV load (≥5×103 copies/ml) (HR: 6.73, 95% CI [1.78–25.45]) were predictive of worse PFS, while IPI ≥3 (HR: 9.12, 95% CI [1.21–68.83]) and elevated plasma EBV load (≥5×103 copies/ml) (HR: 6.26, 95% CI [1.27–30.80]) were associated with worse OS; however, in a multivariate Cox regression model, only elevated plasma EBV load was the independent factor of poorer prognosis for PFS (HR: 14.46, 95% CI [2.57–81.50]) and OS (HR: 7.47, 95% CI [1.48–37.59]) (Table 3). No HIV related characteristics were associated with PFS and OS. Neither HBV nor HCV co-infection was associated with prognosis. The survival curve of plasma EBV load positive patients (n = 18) and plasma EBV load negative patients (n = 16) for PFS and OS were shown in Figure 1C and 1D, reaching significantly statistical difference (p = 0.001 and p = 0.006).

Discussion

Yunnan is located in southwest China, border with Myanmar, Laos and Vietnam, and has been regarded as the most major site of HIV infection epidemic for a long time [14, 15]. Over the decades, people living with HIV/AIDS is increasing in Yunnan, and it is still one of the provinces with highest number of HIV-infected patients in China [18].

DLBCL is the most common pathological subtype of NHL in both the general population and people living with HIV/AIDS [1–3, 19]. A large database study shows that HIV infection continues to be an independent risk factor for death among patients with lymphoma [20]. We analyzed the clinical features and survival outcomes of HIV-infected DLBCL in the setting of cART in our series. Consistent with other recent studies, HIV-infected patients with DLBCL presented with a poor performance status, a high frequency of B symptoms, elevated LDH, advanced Ann Arbor stage and high aaIPI score [5, 6, 9, 17, 20]. Moreover, bulky disease was frequent. EBV infection is found in approximately 10% of HIV negative DLBCL [21]; however, in our study, 53% of patients with HIV positive DLBCL had elevated plasma EBV DNA load, suggesting a higher rate of EBV co-infection. In contrast, the frequency of HBV infection of HIV-infected patients with DLBCL was similar with their HIV-uninfected counterparts reported in Chinese population [11]. Likewise, the frequency of HCV infection was close to that of HIV negative DLBCL in Caucasian population but lower than that in Asian population [22, 23]. Unlike previous study, in which HIV had been diagnosed a median of 15 years previously and nearly 80% had received cART at DLBCL diagnosis [9], patients in our study revealed the late HIV detection and late cART exposure. It could partially be attributed to the less awareness of HIV testing and less initiative for medical care assistance in high risk HIV population.

Before the introduction of anti-CD20 antibody rituximab, HIV-infected patients with DLBCL treated with CHOP therapy showed a similar response rate and survival as those of HIV-uninfected counterparts [24, 25]. Several retrospective studies of DLBCL patients with HIV infection treated with R-CHOP have been reported. In one study from Spain, HIV-infected DLBCL patients had a CR rate of 69% and a 5-year OS rate of 56%, similar to those of 81% and 74% of HIV-uninfected patients [5]. Similarly, in a report from France, the survival outcomes of HIV-infected DLBCL patients (2-year PFS & OS 81% and 81%) did not differ from those of HIV-uninfected patients (2-year PFS & OS 71% and 83%) [9]. Moreover, Sparana et al, concluded R-EPOCH was an effective regimen in HIV-associated NHL, achieving a CR rate of 73% [26]. In this study, a total of 53 HIV-infected DLBCL patients treated between 2011 and 2018 were analyzed. Most of the patients received CHOP+R regimen, and several patients were given EPOCH+R, based on their disease status and financial situation. Additionally, a cooperative group prospective trial reported the safety and efficacy of auto-SCT in HIV positive lymphoma including DLBCL [27]. In our study, three patients underwent auto-SCT after CR were lymphoma free. At the end of treatment, 64% of evaluable patients achieved CR. The 2-year PFS was 50% and OS rate was 60%. The response rate and survival outcome appear to be lower than others, only similar with a two-year OS rate of 63% from a German cohort, in which mostly patients treated with CHOP-like regimen [7]. One of the reasons might be the less use of rituximab. Medical insurance has not covered the cost of rituximab until the recent years. Besides, Yunnan is a remote province and relatively economically backward, thus, some patients could not afford too much in their treatment and a few had low compliance, did not adherent to the recommended courses of treatment. As a result, the high rate of loss to follow-up (16.9%) made our results less solid.

CNS involvement has been recognized to be more common in AIDS-related lymphomas [28]. A retrospective review of database from clinical trials presented that CNS involvement at baseline was not associated with shortened overall survival, but CNS relapse was associated with a short median OS of 1.6 months [28]. Similarly, one patient in our study had a CNS relapse and died quickly. Although the introduction of prognostic model which is used for assessing the risk of CNS disease in DLBCL has guided the CNS prophylaxis in general DLBCL population, the value of this prognostic model in HIV-infected patients of DLBCL remains unclear. Survival difference was not observed with this prognostic model in our data as most patients received intrathecal prophylaxis, suggesting the role of routine CNS prophylaxis in overcoming the unfavorable prognosis of high CNS-IPI.

It has been shown that HIV-related factors, such as a low CD4 cell count and prior history of AIDS are no longer predictive of worse survival outcome in the cART era [29, 30], which is consistent with our results. On the other hand, the levels of HIV–1 RNA load were negative in all the subjects during the chemotherapy. We found that unfavorable performance status, high IPI score and elevated EBV DNA load were associated with poor outcomes. Nevertheless, in multivariable analysis, only elevated plasma EBV DNA load was associated with poor outcomes.

It has been widely accepted that EBV plays an important role in the pathogenesis of lymphomas, such as BL, cHL, DLBCL and natural killer (NK)/T-cell lymphoma [31]. In the setting of HIV infection, EBV infection are more frequent, positive in 30–60% of cases compared with about 10% in the general DLBCL patients [6, 13, 32, 33]. We found that of 53% of our DLBCL cases were positive for plasma EBV DNA, consistent with previously reported prevalence of EBV-load in HIV associated DLBCL [13]. Its high frequency makes EBV a possible factor which contributes to the development of HIV associated lymphomas and be responsible for driving a more aggressive behavior [32]. In contrast to the fact that blood EBV DNA is not predictive of outcomes in HIV-associated HL [34], previous studies have demonstrated that tumor EBV infection status is an independent adverse predictive factor of survival among patients with HIV-infected DLBCL [35, 36]. Meanwhile, Muncunill et al. observed that plasma EBV-load had a negative prognostic impact, and could be used as an early predictor of HIV-related lymphoma [13]. In this study we showed plasma EBV positivity was an independent negative predictor for both PFS and OS. To our knowledge, this is one of the few studies reported with the prognostic value of plasma EBV DNA in HIV-infected DLBCL, suggesting a possibility of measuring the level of plasma EBV DNA for risk stratification.

In HIV negative DLBCL, HBsAg-positive patients have worse clinical features and poor outcomes and the presence of HCV revealed inferior OS when companied with impaired liver function [11, 37]; whereas our results indicated HIV and HBV/HCV co-infected situation in DLBCL did not predict outcomes. Further studies with more samples needed to re-evaluation.

This study provides important real-world data on outcomes of HIV-infected DLBCL patients in China. A limitation of this study is the small sample size, although this is the largest series reported in China. The survival outcomes remain poor and more therapeutic approaches are warranted. Of note, EBV DNA loads at diagnosis have prognostic value and the use of EBV DNA loads in monitoring disease in patients after treatment needs to be further evaluated.

List Of Abbreviations

HIV: Human immunodeficiency virus; DLBCL: Diffuse large B cell lymphoma; BL: Burkitt's lymphoma; NHLs: Non-Hodgkin's lymphomas;PEL: Primary effusion lymphoma; CNS: Central nervous system; cHL: Classic Hodgkin's lymphoma; AIDS: Acquired immunodeficiency syndrome; cART: Combination antiretroviral therapy; OS: Overall survival; EBV: Epstein-Barr virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ECOG: Eastern Cooperative Oncology Group; LDH: Serum lactate dehydrogenase; IPI: International prognostic index; CT: Computed tomography; PET: ^{18}F-fluorodexyglucose positron emission tomography; MRI: Magnetic Resonance Imaging; CR: Complete response; PR: Partial response; PD: Progressive disease; PS: Performance status; auto-SCT: Autologous hematopoietic stem cell transplant; ORR: Overall response rate; NK: natural killer; GC: germinal center.

Declarations

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Author's contributions:JZW analyzed the data and drafted the manuscript. YM contributed to analysis and interpretation of data and revised the manuscript. JZW, YM and HYM contributed to the conception of the study. XL, JCL, CQ, PFT, XCW, XQD, JJG and JHL participated in clinical data collection. YM contributed to the data analysis. WX, JYL and HYM reviewed the manuscript and provided suggestions. All authors read and approved the final manuscript.

Availability of data and materials: The datasets analyzed during the study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no conflicts interest.

Consent for publication: Not applicable.

Ethics approval and consent to participate: This study was approved by Yunnan Provincial Infectious Diseases Hospital/Yunnan AIDS Care Center institutional review board and conducted according to the declaration of Helsinki. Informed consent was obtained from all participants.

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Tables

Table 1: Clinical characteristics of HIV-infected patients with DLBCL

	N=53 (%)	Median (1st -3rd quartile)
Demographics		
Gender		
Male	46 (87%)	
Female	7 (13%)	
Age (years)		42 (35.0-51.0)
HIV-related characteristics		
HIV transmission route		
Intravenous drug use	5 (9%)	
Heterosexual	43 (81%)	
Homosexual	4 (8%)	
Mother to child	1 (2%)	
Years of HIV infection at DLBCL diagnosis		
1 year	33(62%)	0.08 (0.04-0.24)
≥1 year	20(38%)	5.18 (2.07-9.05)
CD4 cell count at DLBCL diagnosis (/μl)		
50	4 (7%)	41.5 (33.5-47.0)
50~199	25 (47%)	132 (100-160)
200~499	21 (40%)	289 (247.0-346.0)
≥500	3 (6%)	532 (516.0-541.5)
cART initiation		
cART prior to chemotherapy	17 (32%)	
cART with chemotherapy (years)	36 (68%)	1.64 (0.48-4.64)
Lymphoma-related characteristics		
Cell-of-origin subtype		
GC	37 (70%)	
Non-GC	16 (30%)	
ECOG performance status score		
0-1	14 (26%)	
2-4	39 (74%)	
LDH above normal	51 (94%)	352 (268.5-628.5)
B symptoms	37 (69%)	
Extra-nodal sites		
0	17 (32%)	
1	23 (43%)	
≥2	13 (25%)	
Ann Arbor stage		
-	13 (25%)	
-	40 (75%)	
aaIPI score		
0-1	9 (17%)	
2-3	38 (72%)	
IPI score		
0-1	0	
2	1 (2%)	
3-5	5 (9%)	
Bulky tumor (≥7.5cm)	38 (72%)	
Bone marrow involvement	7 (13%)	
CNS-IPI score		
0-3	40 (75%)	
4-6	13 (25%)	
Other related characteristics		
EBV (whole blood) [a]		
5×10^3 copies/ml	16 (47%)	
≥5×10^3 copies/ml	18 (53%)	4.13×10^4 (1.24×10^4-7.36×10^4)
HBV		
HBsAg positive	6 (11%)	
HBV-DNA load (copies/ml)		
5×10^2	4 (67%)	
≥5×10^2	2 (33%)	
HCV		
Anti-HCV IgG positive	4 (7.5%)	
HCV-RNA load (IU/ml)		
5×10^2	1 (25%)	
≥5×10^2	3 (75%)	
Comorbidities	5 (9%)	
Time from first complain to diagnosis (months)		2.0 (1.0-5.0)

HIV: human immunodeficiency virus; DLBCL: diffuse large B-cell lymphoma; cART: combination antiretroviral therapy; GC: germinal center; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; B symptoms: fever, night sweats, weight loss, fatigue, and swelling in lymph nodes; CNS: central nervous system; [a]: numbers of missing values, [a]: 19.

Table 2: Evaluation following chemotherapy in HIV-infected patients with DLBCL

	Interval evaluation [a] N=53	At the end of treatment N=53
Able to evaluate	N=47 (%)	N=33 (%)
Complete response	22 (47%)	21 (64%)
Partial response	19 (41%)	1 (3%)
Stable disease	0	0
Progressive disease	3 (6%)	6 (18%)
Death [b]	3 (6%)	5 (15%)
Unable to evaluate	N=6	N=17 (%)
Ongoing treatment	0	2
Having stopped treatment [c]	6	15

HIV: human immunodeficiency virus; DLBCL: diffuse large B-cell lymphoma;

[a]Response evaluation after three or four chemotherapy cycles; [b]Death during the treatment; [c]Stop treatment before be able to evaluate response to chemotherapy could be attributed to personal willingness, and nine cases end up in losing to follow-up.

Table 3: Cox univariable and multivariable analyses of PFS and OS in HIV-infected patients with DLBCL

		PFS				OS			
	N	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P
Gender									
Male	46	1.74, [0.58-5.18]	0.32			2.40, [0.78-7.39]	0.13		
Female	7								
Age (years)									
≤60	47	1.43, [0.42-4.85]	0.57			1.22, [0.28-5.37]	0.80		
>60	6								
Years of HIV infection at DLBCL diagnosis									
<1 year	33	1.05, [0.44-2.51]	0.92			1.01, [0.37-2.76]	0.98		
≥1 year	20								
CD4 cell count at DLBCL diagnosis									
<200 (/µl)	29								
≥200 (/µl)	24	0.64, [0.27-1.50]	0.30			0.49, [0.18-1.33]	0.16		
cART initiation									
cART prior to chemo	17	1.92, [0.71-5.21]	0.20			2.61, [0.75-9.01]	0.13		
cART with chemo	36								
Cell-of-origin subtype									
GC	37	1.86, [0.79-4.37]	0.15			1.90, [0.72-4.99]	0.20		
Non-GC	16								
ECOG performance status score									
0-1	14								
2-4	39	4.73, [1.10-20.26]	**0.036**	10.06, [0.84-120.38]	0.07		0.10		
LDH									
≤UNL	2								
>UNL	51	1.05, [0.14-7.79]	0.97			0.94, [0.12-7.10]	0.95		
B symptoms									
Yes	37	1.30, [0.51-3.34]	0.58			4.01, [0.91-17.56]	0.07		
No	16								
Extra-nodal sites									
0-1	40	0.71, [0.24-2.10]	0.54			0.67, [0.19-2.35]	0.53		
≥2	13								
Ann Arbor stage									
I-II	13								
III-IV	40	2.20, [0.65-7.43]	0.21			5.56, [0.74-41.93]	0.10		
IPI score (all patients)									
0-2	17								
3-5	36	3.65, [1.08-12.34]	**0.037**	1.35, [0.23-7.97]	0.74	9.12, [1.21-68.83]	**0.032**	5.19, [0.65-41.27]	0.12
Bulky tumor (≥7.5cm)									
No	15	1.10, [0.43-2.82]	0.84			0.68, [0.25-1.84]	0.45		
Yes	38								
CNS-IPI score									
0-3	40	0.83, [0.31-	0.72			0.92, [0.30-2.83]	0.89		

		2.25]							
4-6	13								
EBV (serum) [a]									
<5×10^3 copies/ml	16								
≥5×10^3 copies/ml	18	6.73, [1.78-25.45]	**0.005**	14.46, [2.57-81.50]	**0.002**	6.26, [1.27-30.80]	**0.024**	7.47, [1.48-37.59]	**0.015**
HBV									
HBsAg positive	6	0.80, [0.19-3.43]	0.76			0.48, [0.06-3.65]	0.48		
HBsAg negative	47								
HCV									
Anti-HCV positive	4	1.53, [0.35-6.65]	0.59			1.96, [0.44-8.65]	0.38		
Anti-HCV negative	49								

HIV: human immunodeficiency virus; DLBCL: diffuse large B-cell lymphoma; PFS: progression free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; cART: combination antiretroviral therapy; GC: germinal center; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; UNL: upper normal limit; B symptoms: fever, night sweats, weight loss, fatigue, and swelling in lymph nodes; CNS: central nervous system; [a]: numbers of missing values, [a]: 19.

Figures

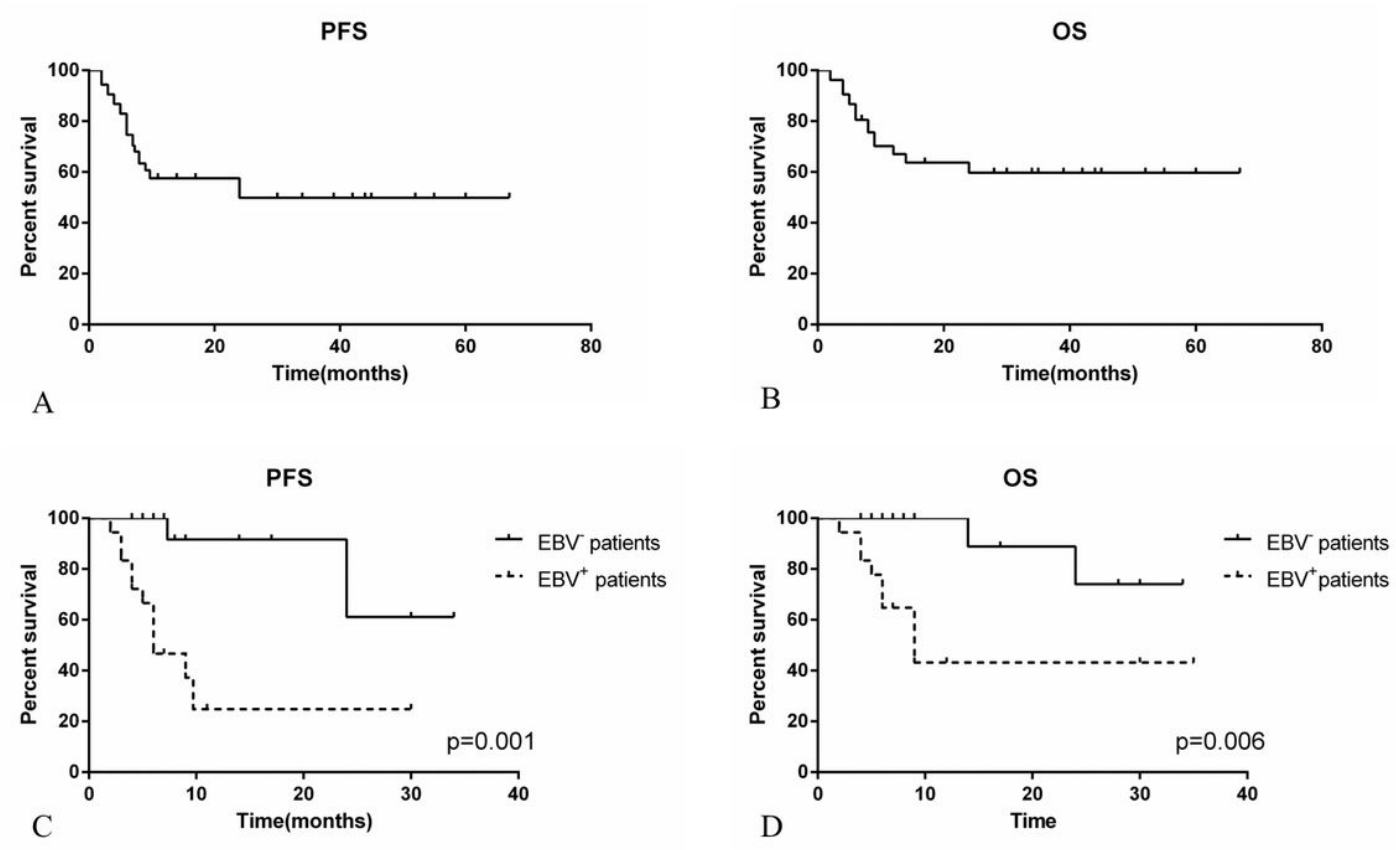

Figure 1

Figure 1: Progression-free and overall survival in HIV-infected patients with DLBCL Panel A showed the PFS for HIV-infected DLBCL patients. Panel B showed the OS for HIV-infected DLBCL patients. Panel C showed the PFS for plasma EBV load positive patients and plasma EBV load negative patients. Panel D

showed the OS for plasma EBV load positive patients and plasma EBV load negative patients. PFS: progression free survival; OS: overall survival; DLBCL: diffuse large B cell lymphoma.