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HIV-associated Burkitt lymphoma: outcomes from a US-UK collaborative analysis

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Key Points

- Prognostic factors for patient outcome were associated with lymphoma characteristics rather than with HIV-related features.
- Lower risk of CNS relapse was observed in patients receiving systemic agents with blood brain barrier penetration.

Data addressing prognostication in patients with HIV related Burkitt lymphoma (HIV-BL) currently treated remain scarce. We present an international analysis of 249 (United States: 140; United Kingdom: 109) patients with HIV-BL treated from 2008 to 2019 aiming to identify prognostic factors and outcomes. With a median follow up of 4.5 years, the 3-year progression-free survival (PFS) and overall survival (OS) were 61% (95% confidence interval [CI] 55% to 67%) and 66% (95%CI 59% to 71%), respectively, with similar results in both countries. Patients with baseline central nervous system (CNS) involvement had shorter 3-year PFS (36%) compared to patients without CNS involvement (69%; $P < .001$) independent of frontline treatment. The incidence of CNS recurrence at 3 years across all treatments was 11% with a higher incidence observed after dose-adjusted infusional etoposide, doxorubicin, vincristine, prednisone, cyclophosphamide (DA-EPOCH) (subdistribution hazard ratio: 2.52; $P = .03$ vs other regimens) without difference by CD4 count 100/mm^3. In multivariate models, factors independently associated with inferior PFS were Eastern Cooperative Oncology Group (ECOG) performance status 2-4 (hazard

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The full-text version of this article contains a data supplement.

ratio [HR] 1.87; $P = .007$), baseline CNS involvement (HR 1.70; $P = .023$), lactate dehydrogenase >5 upper limit of normal (HR 2.09; $P < .001$); and >1 extranodal sites (HR 1.58; $P = .043$). The same variables were significant in multivariate models for OS. Adjusting for these prognostic factors, treatment with cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate, ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) was associated with longer PFS (adjusted HR [aHR] 0.45; $P = .005$) and OS (aHR 0.44; $P = .007$). Remarkably, HIV features no longer influence prognosis in contemporaneously treated HIV-BL.

Introduction

Significant changes have occurred in the epidemiology of HIV-associated non-Hodgkin lymphoma (NHL) since the implementation of combination antiretroviral therapy (cART) in the mid-1990s.[1] The incidence of primary central nervous system (CNS) lymphoma and diffuse large B-cell lymphoma have decreased, whereas, the incidence of Burkitt lymphoma (BL) has remained largely stable with a consequent proportional increase over time.[1-4] Adult BL accounts for up to 35% of the lymphomas associated with HIV.[1,2,5] In contrast with other HIV-associated aggressive NHLs, HIV-related Burkitt lymphoma (HIV-BL) is more common among patients with higher CD4 cell counts and is strongly associated with cumulative HIV viremia.[1,3,6] Moreover, people with HIV have a 10% to 20% lifetime risk of developing BL independent of treatment with cART.[7] HIV-BL usually occurs early in the course of HIV disease and frequently as the initial AIDS-defining illness.[8,9]

cART has enhanced the ability of clinicians to implement intensive multiagent chemotherapy regimens with curative attempt, favorably changing the prognosis of patients with HIV-BL.[4] Regimens including cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) and hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyperCVAD/MA) have shown efficacy with a manageable toxicity profile in HIV-BL.[10-14] The addition of rituximab to the CODOX-M/IVAC regimen resulted in significant improvement of survival in HIV-BL in people concomitantly treated with cART, without long-term immunosuppression and with appropriate control of HIV viremia.[11,12] More recently, a multicenter phase 2 study testing the lower-intensity dose-adjusted infusional etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide (DA-EPOCH) and rituximab regimen, in a risk-adapted approach, demonstrated excellent outcomes with a 4-year event-free survival of 85% (95% confidence interval [CI], 65% to 94%) in 28 patients with HIV-BL.[15] However, studies focusing on people with HIV are relatively small and data regarding prognostic factors and outcomes in HIV-BL patients treated in the cART era remain scarce. The optimal treatment strategies to improve survival and minimize toxicity are thus not established and current recommendations are based on limited data.

We conducted a retrospective multicenter international analysis to identify prognostic factors, survival, and treatment-related outcomes in patients with HIV-BL contemporaneously treated. In this large collaborative effort, we analyzed a cohort of 249 patients with newly diagnosed HIV-BL treated at 35 centers in the United States and United Kingdom.

Methods

This retrospective analysis included a subcohort with HIV-BL from a recent large BL study (n = 641),[16] augmented by data from 5 UK centers. Adult patients (≥18 years) with newly diagnosed HIV-BL treated from 2008 to 2019 with complete clinical and pathological data were entered into a centralized deidentified database and analyzed. The study was approved by the institutional review boards of all participant institutions and was conducted in accordance with the Declaration of Helsinki. Opportunistic infection prophylaxis was undertaken according to institutional guidelines.

Diagnosis was established by local institutional hematopathology expert review without central pathologic review. Cases included BL defined according to the 2016 World Health Organization (WHO) criteria,[17] excluding other newly identified entities (high-grade B-cell lymphoma not otherwise specified, double-/triple-hit lymphoma, etc) based on the careful review of pathology reports. Consistent with WHO guidance,[17] we included 18 cases (7%) with negative or missing *MYC* rearrangement that fulfilled all other criteria for classic BL such as small cell morphology with tingible body macrophages; $BCL2^-$, $CD10^+$, and $BCL6^+$ immunophenotype; and Ki67 staining of 100%. Staging evaluations and therapy for patients were completed at the discretion of treating physicians and by institutional standards.

Variables and end points

Investigators collected detailed demographic, clinicopathologic, and outcome data using a standardized protocol. Performance status (PS) was assigned according to the Eastern Cooperative Oncology Group (ECOG) scale. Serum lactate dehydrogenase (LDH) was standardized relative to institutional upper limit of normal (ULN). Progression-free survival (PFS) was defined according to the 2007 International Working Group criteria as time from diagnosis until disease progression, recurrence, or death from any cause.[18] Overall survival (OS) was calculated from diagnosis until death or last follow-up. Treatment-related mortality (TRM) was defined as death from any cause other than BL due to treatment-related adverse event (causation was determined by the local investigator).

Statistical methods

We described the distribution of continuous variables using medians and interquartile ranges and compared them between groups using the Wilcoxon test; categorical variables were tabulated and compared using the Fisher exact test. Associations between explanatory variables and outcomes were studied in a data set augmented by multiple imputation using chained equations, to account for missing data on ECOG PS (5%), LDH (5%), CD4 count (7%), and viral

load (24%), and use of cART (12%), which were assumed to be missing at random.[19] The imputation model included all analytic variables and outcomes, and produced 30 data copies, among which the coefficients and standard errors from regression models were averaged. We examined binary outcomes (TRM) by logistic regression, associations with PFS or OS in Cox survival models, and the cumulative incidence of CNS recurrence in competing risk models, all stratified by data origin (United States or United Kingdom). Selection of variables for multivariable models was conducted using stepwise forward and backward selection, which converged on the same sets of independent prognostic factors. All estimates are provided with 95% CIs. Analyses were conducted using Stata/MP16.1 (StataCorp, College Station, TX).

Results

Baseline patient characteristics

A total of 255 patients with HIV-BL seen at 35 centers from 2008 to 2019 were identified; however, only 249 treated patients were included in this analysis: 140 from the United States and 109 from the United Kingdom. Six untreated patients were excluded. The majority of patients were male (84%) with a male-to-female ratio of 5:1. The median age at diagnosis was 43 years (range, 23- 77 years) with patients ≥60 years representing only 8% (n = 19). Fifty percent (n = 124) of the patients had an ECOG PS of 0 to 1. LDH was elevated in 85% (n = 211) with LDH >3× the ULN in 49% (n = 123) and >5× the ULN in 39% (n = 97). Advanced-stage (III-IV) disease was almost universal (91%; n = 227); bone marrow (BM) was involved in 46% (n = 112) and 60% (n = 149) of the patients had >1 extranodal (EN) site of disease. The most common EN sites involved at diagnosis were liver (n = 37), bone (n = 28), gastrointestinal tract (n = 28), and kidney/adrenal gland (n = 26). CNS was involved at diagnosis in 24% (n = 61), mainly with leptomeningeal disease (79%; n = 48). Baseline characteristics were similar between patients in the United States and United Kingdom with only significant differences in ECOG PS 2 to 4 and CNS involvement (Table 1).

MYC rearrangement was reported in 93% of the patients. The majority (49%) were tested for t(8;14) followed by break-apart probe in 41%, and *MYC* light chain in 3%. *MYC* rearrangement was not detected in 4% and data were missing in 3% (otherwise classical BL by WHO classification).[17]

Regarding HIV characteristics, the median CD4 count was 217 cells per microliter (range, 90-392 cells per microliter) with most patients (68%) presenting with a CD4 count ≥100 cells per microliter. At the time of HIV-BL diagnosis, HIV viral load was detectable in 55%, undetectable in 21%, and data were missing in 24%; 39% were receiving cART.

Treatment, response, and toxicity

A rituximab-containing regimen was delivered in the majority of the patients (87%). Overall, CODOX-M/IVAC was the most commonly implemented regimen (60%) followed by DA-EPOCH (25%), hyperCVAD/MA (13%), and other regimens (2%). The median numbers of cycles (available in the US data only) were 4 for CODOX-M/IVAC and 5 for DA-EPOCH; 70% of patients treated with hyperCVAD/MA received ≥6 cycles. Treatment preference differed by geography. In the United States, patients most commonly received DA-EPOCH (42%) followed by CODOX-M/IVAC (32%) and hyperCVAD/MA (24%), whereas, in the United Kingdom, 96% received CODOX-M/IVAC. Patients treated with CODOX-M/IVAC in the United Kingdom received full doses of this regimen without dose reductions or schedule modifications suggested in HIV patients.[11] These data are not available for the US cohort. Rituximab was more frequently implemented in the United States (94% vs 79%; $P < .001$). Patients with CNS involvement at diagnosis received CODOX-M/IVAC (53%) followed by DA-EPOCH (31%) and hyperCVAD/MA (16%). Similar baseline features were seen in the US patients selected for DA-EPOCH as those selected for CODOX-M/IVAC or hyperCVAD/MA except for lower median CD4 count (144 vs 259 cells per microliter; $P = .04$) (supplemental Table 1). Data on the dose intensity of the DA-EPOCH regimen are summarized in supplemental Table 2.

CNS prophylaxis with intrathecal chemotherapy was universally implemented across all regimens with the following distribution: CODOX-M/IVAC (98%) and hyperCVAD/MA (94%). All patients treated with these regimens received systemic methotrexate and cytarabine. Patients selected for DA-EPOCH received intrathecal chemotherapy prophylaxis in 92% of the cases, most frequently with methotrexate (79%), followed by methotrexate and cytarabine (16%), and cytarabine (5%). Two patients also received systemic methotrexate for CNS prophylaxis.

The overall response rate (ORR) to frontline therapy was 79% with complete response (CR) in 70% and partial response (PR) in 9%. Progression of disease after frontline therapy was observed in 14%; 7% of patients were not evaluable for response. Patients treated with rituximab-containing regimens achieved higher ORR in comparison with regimens not containing rituximab (81% vs 72%), however, CR rates were similar (71% vs 69%). Progression of disease was more frequently observed in patients treated without rituximab (19% vs 13%; $P = .16$). In patients with baseline CNS involvement, leptomeningeal disease was associated with higher ORR (65%; CR = 48% and PR = 17%) compared with those with parenchymal disease (ORR = 46%; CR = 46%) and the latter was associated with a higher mortality rate (77% vs 52%).

Overall, 34% of patients (n = 84) had lymphoma relapse, with systemic disease only in 23% (n = 58), CNS involvement only in 9% (n = 22), and concomitant systemic and CNS disease in 2% (n = 4). Importantly, we observed a lower risk of lymphoma relapse in patients treated with rituximab-containing regimens compared with those treated without rituximab (32% vs 44%). The mortality rate among relapsing patients was 87% (n = 73).

TRM across all regimens was 10% (n = 25). The highest TRM was observed with hyperCVAD/MA (18%) followed by DA-EPOCH (13%) and CODOX-M/IVAC (7%; $P = .08$). The most common cause of TRM was sepsis/infection in 76% of the patients (supplemental Table 3). The median age of patients experiencing TRM was 46 years (range, 26-63 years); all presented with stage IV disease and a median ECOG PS of 2. Patients with CD4 <100 cells per microliter exhibited a nonsignificant increase in TRM (15% vs 8% for those with CD4 ≥100 cells per microliter; $P = .13$). In a multivariate analysis (supplemental Table 4), factors associated with TRM included treatment with hyperCVAD/MA (odds ratio [OR] = 3.55; 95% CI, 1.11-11.34), LDH >5× the ULN (OR = 4.35; 95% CI, 1.59-11.87), and age (OR = 1.62 for each 10-year increase; 95% CI, 1.06-2.48). Four patients (1.6%) developed secondary

Table 1. Characteristics at diagnosis of BL

Variable	All, n (%); N = 249	US, n (%); 140 (56)	UK, n (%); 109 (44)	*P*
Age, y				
<40	92 (37)	57 (41)	35 (32)	.19
≥40	157 (63)	83 (59)	74 (68)	
Sex				
Male	210 (84)	118 (84)	92 (84)	1.00
Female	39 (16)	22 (16)	17 (16)	
ECOG PS 2-4	112 (47)	41 (32)	71 (65)	<.001
LDH				
>ULN	211 (85)	116 (83)	95 (87)	.38
>3×	123 (49)	67 (48)	56 (51)	.61
>5×	97 (39)	53 (38)	44 (40)	.70
Advanced stage	227 (91)	128 (92)	99 (91)	.82
>1 EN sites	149 (60)	82 (59)	67 (61)	.70
CNS involvement	61 (24)	42 (30)	19 (17)	.026
BM involvement	112 (46)	60 (44)	52 (48)	.70
CD4 count, median (IQR)	217 (90, 392)	212 (94, 392)	218 (90, 391)	.91
Undetectable viral load	52 (21)	25 (18)	27 (24)	.63
CD4, >100 cells/μL	170 (68)	93 (67)	77 (70)	.88
CD4, >50 cells/μL	197 (79)	109 (78)	88 (80)	1.00
cART	96 (39)	53 (38)	43 (39)	.22
Regimen				
CODOX-M/IVAC	150 (60)	45 (32)	105 (96)	<.001
DA-EPOCH	63 (25)	59 (42)	4 (4)	
HyperCVAD/MA	33 (13)	33 (24)	0	
Other	3 (2)	3 (2)	0	
Rituximab-containing regimen	217 (87)	131 (94)	86 (79)	<.001

IQR, interquartile range.

Table 2. Univariate and multivariate analyses of prognostic factors

	Univariate analysis						Multivariate analysis					
	PFS			OS			PFS			OS		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age ≥40 y	0.85	0.57-1.27	.421	0.95	0.62-1.46	.818						
Sex	0.93	0.54-1.62	.802	0.99	0.56-1.75	.964						
LDH> ULN	2.75	1.28-5.91	.009	3.32	1.35-8.13	.008						
LDH> 5× ULN	2.86	1.91-4.29	<.001	3.15	2.05-4.86	<.001	2.09	1.35-3.23	<.001	2.26	1.42-3.59	<.001
Advanced stage	1.67	0.73-3.82	.222	1.87	0.76-4.61	.173						
ECOG PS 2-4	2.45	1.60-3.77	<.001	2.73	1.72-4.34	<.001	1.87	1.18-2.96	.007	2.00	1.22-3.28	.006
CNS involvement	2.68	1.75-4.10	<.001	2.99	1.90-4.70	<.001	1.70	1.08-2.70	.023	1.83	1.12-2.98	.015
>1 EN	1.89	1.23-2.91	.003	2.04	1.29-3.23	.002	1.58	1.01-2.47	.043	1.71	1.06-2.75	.027
BM involvement	1.91	1.28-2.86	.001	2.21	1.43-3.41	<.001						
Undetectable viral load	0.93	0.57-1.52	.783	1.01	0.61-1.68	.965						
CD4 < > 100 cells/μL	1.59	1.03-2.45	.038	1.66	1.05-2.62	.02						
cART	0.88	0.58-1.34	.555	0.96	0.62-1.49	.857						

malignancies after HIV-BL treatment (classical Hodgkin lymphoma = 2, myelodysplastic syndrome = 1, acute promyelocytic leukemia = 1).

Survival analysis

With a median follow-up of 4.5 years, the 3-year PFS and OS in treated HIV-BL patients were 61% (95% CI, 55% to 67%) and 66% (95% CI, 59% to 71%), respectively. Survival was nearly identical in both countries exhibiting a 3-year PFS and OS in the United States of 61% (95% CI, 52% to 68%) and 66% (95% CI, 57% to 74%) compared with 62% (95% CI, 52% to 70%) and 65% (95% CI, 55% to 73%) in the United Kingdom, respectively (Figure 1A-B). Patients with CD4 ≥100 cells per microliter demonstrated better 3-year PFS (65% vs 52% for those with CD4 <100 cells per microliter; $P = .034$) and OS (69% vs 57%, respectively; $P = .027$) (Figure 1C-D). Furthermore,

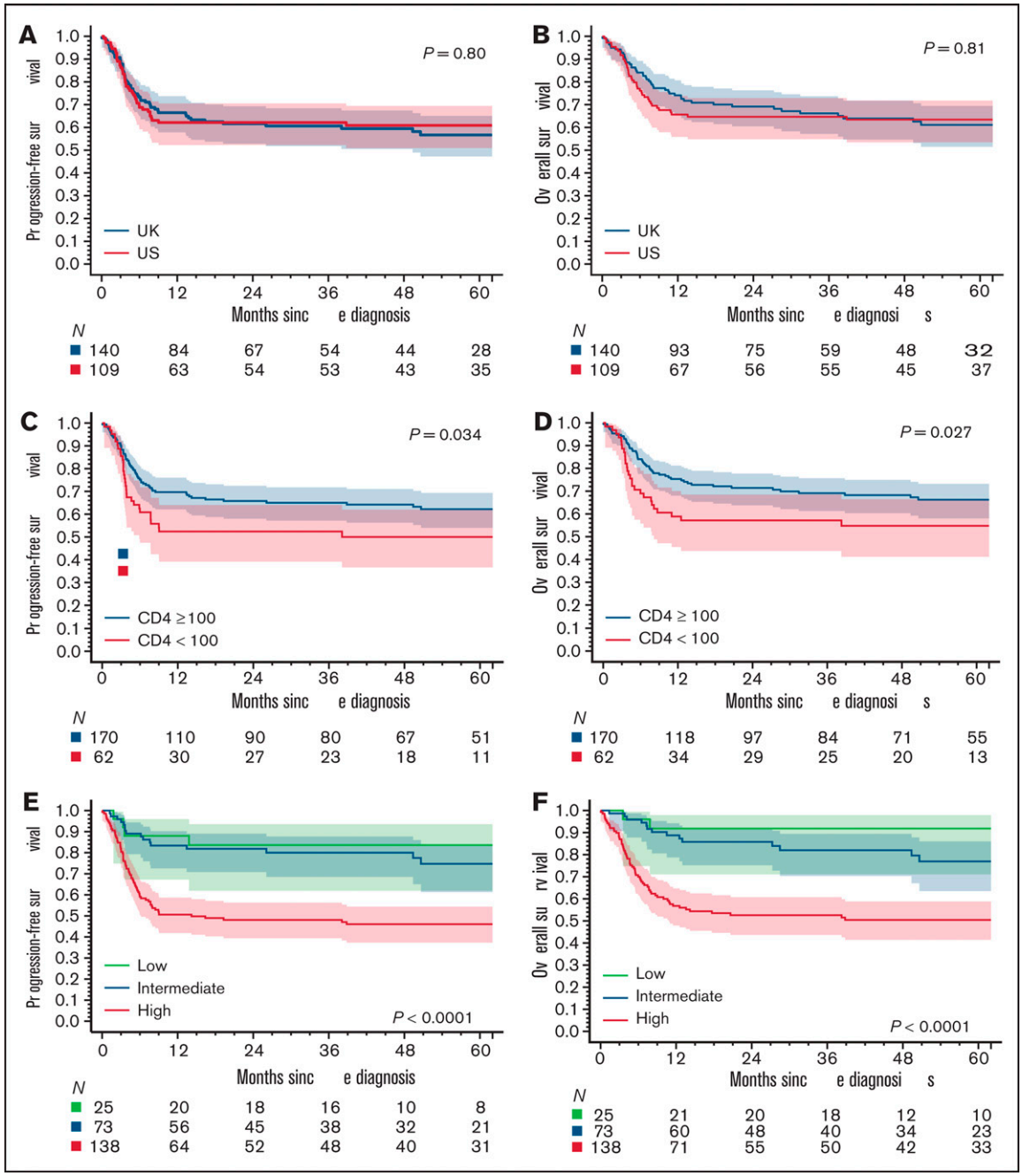

Figure 1. Survival. Kaplan-Meier curves of (A) PFS and OS (B) in HIV-associated Burkitt lymphoma (HIV-BL) patients treated in the United States (US) and United Kingdom (UK). Kaplan-Meier curves of (C) PFS and (D) OS according to CD4 count at HIV-BL diagnosis. Kaplan-Meier curves of (E) PFS and OS (F) by BL–International Prognostic Index (age ≥40 years, LDH >3× ULN, ECOG PS ≥2, and CNS involvement). Group distribution: 11% in the low-risk (no risk factors), 31% in the intermediate-risk (1 factor), and 58% in the high-risk (≥2 factors) group.

patients with CD4 <50 cells per microliter had 3-year PFS of 49% and OS of 52%. When stratified by BL–International Prognostic Index (which includes age ≥40 years, LDH >3× the ULN, ECOG PS ≥2, and CNS involvement as risk factors), 11% were in the low-risk (no risk factors), 31% in the intermediate-risk (1 factor), and 58% in the high-risk (≥2 factors) group, with 3-year PFS of 84%, 80%, and 48%, respectively, and OS of 92%, 82%, and 53%, respectively (Figure 1E-F).

Baseline variables associated with shorter PFS and OS in univariate analysis included: ECOG PS 2 to 4, >1 EN site, positive BM, CNS involvement, LDH > ULN (all levels), and CD4 <100 cells per microliter. In multivariate analysis, the variables independently associated with inferior PFS were ECOG PS 2 to 4 (HR, 1.87; 95% CI, 1.18-2.96), CNS involvement (HR, 1.70; 95% CI, 1.08-2.70); LDH >5× the ULN (HR, 2.09; 95% CI, 1.35-3.23), and >1 EN site (HR, 1.58; 95% CI, 1.01-2.47). The same variables were significant on multivariate analysis for OS (Table 2).

In survival analysis based on frontline treatment, CODOX-M/IVAC was associated with the highest 3-year PFS (66%) compared with 63% after hyperCVAD/MA and 51% after DA-EPOCH, but the difference was not statistically significant ($P = .13$; Figure 2A). Similarly, a statistically nonsignificant difference was observed for 3-year OS (CODOX-M/IVAC, 69%; hyperCVAD/MA, 62%; and DA-EPOCH, 60%) ($P = .53$; Figure 2B). However, adjusting for the 4 prognostic variables from the multivariable model (ECOG PS 2-4, CNS involvement, LDH >5× the ULN, and >1 EN site), treatment with CODOX-M/IVAC (compared with other regimens pooled together) was associated with longer PFS (adjusted HR, 0.45; 95% CI, 0.26-0.79; $P = .005$) and longer OS (adjusted HR, 0.44; 95% CI, 0.24-0.80; $P = .007$). Within the subgroup of patients treated with CODOX-M/IVAC, we observed no significant difference between the United States and United Kingdom in 3-year PFS (74% vs 63%; $P = .79$) and OS (78% vs 65%; $P = .80$). Patients receiving rituximab had numerically higher PFS and OS, but the difference did not reach statistical significance (3-year PFS, 63% with vs 53% without rituximab; $P = .17$ [Figure 2C]; 3-year OS, 66% vs 62%, respectively; $P = .41$ [Figure 2D]).

We observed significantly worse outcomes in patients with baseline CNS involvement (3-year PFS, 36% vs 69% [$P < .001$]; OS, 41% vs 73% [$P < .001$]; Figure 3A-B) independently of frontline regimen. Among patients with baseline CNS involvement, 3-year PFS and OS for hyperCVAD/MA were 40% and 40%, respectively; for CODOX-M/IVAC they were 39% and 38%, respectively; and for DA-EPOCH they were 32% and 46%, respectively ($P = .93$ for interregimen comparison of PFS and $P = .65$ for OS; Figure 3C-D).

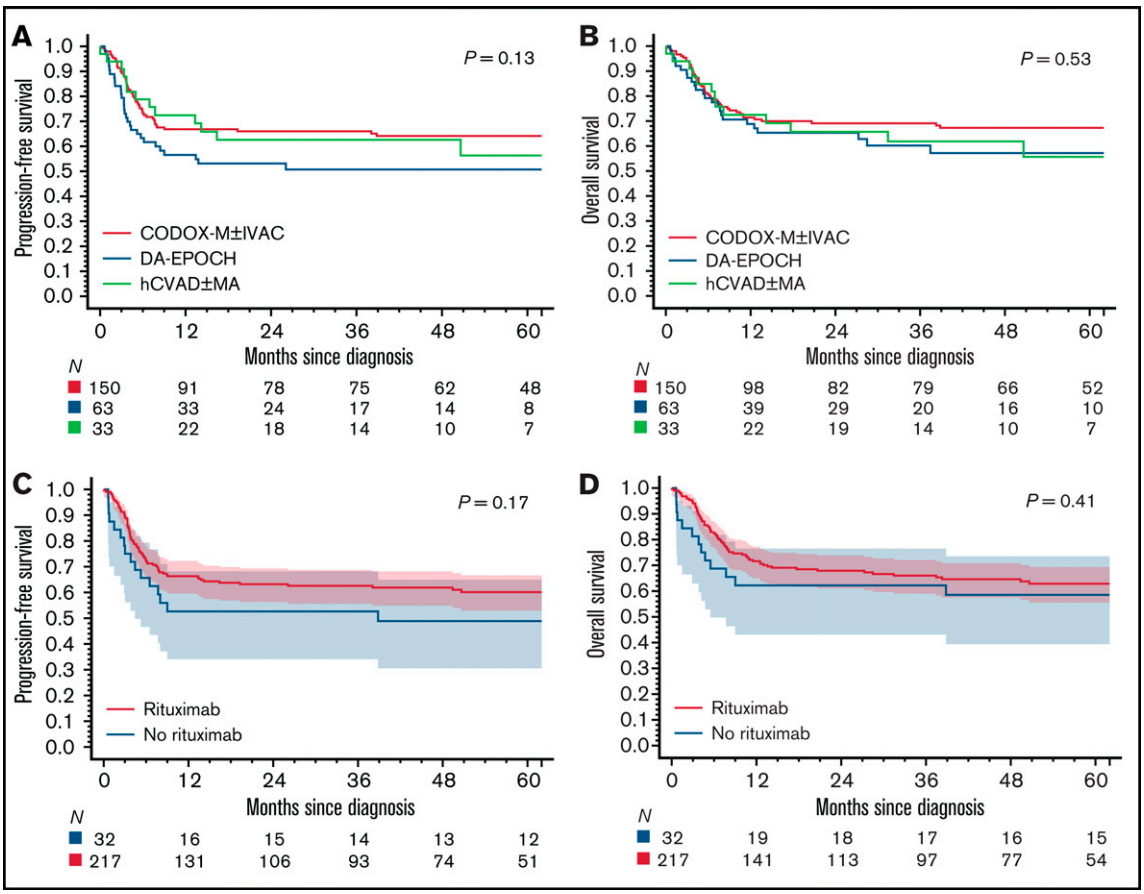

Figure 2. Survival by treatment. Kaplan-Meier curves of PFS (A) and OS (B) according on frontline treatment. Kaplan-Meier curves of PFS (C) and OS (D) based on receipt of rituximab.

The incidences of CNS recurrence at 1 and 3 years across all treatment regimens were 9% and 11%, respectively. Overall, there was no difference in CNS recurrence by country (United States, 11%; United Kingdom, 10%; $P = .85$ [Figure 3E]). Higher cumulative incidence of CNS recurrence was observed with DA-EPOCH (17%) compared with CODOX-M/IVAC (8%) and hyperCVAD/MA (9%) ($P = .03$ for test of DA-EPOCH against others; Figure 3F) with no difference according to CD4 count (10% for <100 cells per microliter vs 12% for ≥100 cells per microliter; $P = .76$).

Discussion

To our knowledge, this study represents the largest analysis of HIV-BL treated with current chemotherapy regimens in the cART era. Relevant findings from this study include the identification of 4 prognostic factors in patients receiving modern chemotherapy platforms, better survival implementing CODOX-M/IVAC compared with DA-EPOCH, lower risk of CNS relapse in patients receiving systemic agents with CNS penetration, higher TRM associated with the

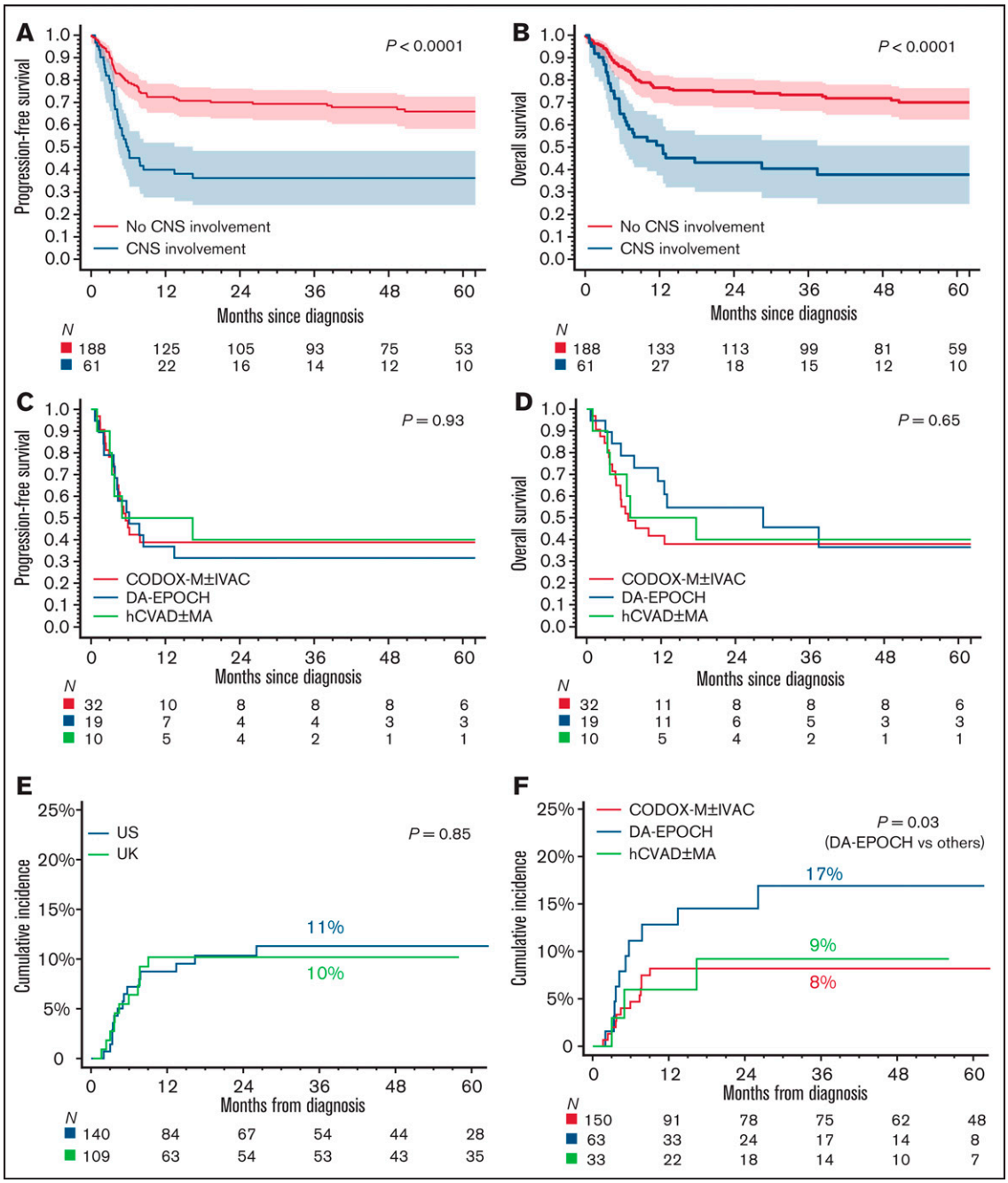

Figure 3. Survival by baseline CNS status and risk of recurrence. Kaplan-Meier curves (A) of PFS and (B) OS according to CNS involvement at diagnosis. Kaplan-Meier curves (C) of PFS and (D) OS in patients with baseline CNS involvement by frontline regimen. Cumulative incidence of CNS relapse according to (E) geography and (F) frontline therapy.

hyperCVAD/MA platform, no TRM benefit with DA-EPOCH compared with CODOX-M/IVAC, and poor survival in patients with baseline CNS involvement irrespective of frontline therapy. The influence of HIV-associated factors on the prognosis of HIV-BL contemporaneously treated remains controversial. A National Cancer Database analysis including 1348 patients with HIV-BL (period 2004-2011) found shorter 5-year OS in HIV-BL compared with non-HIV patients (48% vs 58.5%; $P < .001$, respectively). In multivariable Cox proportional hazard models using propensity score matched data sets, authors found that HIV infection was associated with a significantly increased risk of death (HR, 1.46; 95% CI, 1.24-1.73), suggesting that HIV-related prognostic factors influence outcomes in HIV-BL.[20] Nevertheless, a systematic review incorporating 1546 patients (BL = 26%; n = 399) from clinical trials carried out between 1990 and 2010 in HIV-related lymphoma identified age-adjusted International Prognosis Index as a significant predictor of outcome across all years (HRs, 1.58 and 1.52 for PFS and OS, respectively). Importantly, patients with CD4 <50 cells per microliter demonstrated a substantial improvement in 2-year OS during the period from 2005 to 2010 (65%) compared with 1996 to 2000 (24%).[21] We previously demonstrated similar survival (3-year PFS, 60% vs 65%; $P = .42$) and TRM (13% vs 9%; $P = .17$) in HIV-BL and non-HIV-associated BL in the US cohort, confirming improvement in outcomes in HIV patients.[16] Our present study identified ECOG PS of 2 to 4, baseline CNS involvement, LDH >5× the ULN, and >1 EN site as prognostic factors in HIV-BL. No HIV-related factors influenced survival outcomes and our findings correlate with prior observations in other types of HIV-associated lymphomas.[22,23] Therefore, in HIV-BL contemporaneously treated, our data support that survival is based on lymphoma characteristics and HIV infection does not adversely affect outcome.

Since the landmark results achieved by Magrath et al in 1996, the CODOX-M/IVAC platform underwent subsequent modifications that decreased toxicity but maintained efficacy in treating BL.[24,25] The AIDS Malignancy Consortium (AMC) 048 phase 2 trial modified the original CODOX-M/IVAC regimen adding rituximab, delivering infusional ifosfamide and etoposide, lowering and rescheduling methotrexate, and capping vincristine dose. Thirty-four patients with HIV-BL were enrolled, achieving a 1-year PFS of 69% (95% CI, 51% to 82%) and OS of 72% (95% CI, 53% to 84%). CODOX-M/IVAC was associated with a TRM of 3% (n = 1).[10] Similar survival was retrospectively observed by Montoto et al in 30 HIV-BL patients treated with CODOX-M/IVAC.[12] Relevant observations from this analysis were the presence of undetectable viral load in 88% of the patients and CD4 count >200 cells per microliter in 58% of patients at 6 months upon chemotherapy conclusion. The CARMEN study tested a dose-dense and short-term program in patients with HIV-BL and HIV-associated high-grade B-cell lymphomas. This program was highly effective in 20 patients with an ORR of 90% and 5-year PFS of 70% associated with an acceptable toxicity profile (TRM, 10%), providing further rationale for the selection of intensive chemotherapy regimens in HIV-BL.[26] Our analysis demonstrates geographical differences in the treatment of HIV-BL. CODOX-M/IVAC was universally used in the United Kingdom, however, DA-EPOCH, CODOX-M/IVAC, and hyperCVAD/MA were evenly distributed in the United States without clear survival benefit between the regimens. Importantly, the UK cohort included 65% of patients with an ECOG PS of 2 to 4 without subsequent higher TRM. Therefore, the CODOX-M/IVAC regimen is feasible and effective in HIV-BL, even in those patients with poor performance status at diagnosis, when administered concomitantly with cART.

Another commonly implemented treatment of HIV-BL is hyperCVAD/MA, which demonstrated a CR rate of 92%; however, infectious complications occurred in 85% of patients and all patients without concomitant cART died (n = 4).[13] In our analysis, hyperCVAD/MA exhibited the highest TRM (18%) and was identified as 1 of the principal prognostic factors for TRM in multivariable analysis. These data suggest significant toxicity in this population without a clear survival benefit compared with CODOX-M/IVAC. Thus, our results do not support the use of hyperCVAD/MA in HIV-BL.

DA-EPOCH was postulated as a less-intense treatment obviating the need for high-dose treatment while still highly effective against HIV-BL. The TRM associated with this regimen was up to 4% in HIV and non-HIV BL.[15,27] By contrast, in a study concentrating on HIV-related lymphoma (HIV-BL: 22%, n = 23), DA-EPOCH reported a TRM of 8.5%.[28] This result is closer, though still lower, than our data in which TRM associated with DA-EPOCH was 13%. Our study demonstrated similar TRM between DA-EPOCH and CODOX-M/IVAC. Lower CD4 count was the only significant unfavorable variable observed in the DA-EPOCH cohort vs CODOX-M/IVAC and hyperCVAD/MA; however, we cannot exclude selection bias in the clinician's choice of 1 regimen over the other. DA-EPOCH is associated with several advantages compared with other regimens, including optional outpatient administration, better tolerability in older patients, and a risk-adapted approach possibly decreasing further treatment-related toxicity. Patients at lower risk of CNS involvement may be best selected for DA-EPOCH, and the potential benefits of this regimen in HIV-BL require further study.

CNS involvement at diagnosis was identified as a prognostic factor associated with higher risk of treatment failure in our study. Higher incidence of CNS involvement at diagnosis was observed in the US cohort (30% vs 17%; $P = .026$). The reason for this difference is unclear; however, HIV-related characteristics do not seem to influence this feature, as similar CD4 and viral load levels were observed between both cohorts. The difference might be attributed to the extent of investigations to establish CNS involvement between the United States and United Kingdom, which varied. However, this information could not be accurately collected from all the patients in this retrospective study. Most patients with CNS involvement received CODOX-M/IVAC (53%), followed by DA-EPOCH (31%), and hyperCVAD/MA (16%). However, poor survival was similar across all 3 chemotherapy regimens, pointing to the need for more effective approaches in this patient population. Similar findings were observed in a multicenter study testing DA-EPOCH in adult BL in which cerebrospinal fluid involvement was the most significant variable influencing 4-year event-free survival (45.5% vs 90%; $P = .0004$),[15] although how many of these patients were HIVpositive is unclear.

The relapse rate in our study was higher (34%) than previously reported in clinical trials utilizing DA-EPOCH (2%) and CODOX-M/IVAC (3%) but similar to previous reports with hyperCVAD/MA (33%).[10,13,15] The incidence of CNS recurrence at 1 and 3 years across all regimens was 9% and 11%, respectively. No difference was observed by CD4 count or geography, however, implementation of DA-EPOCH carried a higher risk of CNS relapse (17%; 95% CI, 8.7% to 27.8%) compared with CODOX-M/IVAC and hyperCVAD/MA (8.5%; 95% CI, 4.9% to 13.1%). Although patient

characteristics, heterogeneity in treatment selection, and the retrospective nature of this analysis limit the comparison between treatment platforms, our data suggest a lower risk for CNS recurrence using chemotherapy platforms that incorporate systemic agents with optimal CNS distribution. A comprehensive analysis evaluating risk for CNS event in the US cohort demonstrated a lower 3-year risk for CNS recurrence after CODOX-M/IVAC (4%) or hyperCVAD/MA (3%) compared with DA-EPOCH (13%; subdistribution hazard ratio = 3.57; $P < .001$). Recurrences involving the CNS were more frequent after DA-EPOCH (40%) than after the other 2 regimens (16%; $P < .001$), and this risk was higher independent of baseline CNS involvement, age, ECOG PS, and HIV status.[29]

Caveats of the present study are the lack of detailed data on utilization of prephase chemotherapy, dose modifications, and treatment delays on accounts of its retrospective nature. Use of prephase chemotherapy has shown to improve performance status, and decrease first-cycle toxicity and TRM in aggressive lymphoma.[30,31] Treatment delays and dose reduction may have occurred due to chemotherapy-related toxicity concerns by the treating physician. However, our data demonstrate that even intensive chemotherapy regimens are feasible in people with HIV receiving appropriate supportive care.

In summary, this large international study demonstrated better survival with short and intense multiagent chemotherapy regimens incorporating CNS-penetrating agents such as CODOX-M/IVAC in HIV-BL. We also defined 4 prognostic factors that accurately identified patients at risk for treatment failure. Importantly, HIV-associated variables no longer influence outcome in this population. These prognostic factors should be incorporated in the design of future clinical trials to better stratify HIV-BL patient risk with the ultimate goal of developing a risk-adapted approach. Patients presenting with CNS involvement at diagnosis represent a high-risk subgroup with unmet therapeutical needs. People with HIV are commonly excluded from clinical trials precluding the evaluation of novel agents. Multicenter efforts toward incorporating this population in the design of studies testing novel agents and cellular therapies are urgently needed.

Authorship

Contribution: J.P.A., A.J.O., A.M.E., I.S.L., and K.C. designed and performed research, analyzed data, and wrote the paper; and G.P.C., A.V.D., M. Bower, D.J., C.Z., A. Sperling, S.-H.K., R.V., C.W., S.S., N.R., A.D.P., C. D'Angelo, U.F., D.A.B., S.B., M.C.C., A.G., N.K., Y.K.C., S.K., M.Y., E.R., F.A.P., G.V., R.K., M. Burkart, P.M., A.R., A.C., C. Diefenbach, A.S.-E., A.K., K.A.B., K.M.B., A.M., B.M.H., V.M.O.-N., V.P.K., A.Z., S.M.M., N.E., P.C., S.E.S., M.K., P.V., T.A.F., D.R., S.D.S., A. Stadnik, C.A.P., Y.L., S.N., and S.M. performed research, analyzed data, and wrote the paper.

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