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ORIGINAL REPORT

Dose-Modified Oral Chemotherapy in the Treatment of AIDS-Related Non-Hodgkin's Lymphoma in East Africa

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Africa is burdened by the AIDS epidemic and attendant increase in HIV/AIDS-related malignancies. Pragmatic approaches to therapeutic intervention could be of great value. Dose-modified oral chemotherapy for AIDS-related non-Hodgkin's lymphoma is one such approach.

Patients and Methods
The oral regimen consisted of lomustine 50 mg/m^2 on day 1 (cycle 1 only), etoposide 100 mg/m^2 on days 1 to 3, and cyclophosphamide/procarbazine 50 mg/m^2 each on days 22 to 26 at 6-week intervals (one cycle) for two total cycles in HIV-infected patients with biopsy-proven non-Hodgkin's lymphoma.

Results
Forty-nine patients (21 in Uganda and 28 in Kenya) were treated. The majority of patients were female (59%) and had a poor performance status (63%); 69% of patients had advanced-stage disease; and 18 patients (37%) had access to antiretroviral therapy. In total, 79.5 cycles of therapy were administered. The regimen was well tolerated, had modest effects (decline) on CD4$^+$ lymphocyte counts ($P = .077$), and had negligible effects on HIV-1 viral replication. Four febrile neutropenia episodes and three treatment-related deaths (6% mortality rate) occurred. The overall objective response rate was 78% (95% CI, 62% to 88%); median follow-up time was 8.2 months (range, 0.1 to 71 months); median event-free and overall survival times were 7.9 months (95% CI, 3.3 to 13.0 months) and 12.3 months (95% CI, 4.9 to 32.4 months), respectively; and 33% of patients survived 5 years.

Conclusion
Dose-modified oral chemotherapy is efficacious, has comparable outcome to that in the United States in the pre–highly active antiretroviral therapy setting, has an acceptable safety profile, and is pragmatic in sub-Saharan Africa. The international collaboration has been highly successful, and subsequent projects should focus on strategies to optimize combination antiretroviral therapy and chemotherapy and follow-up tissue correlative studies.

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INTRODUCTION

As the AIDS pandemic advances, the burden of neoplastic disease is increasing in developing nations.[1] In resource-constrained settings, intravenous chemotherapy and supportive care for patients with AIDS and cancer are challenging, and there is little published information on treatment outcomes.[2-5] Systemic chemotherapy for AIDS and other virus-associated tumors in this setting report mortality rates ranging between 20% and 66% and a 15-week median survival duration for AIDS-related Burkitt's lymphoma.[1,6-8]

Resource-constrained settings need the development of simple, less myelotoxic therapeutic interventions for cancer.[3-5] We hypothesized that dose-modified oral chemotherapy using a regimen that has had demonstrable activity in AIDS-related non-Hodgkin's lymphoma in the pre–highly active antiretroviral therapy (HAART) era in the United States would be efficacious and enhance the therapeutic index.[9-11] Rationale for the four-drug combination (lomustine, etoposide, cyclophosphamide, and procarbazine) has been published.[9] What is especially notable is the absence of anthracyclines and hence the avoidance of cardiotoxicity and the presence of agents that cross the blood-brain barrier (lomustine and procarbazine). Corticosteroids were also omitted because of additional immunosuppressive effects and potential tumor growth-promoting

effects in patients with Kaposi's sarcoma (endemic and AIDS-related disease) in a region of the world with the highest incidence.[12-16] Published studies confirmed that dose modification of chemotherapy lessened myelotoxicity without compromising efficacy in the pre-HAART era in the United States.[17,18] On the basis of this rationale, we report our results of dose-modified oral chemotherapy for the treatment of AIDS-related lymphoma in East Africa.

PATIENTS AND METHODS

Patient Selection Criteria

All patients were evaluated and treated at the national referral centers in Uganda (Uganda Cancer Institute) or Kenya (Kenyatta National Hospital). Patients ≥ 18 years of age with biopsy-proven measurable or assessable non-Hodgkin's lymphoma, no prior therapy, and documented HIV-positive serology were eligible for participation. Patients were required to have Eastern Cooperative Oncology Group performance status of ≤ 3, an estimated life expectancy of more than 6 weeks, and acceptable end organ function (WBC ≥ 3,000/μL or granulocytes ≥ 1,500/μL, platelets ≥ 75,000/μL, creatinine < 3.0 mg/dL, and total bilirubin < 3.0 mg/dL). All patients underwent a thorough physical examination with assessment of involved sites of disease including tumor measurement, bone marrow aspiration, and CSF analysis to exclude leptomeningeal disease. On-study staging chest radiography and abdominal ultrasonography were discretionary, which is aligned with current practice in East Africa.

Treatment Plan and Patient Follow-Up

The chemotherapy regimen consisted of lomustine, etoposide, cyclophosphamide, and procarbazine. All drugs were administered orally according to the dose schedule (Table 1), with modifications as outlined in Table 2 and the Appendix (online only). A cycle of therapy comprised two 3-week treatment periods for a total of 12 weeks of therapy. At the end of two cycles, patients were evaluated for response, observed at 3-month intervals over the first year, and observed for survival thereafter.

Pathology Review

All patients had tissue pathology confirmation of lymphoma in East Africa at the time of enrollment. At study conclusion, tumor biopsies including hematoxylin and eosin–stained tissue sections and formalin-fixed paraffin-embedded tissue blocks were transferred and reviewed in Cleveland, Ohio. Tumors were graded according to the WHO classification scheme whenever possible.[19] In some cases, the precise WHO classification was not possible as a result of inadequate tissue quality; therefore, all tumors were graded as low-, intermediate-, or high-grade lymphoma by Working Formulation criteria.[20] The Mid-Region AIDS and Cancer Specimen Resource (Columbus, OH) provided lymphoma subtype using a tissue microarray (TMA) method described in the Appendix.[21]

Ethical Review

Signed informed consent was obtained from all patients in keeping with international, institutional, and US Food and Drug Administration guidelines and is fully described in the Appendix.[22,23]

Table 1. Dosing Schedule

Drug	Dose (mg/m^2)
Lomustine	50 day 1, cycle 1 only
Etoposide	100 days 1-3, each cycle
Cyclophosphamide	100 days 22-26, each cycle
Procarbazine	100 days 22-26, each cycle

NOTE. Protocol-prescribed oral chemotherapy was based on blood counts that guided dosing on days of chemotherapy administration (i.e., days 1 and 22) every cycle. A cycle of therapy was 6 weeks, consisting of two 3-week portions of chemotherapy. Two cycles were administered. Lomustine was omitted for cycle 2.

Table 2. Dose Modifications

WBC Count (/μL)	Platelet Count (/μL)	% Drug Dose (for each drug)
≥ 3,000	≥ 100,000	100
≥ 1,500-2,999	≥ 50,000-99,999	50
≤ 1,499	≤ 49,999	0

NOTE. All patients received chemotherapy provided that WBC count was ≥ 1,500/μL and platelet count was ≥ 50,000/μL. Treatment was delayed until WBC ≥ 1,500/μL and platelets ≥ 50,000/μL or until 3 weeks elapsed, whichever occurred first. At that time, if counts still did not allow treatment, patients were taken off protocol. For patients experiencing febrile neutropenia, upon recovery, the next course of treatment was at 50% of the dose at which this event occurred, provided this was attributed to the chemotherapy.

Data Safety and Monitoring Plan, Toxicity, and Response Assessment

There was a project-specific Data Safety and Monitoring Plan (DSMP), which was fully integrated into the National Cancer Institute–approved institutional plan of the Case Comprehensive Cancer Center. On-site audits were conducted in 2003, 2004, 2005, and 2007. An independent review team at each audit had final authority to reconcile toxicity and response assessments including categories for unconfirmed complete response (CR) and unconfirmed partial response (PR).[24-26] Response criteria and DSMP are described in the Appendix.

Outcome End Points and Statistical Analyses

Three patients were enrolled but not treated and thus excluded from analyses. The rate of confirmed non-Hodgkin's lymphoma diagnosis from pathology analysis and the overall rate of pathology analysis were estimated and their 95% CIs determined using Wilson's method.[27] The survivor function was estimated using the Kaplan-Meier method[28] and analyzed separately for numerous covariates including body mass index[29] and the following prognostic scales: International Prognostic Index (IPI),[30] HIV score,[31] and the AIDS Clinical Trials Group 142 prognostic index.[32] Differences between and among groups were examined using the log-rank test. To control the effect of prognostic factors on event-free survival (EFS) and overall survival (OS) simultaneously, multiple Cox regression model was used after checking proportional hazards assumption.[33] For CR data, logistic regression was used to identify the factors that predict the outcome of response. The response rate and its 95% CI were estimated using Wilson's method.[27] The profiles of lymphocyte counts and RNA levels were compared by partitioning the time period into three intervals and using the Kruskal-Wallis test followed by pairwise comparison without adjusting for multiple comparison. The effects of numerous covariates on log($CD4^+$ lymphocytes) and log(RNA levels) and their temporal pattern were further examined by generalized linear models.[34,35] All tests were two-sided, and $P \leq .05$ was considered statistically significant.

RESULTS

Patient Characteristics

From among 149 patients with confirmed lymphoma and positive HIV serology, 52 were enrolled (35% recruitment rate), and 49 received oral chemotherapy between May 2001 and August 2005 (Table 3). Patient recruitment was temporarily suspended between December 2002 and July 2003 to replenish an expired drug supply. The three patients who were enrolled and not treated included two patients in Uganda (one died within 4 days of signing consent during evaluation, and the other patient voluntarily withdrew consent after completing screening) and a single patient in Kenya (the patient and physician mutually decided that it was best not to treat after completing screening because he resided > 350 miles from Nairobi).

Table 3. Patient Demographics and Clinical Characteristics, Clinical Staging Procedures, and Pathology Review and TMA Immunophenotype

Patient Demographics and Clinical Characteristics	No. of Patients		
	Uganda	Kenya	Total
Patients screened	144	113	257
Patients with confirmed lymphoma	140	112	252
Patients with confirmed HIV serology	65	84	149
Patients registered	23	29	52
Patients treated and analyzed	21	28	49
Sex			
Male	7	13	20
Female	14	15	29
Age, years			
Median	40	36.5	39
Range	18-57	26-64	18-64
Performance status			
0	5	0	5
1	6	7	13
2	6	7	13
3	4	14	18
Clinical stage			
I	2	4	6
II	2	7	9
III	2	2	4
IV	15	15	30
A	5	1	6
B	16	27	43
CD4 count, cells/μL			
Median	123	206.5	198
Range	5-1,364	21-409	5-1,364
Plasma HIV viral load, copies/mL			
Median	338,864	55,000	99,741
Range	831-11,700,000	Undetectable-> 750,000	Undetectable-11,700,000
Antiretroviral therapy			
None	12	19	31
Yes	9	9	18
Prior AIDS			
Yes	13	20	33
No	8	8	16
Extranodal sites			
≤ 1	14	21	35
> 1	7	7	14
LDH, U/L (n = 35)			
Median	670.5	520	550
Range	282-2,375	124-1,338	124-2,375
Prior thrush			
No	15	4	19
Yes	6	24	30
Prior opportunistic infection			
No	8	8	16
Yes	13	20	33
Albumin, g/L			
Median	3.2	3.2	3.2
Range	1.4-5.0	2.1-4.4	1.4-5.0
Hematocrit, %			
Median	29.3	33.6	31.5
Range	14.3-42.0	19.4-43.1	14.3-43.1
Body mass index, kg/m^2			
Median	18.8	25.5	21.1
Range	12-29.3	16.6-33.2	12-33.2

(continued on following page)

Table 3. Patient Demographics and Clinical Characteristics, Clinical Staging Procedures, and Pathology Review and TMA Immunophenotype (continued)

Patient Demographics and Clinical Characteristics	No. of Patients		
	Uganda	Kenya	Total
Second-line mCHOP			
No	14	24	38
Yes	7	4	11
Clinical staging procedures at baseline			
Physical examination and tumor measurement	21	28	49
Bone marrow aspiration biopsy	20	28	48
Lumbar puncture for CSF cytology	19	27	46
Chest radiograph	21	28	49
Abdominal sonography	21	28	49
Computed tomography (site specified)	1 (abdomen in India)	2 (both neck)	3
Pathology review in East Africa (based on hematoxylin and eosin staining)			
Tumor grade (n = 49) by Working Formulation			
High grade	16	15	31
Intermediate to high grade	1	0	1
Intermediate grade	4	12	16
Low grade	0	1	1
Total	21	28	49
Pathology review in United States (review of histopathology slides and TMA)			
Tumor grade (n = 33) by Working Formulation			
High grade	8	8	16
Intermediate to high grade	1	3	4
Intermediate grade	5	5	10
Low to intermediate grade	0	2	2
Hodgkin's lymphoma	0	1	1
Total	14	19	33
TMA immunophenotype (n = 28)			
B-cell lymphoma (not otherwise specified)	0	4*	4
Diffuse large-cell lymphoma	1†	6‡	7
Lymphoblastic lymphoma	0	3§	3
Burkitt's lymphoma	1‖	2¶	3
Plasmacytoid/plasmablastic lymphoma	2#	1**	3
Hodgkin's lymphoma	0	1	1
Insufficient number of intact cells (necrosis)	5	2	7
Total	9	19	28

Abbreviations: TMA, tissue microarray; LDH, lactate dehydrogenase; mCHOP, dose-modified cyclophosphamide, doxorubicin, vincristine, and prednisone.
* $CD20^+$.
†*c-myc* positive and $CD20^+$.
‡$CD20^+$, n = 5; $CD30^+$, n = 1.
§TDT positive, n = 1; 2 $CD79A^+$, n = 2.
‖EBER positive, *c-myc* positive, and $CD20^+$.
¶EBER positive, n = 1; $CD20^+$, n = 2.
#EBER positive, *c-myc* positive/$CD20^+$ (n = 1), $CD30^-$, and $CD79A^-$.
**EBER positive, $CD138^+$, MUM1 positive, TDT negative, and CD30–.

The majority of patients were female (59%) and had poor performance status (63%), advanced stage disease (69%), and prior AIDS diagnosis (67%); 37% of patients had access to antiretroviral therapy during the course of study, and 22% received subsequent second-line, dose-modified cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Thirty of the 33 reviewed patients had high-grade (n = 16), intermediate- to high-grade (n = 4), or intermediate-grade (n = 10) lymphoma.

Pathology Review

Thirty-three (67%) of 49 patients had tumor biopsy specimens submitted for pathology review and confirmation of lymphoma diagnosis; 28 samples were submitted for tumor immunophenotyping using TMA methodology (Table 3). The confirmed non-Hodgkin's lymphoma diagnosis rate was 31 (94%) of 33 patients (95% CI, 80% to 98%); of these 31 patients, 25 had TMA immunophenotyping performed. The overall proportion of pathology analyses was 32 (65%; including a patient with confirmed Hodgkin's lymphoma) of 49 patients (95% CI, 51% to 77%). *c-myc* gene rearrangements were confirmed in one patient with Burkitt's lymphoma (two patients had no probe signal), one patient with plasmacytoid, and one patient with diffuse large B-cell lymphoma. Six other samples had normal *c-myc* arrangements, and the remainder had no probe signal.

Treatment Course and Toxicity

A total of 79.5 cycles of therapy were administered; 32 patients (65%) completed the two protocol-prescribed courses; and therapy was well tolerated (Table 4). Only three patients (6%) developed CNS relapse. There were no difficulties with oral chemotherapy and protocol compliance. There was negligible nausea and vomiting and no cardiotoxicity. Dose modifications were required for hematologic toxicity but no other toxicity. No patients discontinued therapy as a result of nonresolution of intervening myelotoxicity. There were four episodes of grade 3 or 4 febrile neutropenia (5% of cycles) and four grade 3 infections. There were eight deaths during chemotherapy, and three were considered directly related to chemotherapy (6% treatment mortality rate; Table 4).

Impact of Chemotherapy on $CD4^+$ Lymphocytes and HIV-1 Plasma RNA

Eighteen patients (37%) received antiretroviral therapy at the start, during, or immediately on completion of chemotherapy. More patients were started on antiretroviral therapy during the later part of the study as access expanded in East Africa; seven patients received therapy in 2001 to 2003, and 11 received therapy in 2004 to 2005, corresponding to the roll out of national drug access programs. Patients with access to antiretroviral therapy over the course of the study had improved survival ($P = .0007$; Fig 1A). Oral chemotherapy had modest impact (decline) on $CD4^+$ lymphocyte counts ($P = .077$) and no adverse effects on HIV-1 viral replication (Table 5). An increased incidence of opportunistic infections was not observed during chemotherapy. In separate multiple linear regression analyses, antiretroviral therapy ($P = .013$) and days after onset of chemotherapy ($P < .0001$) were predictors of $CD4^+$ lymphocyte counts, and antiretroviral therapy ($P = .018$) was a significant predictor of HIV-1 RNA plasma levels.

Response and Survival

Forty (82%) of the 49 patients were assessable for response. The overall objective response rate (CR/unconfirmed CR + PR/uncon-

Table 4. Treatment Course and Toxicity

Treatment and Toxicity	Uganda (n = 21)	Kenya (n = 28)	Total (n = 49)
Total No. of cycles of therapy	32.5	47	79.5
Median per patient	2	2	2
Range per patient	0.5-2.0	0.5-2.0	0.5-2.0
Toxicity, No. of patients			
Grade 3 diarrhea/dehydration	1	2	3
Grade 3 infection (OI)*	4	0	4
Grade 3 neutropenia	6	2	8
Grade 4 dehydration	1	0	1
Grade 3/4 febrile neutropenia	3	1	4
Grade 4 ANC/thrombocytopenia	3	4	7
Toxicity (grade 5, death), No. of patients			
Treatment related	2	1	3
Not treatment related†	1	4	5

Abbreviations: OI, opportunistic infection; ANC, absolute neutrophil count.
*The four grade 3 infections included two cryptococcal meningitis, one *Pneumocystis* pneumonia, and one tuberculosis.
†The five other causes of death on study that were not considered treatment-related included progressive lymphoma in two patients, progressive AIDS in two patients, and undetermined cause in one patient with no associated myelosuppression.

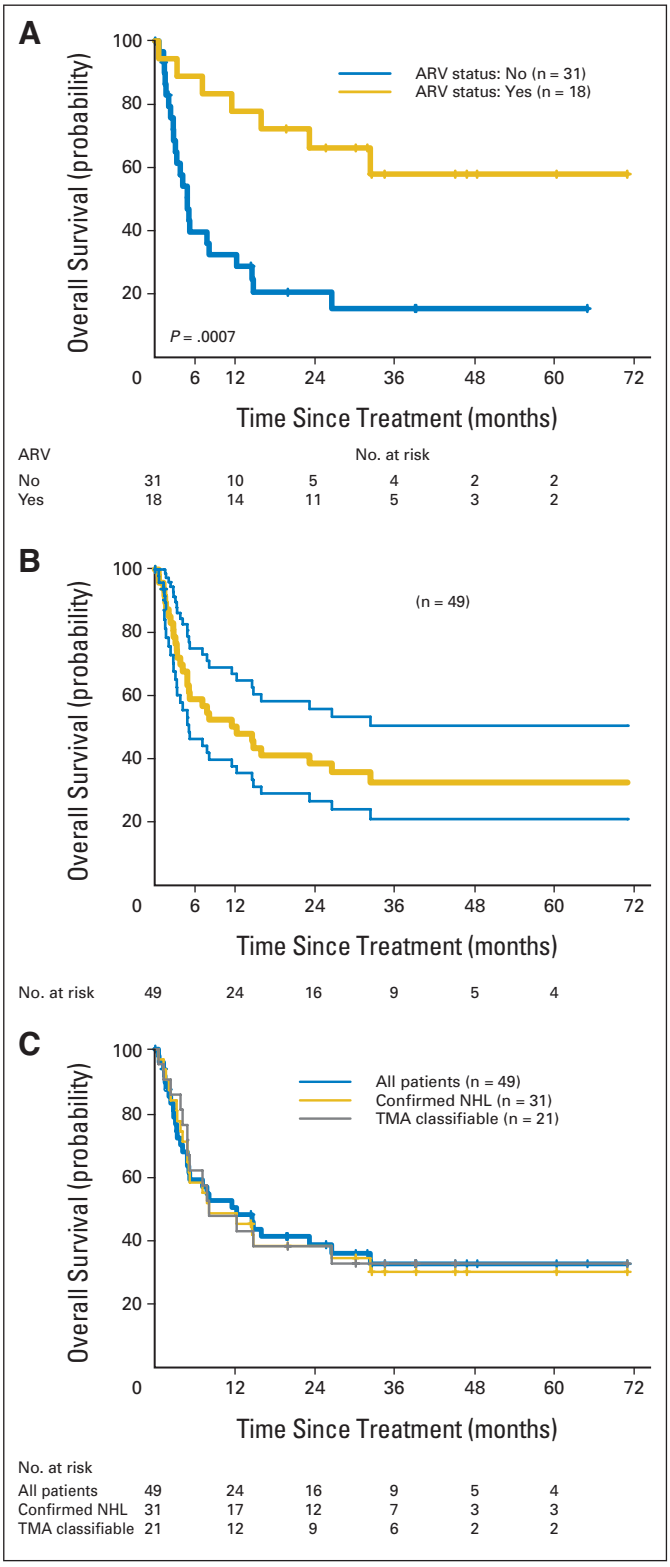

Fig 1. (A) Kaplan-Meier (KM) estimation of overall survival (OS) stratified by antiretroviral (ARV) status. (B) KM estimation of OS with 95% CIs. The median OS time was 12.3 months (95% CI, 4.9 to 32.4 months). The three cases of confirmed Burkitt's lymphoma survived 7.2, 12.3, and 14.8 months. (C) KM estimation of OS of all 49 treated patients superimposed on KM estimations from 31 confirmed non-Hodgkin's lymphoma (NHL) patients and from 21 subtyped (tissue microarray [TMA]) patients. (D) KM estimation of OS by intermediate and high tumor grade. Tumor grade was based on a composite of confirmed tumor grade and African grade for patients not reviewed or confirmed in United States.

Table 5. Impact of Oral Chemotherapy on $CD4^+$ Lymphocyte Counts and HIV-1 Plasma RNA

Time Point	$CD4^+$ Lymphocyte Count				HIV-1 Plasma RNA			
	No. of Patients	Median (cells/μL)	Range (cells/μL)	P*	No. of Patients	Median (copies/mL)	Range (copies/mL)	P*
Baseline	49	198	5-1,364	—	45	102,000	0-11,750,000	—
3-70 days	32	150.5	4-586	.077 (overall)	30	119,455	325-1,810,000	.904 (overall)
> 70 days	21	88	5-304	.027 (*v* baseline)	19	78,683	200-8,200,000	—

*P values were based on 21 patients with $CD4^+$ lymphocyte count and 19 patients with HIV-1 plasma RNA who had complete data at the three time points.

firmed PR) was 78% (95% CI, 62% to 88%), and the CR/unconfirmed CR response rate was 58% (95% CI, 42% to 71%; Appendix Table A1, online only). To identify factors that predict CR, a logistical regression was used. In univariate analysis, only antiretroviral therapy was significantly related to CR ($P = .005$). Comparing patients without antiretroviral therapy, the odds of having a CR for patients with antiretroviral therapy was increased less than 12-fold. The median OS time was 12.3 months (95% CI, 4.9 to 32.4 months; Fig 1B). The Kaplan-Meier estimations of survivor function for three cohorts (all 49 treated patients, 31 confirmed non-Hodgkin's lymphoma patients, and 21 TMA-classifiable patients) were essentially identical (Fig 1C). The Kaplan-Meier estimate of survivor function by tumor grade is shown in Appendix Fig A1 (online only). At time of last follow-up in July 2007, 33% of patients had survived 5 years, and 30 patients had died. Causes of death included treatment (n = 3), progressive AIDS (n = 11), progressive lymphoma (n = 7), both progressive lymphoma and AIDS (n = 6), and undetermined cause (n = 3). The median follow-up duration was 8.2 months (range, 0.1 to 71 months).

Prognostic Analyses of Outcome

Numerous variables and three prognostic scales were analyzed for effects on EFS and OS by univariate Cox model (Appendix Table A2, online only). In univariate analysis, serum lactate dehydrogenase (LDH; $P = .0004$) and hemoglobin ($P = .002$) were the only continuous covariates that were significantly related to EFS and OS (Table 6).

Table 6. Effect of Continuous Covariates on OS Estimated by Univariate Analysis and Effects of IPI and Other Covariates on OS Estimated by Multivariate Analysis

Factor	Coefficient (β)	Hazard Ratio	P
Effect of continuous covariates on OS			
Age, per year increase	−0.026	0.974	.202
LDH, per 100 U/L increase	0.156	1.17	.0004
$CD4^+$ count, per 100/μL decrease	−0.22	1.25	.167
HIV-1 RNA, per 10^7 copies/mL increase	0.76	2.14	.442
Albumin, per 1 g/L decrease	−0.225	1.25	.379
Hemoglobin, per 1 g/dL decrease	−0.292	1.34	.002
Body mass index, per 1 point increase	0.024	1.02	.493
Effect of IPI and other covariates on OS			
Sex, female *v* male	−0.34	0.715	.444
Hemoglobin, 1 g/dL decrease	−0.154	1.17	.184
Antiretroviral therapy, no *v* yes	1.05	2.87	.035
IPI, index increase by 1	0.557	1.75	.034
Tumor grade, high *v* intermediate	−0.147	1.16	.766

Abbreviations: OS, overall survival; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Besides sex, those factors that were significant in univariate analysis were further included in the multiple Cox regression model after checking proportional hazard assumption (Table 6). The IPI was defined by age, stage, performance status, and extranodal sites of disease and excluded LDH. The IPI ($P = .034$) and access to antiretroviral therapy ($P = .035$) were significantly related to survival after controlling for the effects of other covariates. With every increase of the IPI index by 1, the hazard of dying was increased 1.75-fold ($P = .034$). Similarly, the hazard ratio of patients without antiretroviral therapy compared with those with access was 2.87 ($P = .035$).

DISCUSSION

To our knowledge, this is the first prospective study of the treatment of AIDS-related non-Hodgkin's lymphoma conducted in sub-Saharan Africa, a region of the world with a high burden of HIV disease.[1,2,36,37] Several clinical observations from this study are noteworthy and provide a departure point to better understand the natural history of lymphoma in Africa. Foremost among these is that the study design was hypothesis driven, pragmatic, and fully aligned with current clinical practices. Oral chemotherapy is advantageous, with demonstrable efficacy and an acceptable safety profile. The 6% treatment mortality rate is a seminal observation and compares favorably to the 20% to 66% treatment mortality encountered in patients with advanced AIDS-related malignancies or endemic Burkitt's lymphoma.[1,6,7] Demonstrable antitumor activity was also observed with a less myelosuppressive, non–dose-intense chemotherapy regimen in patients with high-grade disease including patients with AIDS-related Burkitt's lymphoma. Only three patients (6%) had leptomeningeal relapse, substantiating clinical benefit from inclusion of drugs in the oral regimen that are known to cross the blood-brain barrier.

Our histopathology review and lymphoma subtype analysis at study closure were instructive. Working Formulation criteria for lymphoma classification is the current standard of pathology in East Africa.[20] The 33 patients with tissue blocks and original hematoxylin and eosin tissue sections presented challenges on review. Of the 16 patients excluded, the majority were patients referred from upcountry and regional hospitals in Uganda and Kenya to the national referral centers in our study. All of these patients had written pathology reports substantiating lymphoma diagnosis. Biopsy materials could not be retrieved from these remote locations, which were often hundreds of miles away. We undertook CI estimations of our pathology review—confidence in establishing a diagnosis of lymphoma in tissues that were available and overall confidence in pathologic diagnosis. There is acceptable confirmation of non-Hodgkin's lymphoma in patients reviewed for confirmation of lymphoma. In Figure 1C, all

three Kaplan-Meier survival plots identify comparable outcomes irrespective of the assurance of diagnosis; thus, bias as a result of inappropriate diagnosis is less likely. Nonetheless, the TMA-based lymphoma subtype analyses identified a wide spectrum of lymphomas in the backdrop of HIV infection in sub-Saharan Africa. This diversity of lymphoma subtype was unexpected.[38,39] It will be worthwhile for future capacity-building efforts to enable pathology contributions to focus on additional training and support for this vital endeavor to further our phenotypic and molecular characterization of treated cancers.

It is notable that we did not encounter profound immunosuppression in our East African patients (median $CD4^+$ count, 198 cells/μL) compared with that reported in US trials in the pre-HAART era ($CD4^+$ count range of 47 to 117 cells/μL at presentation).[9,11,17,26,40,41] Patients with AIDS in Africa have been reported to present with slightly higher $CD4^+$ counts with onset of opportunistic and neoplastic complications.[42,43] Of interest is the apparent critical role that antiretroviral therapy plays in the management of patients with AIDS-related lymphoma in this setting. Oral chemotherapy had modest effects on $CD4^+$ lymphocyte counts. There was no increase in opportunistic infection over the course of therapy, and there were negligible effects on underlying HIV-1 viral replication. Chemotherapy does not adversely affect HIV-1 viral replication in US adults and children with AIDS-related lymphoma, and this appears to be the case as well in Africa.[18,44,45] Clearly, treatment of both disease processes (ie, HIV infection and neoplastic disease) is required for patient survival. Oral chemotherapy as prescribed in our study is compatible with contemporary antiretroviral usage in sub-Saharan Africa.

The IPI proved to be the most discriminating of the three prognostic scales for AIDS-related lymphoma that we analyzed, which has also been reported by others.[46] On the basis of extensive physical examination and bone marrow and CSF examination, our results are remarkably consistent with published prognostic scales such as the IPI and AIDS Clinical Trials Group score. Admittedly, patients may be understaged as a result of lack of computed tomography and magnetic resonance imaging. It is important to point out, however, that careful scrutiny of essential findings on physical examination can be made in resource-constrained settings to identify the extent of extranodal involvement and to incorporate findings into various staging and prognostic classifications. Many of our patients had massively enlarged lymph nodes or extranodal masses that ulcerated the skin surface and extended to the musculature of the chest wall, abdominal wall, or groin and had massive organomegaly (hepatomegaly) for which it is entirely appropriate to assign extranodal involvement. Staging criteria allow for such assignment. This was performed and was captured in our staging evaluation in the absence of robust radiographic imaging capability. Additionally, patients underwent on-study bone marrow aspiration and CSF cytologic analysis, which are routinely performed in this setting.

As we proceed with future studies, our experience will help guide prognostic scales more adapted and suitable to sub-Saharan Africa. As an initial departure, we feel that these analyses are important to disseminate. Baseline hemoglobin and albumin may be incorporated or substituted for LDH as useful covariates to provide further independent prognostic information in subsequent trials because these are more readily available in East Africa. Access to antiretroviral therapy was also predictive of CR and prognostic of survival. All of these factors may guide therapeutic options in future trials in Africa.

The adoption of dose-modified oral chemotherapy, the use of targeted laboratory and limited radiographic assessments, and the capability to pursue tumor biopsy pathology confirmation during this clinical trial are aligned with current clinical practices in sub-Saharan Africa. Cost-effective therapeutic strategies for the management of HIV disease in Africa are clearly warranted.[47] Even with the emerging availability of HAART, the safety of dose-modified oral chemotherapy is important new information. As in most developing countries, HAART is more available than chemotherapy safety monitoring. Over the course of this study, which was closely monitored, ethical considerations did not seem to present new hurdles. Our project-specific DSMP was well informed, and the ability to conduct on-site audits greatly complemented the conduct of this study.

Developing countries, which are generally overwhelmed by the burden of AIDS, have focused their limited resources more on public health and less on personal health. Limitations are reflected in lack of sophisticated radiology, clinical laboratory, blood transfusion, and histopathology.[2,48-50] These limitations influenced the decision to prospectively evaluate a nonmyelosuppressive chemotherapy regimen for AIDS-related lymphoma and the choices made within this protocol. Although understaging of patients may have occurred as a result of lack of computed tomography/magnetic resonance imaging access, this is balanced by initial presentation at more advanced stages of disease than occurs in developed countries, allowing physical examination to be a reasonably reliable instrument of measure. Laboratory testing reflects use of available tests rather than those more commonly used in developed countries, which may limit comparability. This does not discount the usefulness of the tests used. Diagnostic pathology is not supported or organized in the same manner as in developed countries, and the limitations encountered with tissue studies was greater than anticipated. The prevalence and distribution of lymphoma subtypes throughout Africa, particularly among persons with AIDS, are currently not known. Although these limitations are immediate hurdles, there are several groups (eg, African Organisation for Research and Training in Cancer and National Institutes of Health) that are moving forward to mitigate these limitations that affect Africa. At the 50th Anniversary of the Discovery of Burkitt Lymphoma conference in 2008, these points were articulated and reported, as follows: "disease patterns have not been fully documented but diagnosis for the majority is still by morphology alone; there is a need to formulate and implement standards for lymphoma diagnosis and classification; and Africa is at the stage that the industrialized world was at in the 1960s and 1970s."[49] Our demonstration clearly informs about possible ways forward.

In summary, it is feasible to develop evidence-based, pragmatic therapeutic intervention to treat patients with advanced AIDS-associated malignancies in East Africa. This National Cancer Institute R01 project supported, to our knowledge, the first trial ever conducted on the African continent for AIDS-related non-Hodgkin's lymphoma. Its success provides a springboard for capacity building; further phenotypic and molecular characterization of lymphoma subtypes; and collaborative efforts to frame alternative, less myelotoxic therapeutic strategies suitable for evaluation in the resource-constrained setting. Successor projects should focus on strategies to optimize combination antiretroviral therapy and chemotherapy and follow-up correlative tissue and laboratory studies.

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The author(s) indicated no potential conflicts of interest.

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