Ferrata Storti Foundation

Haematologica 2021
Volume 106(3):730-735

Response-adapted therapy with infusional EPOCH chemotherapy plus rituximab in human immunodeficiency virus-associated, B-cell non-Hodgkin lymphoma

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ABSTRACT

Four cycles of rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy is as effective as six cycles in low-risk diffuse large B-cell lymphoma (DLBCL). Here we report a post-hoc analysis of a prospective clinical trial in patients with human immunodeficiency virus-associated DLBCL and high-grade lymphoma treated with four to six cycles of EPOCH plus rituximab based on a response-adapted treatment strategy. One hundred and six evaluable patients with human immunodeficiency virus-associated DLBCL or high-grade CD20^{+} non-Hodgkin lymphoma were randomized to receive rituximab (375 mg/m^{2}) given either concurrently prior to each infusional EPOCH cycle, or sequentially (weekly for 6 weeks) following completion of EPOCH. EPOCH consisted of a 96-hour intravenous infusion of etoposide, doxorubicin, and vincristine plus oral prednisone followed by an intravenous bolus of cyclophosphamide every 21 days for four to six cycles. Patients received two additional cycles of therapy after documentation of a complete response by computed tomography after cycles 2 and 4. Sixty-four of 106 evaluable patients (60%; 95% confidence interval [95% CI]: 50%-70%) in both treatment arms had a complete response. The 2-year event-free survival rates were similar in the 24 patients with complete response who received four or fewer cycles of EPOCH (78%; 95% CI: 55%-90%) due to having achieved a complete response after two cycles, compared with those who received five or six cycles of EPOCH (85%; 95% CI: 70%-93%) because a complete response was first documented after cycle 4. A response-adapted strategy may permit a shorter treatment duration without compromising therapeutic efficacy in patients with human immunodeficiency virus-associated lymphoma treated with EPOCH plus rituximab, which merits further evaluation in additional prospective trials. *Clinical Trials.gov identifier NCT00049036.*

Introduction

Six cycles of the anti-CD20 antibody rituximab (R) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy are recommended by the European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) practice guidelines for the treatment of diffuse large B-cell lymphoma (DLBCL),[1,2] a recommendation supported by popu-

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Received: November 19, 2019.

Accepted: February 25, 2020.

Pre-published: February 27, 2020.

https://doi.org/10.3324/haematol.2019.243386

lation-based data demonstrating similar outcomes after six or eight cycles of therapy.[3] Poeschel *et al.* reported the non-inferiority of four cycles of R-CHOP (followed by 2 additional doses of rituximab) compared with six cycles of R-CHOP in a randomized, phase III trial that included 588 immunocompetent patients with stage I-II DLBCL aged 18-60 years and an age-adjusted International Prognostic Index score of 0, indicating that de-escalation of treatment duration may be safely achieved without compromising curability in an appropriately selected patient population.[4] This provides a foundation for evaluation of therapeutic de-escalation in other settings using other strategies.

Infusional administration of cytotoxic therapy has been explored as a potential strategy in patients with poor-risk lymphoma,[5-8] including human immunodeficiency virus (HIV)-associated lymphoma.[9-13] Based upon these considerations, the AIDS Malignancy Consortium conducted a randomized, phase II trial of rituximab (375 mg/m^2) given either concurrently prior to each infusional EPOCH chemotherapy cycle, or sequentially (weekly for 6 weeks) following completion of all chemotherapy in patients with HIV-associated DLBCL and high-grade lymphoma.[14] EPOCH consisted of a 96-hour intravenous infusion of etoposide, doxorubicin, and vincristine together with oral prednisone followed by an intravenous bolus of cyclophosphamide given every 21 days for four to six cycles, with cyclophosphamide dose adjusted based on pretreatment CD4 lymphocyte count, and subsequently escalated or reduced based on the absence or presence of treatment-associated cytopenias. The prespecified primary efficacy complete response endpoint of 75% was met in the concurrently treated arm (73%, 95% confidence interval [95% CI]: 58%-85%), but not in the arm treated sequentially (55%, 95% CI: 41%-68%).[14] Patients were assessed by computed tomography (CT) of the chest, abdomen, and pelvis after every two cycles of EPOCH chemotherapy, and were treated for two cycles beyond achieving a complete response for a minimum of four and a maximum of six cycles of EPOCH. Two-year time to progression rates were similar in the concurrently treated arm (75%, 95% CI: 63%-88%) and the sequentially treated arm (71%, 95% CI: 59%-84%). Inspired by the successful de-escalation of R-CHOP therapy to four cycles documented in a low-risk population with DLBCL,[4] here we report a post-hoc analysis of the outcomes of patients with HIV-associated DLBCL and high-grade lymphoma with higher risk features who achieved a complete response when treated with four or fewer cycles of therapy, based on having achieved a complete response after two cycles of EPOCH.

Methods

Eligibility criteria and study conduct

Details regarding eligibility criteria, treatment, and clinical outcomes up to 2 years were previously reported.[14] Briefly, eligibility criteria included: (i) CD20$^+$ B-cell non-Hodgkin lymphoma, including DLBCL, Burkitt/Burkitt-like lymphoma, or other aggressive lymphomas; (ii) HIV infection; (iii) stage II-IV disease (or stage I disease with an elevated serum lactate dehydrogenase concentration); (iv) Eastern Cooperative Oncology Group performance status of 0-2; (v) age 18 years or older;[5] and (vi) adequate organ function, similarly to prior trials by the AIDS Malignancy Consortium.[15] The study was reviewed and approved by the Cancer Evaluation Therapy Program of the National Cancer Institute, and by the institutional review board at each participating institution. All patients provided written informed consent to their inclusion in the analysis.

Response assessment and duration of therapy

Response was defined by the 1999 International Response Criteria for Non-Hodgkin Lymphoma (which utilizes anatomical but not functional imaging).[16] Response was evaluated after every two cycles of EPOCH therapy with CT of the chest, abdomen, and pelvis, and continued for two cycles beyond the achievement of a complete response for a minimum of four and a maximum of six cycles, including after completion of R-EPOCH in the concurrently treated arm, and after completion of EPOCH alone and following rituximab alone in the sequentially treated arm. All patients had a bone marrow evaluation and lumbar puncture for cerebrospinal fluid cytological examination at baseline. A repeat bone marrow evaluation for confirmation of complete response was required after completion of therapy if the baseline study demonstrated lymphomatous marrow involvement. 2-Deoxy-2-[fluorine-18]fluoro-D-glucose (FDG) positron emission tomography (PET) scans were not required or consistently performed, and when done were usually performed at the completion of therapy. Event-free survival, time to progression, and overall survival were estimated using the method of Kaplan and Meier. Event-free survival was defined as the time between registration and either relapse or progression of lymphoma or death from any cause (thus corresponding to progression-free survival in other reports[17]). Time to progression was defined as time to progression or relapse of lymphoma, with deaths from other causes censored. Patients were followed for survival and recurrence up to 5 years after registration. We performed a post-hoc analysis to evaluate the outcomes for patients who received only four cycles of therapy due to achieving a complete response, as determined by CT scan, after two cycles of therapy, compared with those who required five or six cycles of therapy who achieved a complete response after four cycles of therapy.

Results

Patients and response to therapy

A total of 106 evaluable patients were enrolled and initiated treatment at 20 sites of the AIDS Malignancy Consortium between December 2002 and April 2006 and are included in this analysis, as in the original, previously described analysis.[14] The disposition and outcomes of all patients enrolled are shown in Figure 1. A complete response was achieved by 64 of the 106 patients (60%, 95% CI: 50%-70%) who received any protocol therapy. The null hypothesis of a complete response rate of 50% was rejected in favor of the alternative of 75% for the concurrently treated arm (P=0.005), but not for the sequentially treated arm (P=0.394). Of the 64 patients who had a complete response, 24 received four or fewer cycles of R-EPOCH: 14/35 (40%) in the concurrently treated arm and 10/29 (34%) in the sequentially treated arm.

Characteristics of patients treated with four or fewer *versus* five or six cycles of EPOCH therapy

Of 64 patients who achieved a complete response, 24 (38%, 95% CI: 26%-51%) received four or fewer cycles of EPOCH based on their having achieved early complete response after two cycles of therapy, whereas the remaining 40 (63%, 95% CI: 50%-74%) received five or six

cycles of therapy. The characteristics of the entire study population, and patients who received four or fewer *versus* five or six cycles are shown in Table 1. The characteristics of the two groups were generally comparable to each other, and to those of the entire study population, with respect to gender, median age, baseline CD4 count, concurrent antiretroviral therapy, histology, and bone marrow involvement at baseline.

Information regarding histological subtype (germinal center B-cell [GCB] subtype *vs*. non-GCB subtype) was available for only 21 of the 64 patients who had a complete response, with no significant difference in number with non-GCB subtype for those who received four or fewer cycles compared with those who received five or six cycles (3/8 *vs*. 5/13 patients, *P*=1.000 Fisher exact test).

Treatment administered

A total of 322 cycles of EPOCH therapy were given to

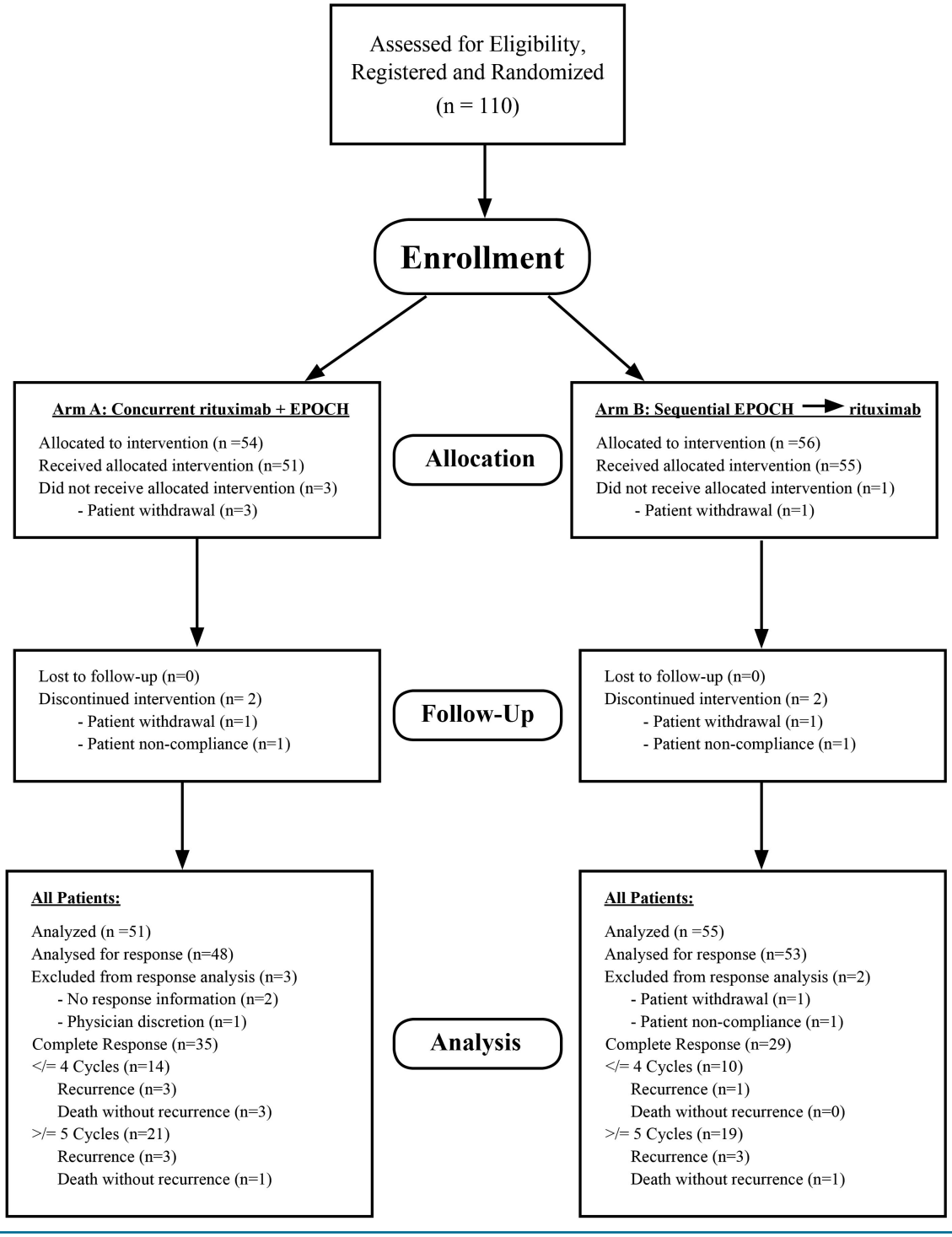

Figure 1. Consort diagram.

all 64 patients who achieved a complete response. Among the 24 who received four or fewer cycles, five received fewer than four cycles. The reasons for this were disease progression after achieving a complete response (n=1), physician's decision (n=1), or other reasons (n=3). Among the 40 who received five or six cycles of EPOCH, 36 received six cycles and four received five cycles due to physicians' decision (n=3) or unknown reasons (n=1).

Table 1. Characteristics of the entire population and complete responders stratified by number of EPOCH treatment cycles.

	Entire population	CR ≤4 cycles	CR 5-6 cycles
N. treated	106	24	40
Male gender, n (%)	91 (86%)	19 (79%)	37 (93%)
Median age, years	44	43.5	44
CD4 cell count			
Median	191/μL	237/μL	230.5/μL
N (%) of patients with ≤100/ L	33 (31%)	5 (21%)	12 (30%)
Concurrent antiretroviral therapy, n (%)	75 (71%)	16 (67%)	29 (75%)
Concurrent or sequential rituximab, n (%)			
Concurrent	51 (48%)	14 (42%)	21 (53%)
Sequential	56 (52%)	10 (58%)	19 (47%)
Local histology, n (%)*			
Diffuse large cell	78 (74%)	17 (71%)	28 (70%)
High grade	25 (33%)	7 (29%)	12 (30%)
Bone marrow involvement at diagnosis, n (%)	15 (14%)	5 (21%)	3 (8%)
Stage III-IV, n (%)	84 (79%)	17 (71%)	30 (75%)
Elevated LDH, n (%)	72 (68%)	15 (63%)	28 (70%)
ECOG PS 2, n (%)	25 (24%)	3 (13%)	10 (25%)
Age-adjusted IPI risk factors, n (%)			
0	8 (8%)	0	5 (12%)
1	28 (26%)	12 (50%)	8 (20%)
2	51 (48%)	10 (40%)	19 (48%)
3	19 (18%)	2 (10%)	8 (20%)

* pathology as determined by local pathologist. CR: complete response; LDH: lactate dehydrogenase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index.

Table 2. Clinical outcomes for entire population and complete responders stratified by number of EPOCH treatment cycles.

	Entire population	CR ≤4 cycles	CR 5-6 cycles
Number	106	24	40
Median follow-up (range)	30 months (0-68)	36.5 months (1-67)	40 months (5-66)
N. relapsed after CR	10/64 (16%) (95% CI: 8%- 27%)	4/24 (17%) (95% CI 5%-37%)	6/40 (15%) (95% CI 6%-30%)
EFS rate, % (95% CI)			
At 1 year	71% (61%-79%)	91% (69%-98%)	90% (76%-96%)
At 2 years	64% (54%-73%)	78% (55%-90%)	85% (70%-93%)
Time to progression, % (95% CI)			
At 1 year	77% (67%-84%)	91% (69%-98%)	92% (78%-97%)
At 2 years	73% (63%-81%)	91% (69%-98%)	87% (72%-94%)
OS rate, % (95% CI)			
At 1 year	78% (68%-85%)	91% (69%- 98%)	95% (81%-99%)
At 2 years	68% (58%-76%)	78% (55%-90%)	90% (75%-96%)

CR: complete response; 95% CI. 95% confidence interval; EFS: event-free survival, OS: overall survival.

Clinical outcomes by number of EPOCH treatment cycles in complete responders

Outcome data for the 106 patients in the entire study population, and the 64 patients who achieved complete response are shown in Table 2 and Figure 2A-C. After a median follow-up of 30 months (range, 0-67 months) for all treated patients, 36 (34%, 95% CI: 25%-44%) died, with relapsed lymphoma being the cause of death in eight (8%, 95% CI: 3%-14%). After a median follow-up of 38.5 months (range, 1-66 months) in the 64 patients who achieved a complete response, 11 (17%, 95% CI: 9%-29%) died, five (8%, 95% CI: 3%-18%) with relapsed lymphoma as the cause of death. Outcomes were similar for those treated with four or fewer cycles compared with those given five or six cycles with respect to rates of 2-year event-free survival (78% *vs.* 85%), time to progression (91% *vs.* 87%), and overall survival (78% *vs.* 90%).

Discussion

In the absence of prospective comparative data in HIV-associated lymphoma, six cycles of rituximab plus infusional EPOCH is considered a preferred regimen for first-line treatment of HIV-associated DLBCL, HHV8-positive DLBCL, primary effusion lymphoma, and is also among the preferred regimens for HIV-associated Burkitt lymphoma in the 2019 NCCN guidelines.[2,18] These recommendations were driven by the effectiveness of R-EPOCH in individual phase II trials in HIV-associated DLBCL and high-grade lymphoma,[19,20] and results from a large meta-analysis that demonstrated greater efficacy for R-EPOCH as compared to R-CHOP in HIV-associated lymphoma.[21] On the other hand, a phase III trial comparing R-CHOP with R-EPOCH in immunocompetent patients with DLBCL found no difference in efficacy.[17] Retrospective analysis showed that a high proliferation rate was associated with better prognosis in HIV-associated lymphomas when treated with infusional R- EPOCH but not with R-CHOP, suggesting that tumors with high proliferation rates, such as high-grade lymphoma and a subset of DLBCL may be those most likely to benefit from infusional EPOCH chemotherapy.[22] The findings from our study suggest that patients with HIV-associated lymphoma who achieve a complete response after two cycles of EPOCH plus rituximab have excellent outcomes when therapy is limited to four cycles, thereby sparing toxicity associated with longer treatment durations.

Dunleavy *et al.* reported a phase II study including 33 patients with HIV-associated DLBCL who received three to six cycles of dose-dense rituximab (SC-EPOCH-RR), of whom 79% received three cycles of therapy based on a risk-adapted approach of treating for one cycle beyond a negative interim PET-CT after cycle 2.[23] At the median follow-up of 5 years, the progression-free survival rate was 84%, although outcomes were excellent only for those with GCB subtype lymphoma (95% for GCB *vs.* 44% for non-GCB subtype).[23] Only about one-third of patients in our trial had information regarding GCB or non-GCB subtype, and outcomes were similar irrespective of subtype. Future studies evaluating risk-adapted therapy may need to integrate histological subtyping, be limited to the GCB

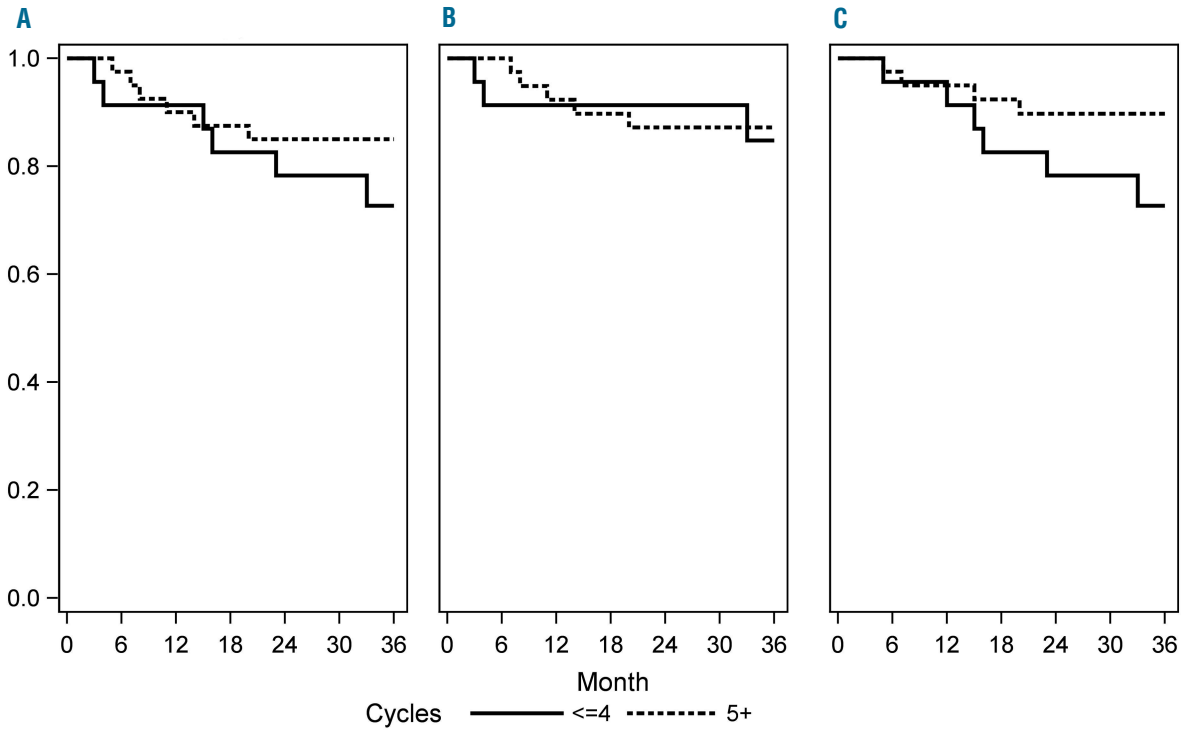

Figure 2. Kaplan-Meier estimates of outcomes in patients achieving complete response to response-adapted EPOCH chemotherapy, stratified by number of treatment cycles. (A-C) Patients are stratified into two groups: a group that received four or fewer cycles of EPOCH chemotherapy and a group that received five or six cycles. Estimates are shown for event-free survival (A), time to progression (B) and overall survival (C).

lymphoma subtype and consider other molecular characteristics that have prognostic relevance.[24]

Interim restaging is recommended to identify patients whose disease has not responded well to, or has progressed, on induction therapy after two to four cycles of therapy.[2] Staging is recommended using FDG-PET integrated with CT (FDG-PET/CT) at diagnosis, after two to four cycles of therapy, and at the end of treatment.[2] A negative PET scan after two to four cycles of induction therapy has been associated with significantly higher event-free survival and overall survival rates in some studies,[25-28] but not others.[29-32] Although several studies failed to show improvement in clinical outcomes when therapy was tailored to FDG-PET/CT response,[33,34] these studies were designed to evaluate more aggressive therapy in patients with persistent FDG-avid lesions, not de-escalation of therapy in patients who had an early FDG response. Differentiation of reactive adenopathy from active lymphoma may be challenging in patients with HIV-associated lymphoma, although this may be less problematic in patients with well-controlled viremia.[35] Although preliminary results reported by Dunleavy *et al.*[23] regarding use of interim FDG-PET/CT as a pharmacodynamic biomarker for tailoring de-escalation appears promising in HIV-associated lymphoma, further study is required in multicenter prospective clinical trials.

Our analysis has several strengths and limitations. The strengths include the prospective nature of the trial, and the protocol-specified guidelines for treatment duration based on radiographic response. The limitations include the post-hoc analysis examining response durability based on rapidity of response and number of treatment cycles, and the fact that the observations were not based on an adequately powered comparison between the standard approach of six treatment cycles compared with a risk-adapted approach. Nevertheless, given recent evidence that four cycles of R-CHOP constitute adequate therapy for a low-risk population,[4] the findings of our study indicating the feasibility of a response-adapted de-escalation strategy in a higher-risk population with HIV-associated lymphoma, and the clinical utility of interim FDG/PET, there is now a compelling rationale to prospectively evaluate the use of interim FDG-PET/CT after two cycles of therapy, rather than CT as used in our trial, in order to assess response to guide treatment duration in patients with HIV-associated lymphoma.

Disclosures

No conflicts of interest to disclose.

Contributions

The manuscript was written by JAS and was approved by all co-authors. The clinical protocol was written by JAS, JYL, and LDK. The data and statistical analyses were performed by JYL and administrative support and oversight were provided by RM. Pathological review of tumor specimens was performed by EC and AC. Individuals who contributed subjects to the trial included JAS, LDK, JCR, RFA, DA, AN, DHH, LR, EC, WW, and AC.

Acknowledgments

This study was coordinated by the AIDS Malignancy Consortium (Ronald Mitsuyasu, MD, Chair).

Funding

This study was supported in part by Public Health Service grant n. UM1CA121947, the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services.

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