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Response-adapted therapy with infusional EPOCH chemotherapy plus rituximab in HIV-associated, B-cell non-Hodgkin's lymphoma

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ABSTRACT

Four cycles of rituximab plus CHOP chemotherapy is as effective as 6 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 HIV-associated DLBCL and high-grade lymphoma treated with 4–6 cycles of EPOCH plus rituximab based a response-adapted treatment strategy. 106 evaluable patients with HIV-associated DLBCL or high-grade CD20-positive non-Hodgkin's lymphoma were randomized to receive rituximab (375 mg/m²) 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 IV infusion of etoposide, doxorubicin, and vincristine plus oral prednisone followed by IV bolus cyclophosphamide every 21 days for 4 to 6 cycles. Patients received 2 additional cycles of therapy after documentation of a complete response (CR) by computerized tomography after cycles 2 and 4. 64 of 106 evaluable patients (60%, 95% CI 50%, 70%) had a CR in both treatment arms. The 2-year event-free survival (EFS) rates were similar in the 24 patients with CR who received 4 or fewer EPOCH cycles (78%, 95% confidence intervals [55%, 90%]) due to achieving a CR after 2 cycles, compared with those who received 5-6 cycles of EPOCH (85%, 95% CI 70%, 93%) because a CR was first documented after cycle 4. A response-adapted strategy may permit a shorter treatment duration without compromising therapeutic efficacy in patients with HIV-associated lymphoma treated with EPOCH plus rituximab, which merits further evaluation in additional prospective trials. Clinical Trials.gov identifier NCT00049036

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INTRODUCTION

Six cycles of the anti-CD20 antibody rituximab plus “CHOP” (cyclophosphamide, doxorubicin, vincristine, and prednisone) or “CHOP-like” chemotherapy is recommended by 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 population-based data demonstrating similar outcomes for 6 as compared to 8 cycles of therapy.(3) Poeschel et al have reported non-inferiority of 4 cycles of R-CHOP (followed by 2 additional doses of rituximab) compared with 6 cycles of R-CHOP in a randomized phase III trial that included 588 immunocompetent patients with stage I-II DLBCL age 18-60 years and an age-adjusted International Prognostic Index (IPI) 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 HIV-associated lymphoma.(9) (10) (11) (12) (13) Based upon these considerations, the AIDS Malignancy Consortium (AMC) previously reported a randomized phase II trial of rituximab (375 mg/m²) 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 IV infusion of etoposide, doxorubicin, and vincristine plus oral prednisone followed by IV bolus cyclophosphamide given every 21 days for 4-6 cycles, with cyclophosphamide dose adjusted based on pretreatment CD4 lymphocyte count, and subsequently escalated or reduced based on absence or presence of treatment-associated cytopenias. The prespecified primary efficacy complete response (CR) endpoint of 75% was met for the concurrent arm (73%; 95% confidence intervals [CI] 58%, 85%), but not the sequential arm (55%, 95% CI 41%, 68%).(14) Patients had computerized tomography (CT)
of the chest, abdomen, and pelvis after every 2 cycles of EPOCH chemotherapy, and were treated for 2 cycles beyond achieving a CR for a minimum of 4 and maximum of 6 cycles of EPOCH. Two-year time to progression (TTP) rates were similar in the concurrent arm (75%, 95% confidence intervals [CI] 63%-88%) and sequential arm (71%, 95% CI 59%, 84%). Inspired by the successful deescalation of therapy to 4 cycles for R-CHOP noted 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 CR treated with 4 or fewer cycles of therapy, based on achieving a CR after 2 cycles of EPOCH.

METHODS

Eligibility Criteria and Study Conduct. Details regarding eligibility criteria, treatment, and clinical outcomes out to 2 years were previously reported.(14) Briefly, eligibility criteria included: (1) CD20-positive B-cell non-Hodgkin lymphoma, including DLBCL, Burkitt/Burkitt-like lymphoma, or other aggressive lymphomas, (2) HIV infection, (3) stage II-IV disease (or stage I disease with an elevated serum lactate dehydrogenase [LDH]), (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, (5) age 18 years or older, (5) and adequate organ function similar to prior AMC trials.(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.

Treatment, 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 2 cycles of EPOCH therapy with computerized tomography of the chest, abdomen, and pelvis, and continued for 2 cycles beyond achieving a CR for a minimum of 4 and maximum of 6 cycles, including after completion of R-EPOCH in the concurrent arm, and after completion of EPOCH alone and following rituximab alone in the sequential arm. All patients had a bone marrow
evaluation and lumbar puncture for cerebrospinal fluid cytologic exam at baseline. A repeat bone marrow evaluation for CR confirmation was required after completion of therapy if the baseline study demonstrated lymphomatous marrow involvement. FDG-PET scans were not required or consistently performed, and when done were usually performed at the completion of therapy. Event-free survival (EFS), time to progression (TTP), and overall survival (OS) were estimated using the method of Kaplan and Meier. EFS was defined as the time between registration and either relapse or progression of lymphoma or death from any cause (corresponds to progression-free survival in other reports(17)). TTP 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 post-hoc analysis to evaluate the outcomes for patients who received only 4 cycles of therapy due to achieving a CR by CT scan after 2 cycles of therapy, compared with those who required 5-6 cycles of therapy who achieved a CR after 4 cycles of therapy.

RESULTS

Patient Population and Response to Therapy

A total of 106 evaluable patients enrolled and initiated treatment at 20 AMC sites between December 2002 and April 2006 and are included in this analysis, as in the original analysis, previously described.(14) The disposition and outcomes for all patients enrolled is shown in Figure 1. CR occurred in 64 of 106 patients (60%, 95% CI 50%, 70%) who received any protocol therapy. The null hypothesis that the CR rate is 50% was rejected in favor of the alternative of 75% for the concurrent arm (p=0.005), but not the sequential arm (p=0.394). Of the 64 patients with CR, the number who received 4 cycles of R-EPOCH was 14/35 (40%) in the concurrent arm and 10/29 (34%) in the sequential arm.

Characteristics Of Patients Treated with 4 or Less versus 5-6 Cycles of da-EPOCH
Of 64 CRs, 24 patients (38%, 95% CI 26%, 51%) received 4 or fewer cycles of EPOCH based on achieving early CR after 2 cycles of therapy, whereas the remaining 40 (63%, 95% CI 50%, 74%) received 5-6 cycles of therapy. The characteristics of the entire study population, and patients who received 4 or fewer versus 5-6 cycles are shown in Table 1. The characteristics of the two groups were generally comparable to each other, and to 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 histologic subtype (GCB vs. non-GCB subtype) was available only in 21 of 64 patients who had a CR, with no significant difference in number with non-GCB subtype for those who received 4 or fewer cycles compared with those who received 5 or 6 cycles (3/8 versus 5/13 patients P=1.000 Fisher’s exact test).

**Treatment Administered**

For the groups that achieved CR, a total of 322 EPOCH cycles were given to all 64 patients. Among the 24 who received 4 or fewer cycles, 5 received less than 4 cycles. The reasons for this included disease progression after achieving a CR (N=1), physician decision (N=1), or other reasons (N=3). Among the 40 who received 5-6 cycles of EPOCH, 36 received 6 cycles and 4 received 5 cycles due to physician decision (N=3) or unknown reasons (N=1).

**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 CR, are shown in Table 2 and Figure 2a-c. After a median follow-up of 30 months (range 0-67 months) in all treated patients, 36 (34%, 95% CI 25%, 44%) died, with relapsed lymphoma as the cause of death in 8 (8%, 95% CI 3%, 14%) patients. After a median follow-up of 38.5 months (range 1-66 months) in the 64 patients who achieved a CR, 11 (17%, 95% CI 9% 29%) died, 5 (8%, 95% CI 3%, 18%) with relapsed lymphoma as the cause of
death. Outcomes were similar for those treated with 4 or fewer cycles compared with 5-6 cycles with respect to recurrence rates for 2-year EFS (78% vs. 85%), TTP (91% vs. 87%), and OS (78% vs. 90%).

**DISCUSSION**

In the absence of prospective comparative data in HIV-associated lymphoma, 6 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’s lymphoma in the 2019 NCCN guidelines. (2) (18) These recommendations were driven by the effectiveness of R-EPOCH reported 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 showed no difference in efficacy.(17) Retrospective analysis has shown that high proliferation rate was associated with better prognosis in HIV-associated lymphomas when treated with infusional R-EPOCH but not 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 CR after two cycles of EPOCH plus rituximab have excellent outcomes when therapy is limited to 4 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 3 to 6 cycles of dose-dense rituximab (SC-EPOCH-RR), of whom 79% received 3 cycles of therapy based on a risk-adapted approach of treating for 1 cycle beyond a negative interim PET-CT after cycle 2; at the median follow-up of 5 years, the progression free
survival rate was 84%, although outcomes were excellent only for those with germinal center B-cell (GCB) subtype (95% for GCB vs. 44% for non-GCB subtype). (23) Only about one-third of patients in our trial had information regarding GCB vs. non-GCB subtype, and outcomes were similar irrespective of subtype. Future studies evaluating risk-adapted therapy may need to integrate histologic subtyping, and need to be limited to the GCB lymphoma subtype and consider other molecular characteristics that has prognostic relevance. (24)

Interim restaging is recommended to identify patients whose disease has not responded well to, or has progressed, on induction therapy after 2-4 cycles of therapy. (2) Staging is recommended using positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG) integrated with computed tomography (FDG-PET/CT) at diagnosis, after 2-4 cycles of therapy, and at the end of treatment. (2) A negative PET scan after 2 to 4 cycles of induction therapy has been associated with significantly higher EFS and OS rates in some studies (25) (26) (27) (28), but not others. (29) (30) (31) (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 regarding use of interim FDG-PET/CT as a pharmacodynamic biomarker for tailoring deescalation appears promising in HIV-associated lymphoma, further study is required in multicenter prospective clinical trials.

Our analysis has several strengths and limitations. Strengths include the prospective nature of the trial, and the protocol-specified guidelines for treatment duration based on radiographic response. Limitations include the post-hoc analysis examining response durability based on rapidity of response and number of treatment cycles, and the fact that these
observations are not based on an adequately powered comparison between the standard approach of 6 treatment cycles compared with a risk-adapted approach. Nevertheless, given recent evidence that 4 cycles of R-CHOP is adequate therapy for a low-risk population(4), the findings from our study indicating the feasibility of a response-adapted deescalation strategy in a higher risk population with HIV-associated lymphoma, and the clinical utility of interim FDG/PET, there is now compelling rationale to prospectively evaluate the use of interim FDG-PET/CT after 2 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.
**Author contributions:** The manuscript was written by J.A.S. and was approved by all co-authors. The clinical protocol was written by J.A.S., J.Y.L., and L.D.K. The data and statistical analysis were performed by J.Y.L., and administrative support and oversight was provided by R.M. Pathologic review of tumor specimens was performed by E.C. and A.C. Individuals who contributed subjects to the trial included J.A.S., L.D.K., J.C.R., R.F.A., D.A., A.N., D.H.H., L.R., E.C., W.W., and A.C.. The authors have no financial disclosures or conflicts of interest to report.

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References:


**Figure Legends:**

**Figure 1.** Consort diagram

**Figure 2.** Kaplan-Meier estimates in those achieving complete response using response adapted EPOCH chemotherapy stratified by number of treatment cycles (≤ 4 cycles vs. 5-6 cycles). The figures include estimates for (a) event-free survival (b) time to progression, and (c) overall survival.
Assessed for Eligibility, Registered and Randomized (n = 110)

Enrollment

Arm A: Concurrent rituximab + EPOCH
Allocated to intervention (n=54)
Received allocated intervention (n=51)
Did not receive allocated intervention (n=3)
- Patient withdrawal (n=3)

Lost to follow-up (n=0)
Discontinued intervention (n=2)
- Patient withdrawal (n=1)
- Patient non-compliance (n=1)

Arm B: Sequential EPOCH → rituximab
Allocated to intervention (n=56)
Received allocated intervention (n=55)
Did not receive allocated intervention (n=1)
- Patient withdrawal (n=1)

Lost to follow-up (n=0)
Discontinued intervention (n=2)
- Patient withdrawal (n=1)
- Patient non-compliance (n=1)

Analysis

All Patients:
Analyzed (n=51)
Analysed for response (n=48)
Excluded from response analysis (n=3)
- No response information (n=2)
- Physician discretion (n=1)
Complete Response (n=35)
\( \leq 4 \) Cycles (n=14)
- Recurrence (n=3)
- Death without recurrence (n=3)
\( \geq 5 \) Cycles (n=21)
- Recurrence (n=3)
- Death without recurrence (n=1)

All Patients:
Analyzed (n=55)
Analysed for response (n=53)
Excluded from response analysis (n=2)
- Patient withdrawal (n=1)
- Patient non-compliance (n=1)
Complete Response (n=29)
\( \leq 4 \) Cycles (n=10)
- Recurrence (n=1)
- Death without recurrence (n=0)
\( \geq 5 \) Cycles (n=19)
- Recurrence (n=3)
- Death without recurrence (n=1)