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Feasibility of interim positron emission tomography (PET)-adapted therapy in HIV-positive patients with advanced Hodgkin Lymphoma (HL): a sub-analysis of SWOG S0816 phase 2 trial

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Dear Editor

Malignancies represent the leading cause of death in patients infected with HIV [1]. Such individuals manifest increased incidence of both AIDS-defining cancers (e.g., Kaposi sarcoma and non-Hodgkin lymphoma) as well as non-AIDS-defining cancers prevalent in the general population [2,3]. While the incidence of the former has been decreasing with introduction of highly active anti-retroviral therapy (HAART) [1,4], HIV-infected individuals remain at an increased risk of mortality due to non-AIDS-defining malignancies, e.g. lung, colorectal, breast cancer and melanoma, compared to individuals without HIV [5].

Of non-AIDS-defining malignancies, the risk of Hodgkin lymphoma (HL) is increased >10-fold among patients with HIV, and is only second to anal cancer [3,6]. Patients with HIV-HL typically present with advanced stage disease with extranodal involvement, accounting for higher risk scores than HIV-negative counterparts [7,8]. Despite a higher incidence of adverse features, the prognosis of HIV-HL in the HAART era remains favorable [5,9]; the

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majority of patients achieve long-term survival and thus are at risk for late effects from treatment. Standard ABVD therapy (adriamycin, bleomycin, vinblastine, dacarbazine) is associated with a complete response (CR) rate of 74% and a five-year overall survival (OS) of 81%, akin to those in non-HIV-HL, and is well-tolerated in this patient population [8]. In a large prospective cohort (Lymphovir), 94% of patients with HIV-HL treated with ABVD were alive at two years [7].

Consequently, as in HIV-negative HL, it is paramount to identify therapeutic strategies which will diminish short-term and long-term therapy-related toxic effects without compromising cure rates in HIV-HL.

Pre-treatment identification of patients at risk for treatment failure has been challenging in the general population of HL patients. While predictive of outcome, neither the International Prognostic Score (IPS) nor tumor infiltration with macrophages, as determined at diagnosis, define therapy. By contrast, interim FDG-PET imaging (18 F-fluoro-deoxy-glucose positron emission tomography) performed after 2 cycles of chemotherapy (PET2) was a strong predictor of ultimate treatment outcome in patients with HL receiving ABVD [10,11]. In this setting, only 13–45% of PET2-positive advanced-stage HL patients achieve long term progression-free survival (PFS) if continued on treatment with ABVD [10,11]. While these early studies preceded adoption of the 5-point Deauville scale, they demonstrated the potential for functional imaging in determining treatment changes. In United States Intergroup Study, S0816, therapy escalation for interim PET-positive patients appeared to improve outcomes [12]. Specifically, intensification of chemotherapy to escalated-dose BEACOPP (eBEACOPP; bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) among PET2-positive patients (after ABVD) resulted in a 2-year progression-free survival of 64%, substantially higher than expected. The combination of excellent long-term outcomes and the promise of response-adapted therapy justifies evaluating a PET-adapted approach in HIV-HL. Here, for the first time, we report on the outcomes of the HIV-positive patients with HL enrolled on SWOG S0816, a multicenter Phase 2 trial of response-adapted therapy of stage III-IV HL using interim FDG-PET imaging.

This study was part of a US Intergroup trial which enrolled patients with advanced HL; full details and protocol have been published [12]. Briefly, the HIV-positive cohort of the study enrolled patients aged 18–60 years with previously untreated stage III–IV classical HL. Patients with multi-drug resistant HIV infection or concurrent AIDS-defining conditions were excluded. Eligible patients had CD4 counts $\geq 150/\mu\text{L}$ at registration or $>250/\mu\text{L}$ at any time within 8 months prior to HL diagnosis. All patients received 2 cycles of ABVD followed by an interim FDG-PET, reviewed centrally with application of the 5-point scale (Deauville criteria). Patients with a negative PET2 (Deauville ≤ 3) subsequently received 4 additional cycles of ABVD, while PET2-positive patients received 6 cycles of BEACOPP standard regimen (notably, patients with non-HIV-HL received escBEACOPP). The study pursued two co-primary objectives: 1) to estimate the 2-year PFS rate in patients with advanced HL treated with response-adapted therapy and 2) to estimate the 2-year PFS rate in PET-positive patients who were subsequently treated with BEACOPP. Secondary objectives of the study were to prospectively evaluate overall response rate (ORR), PFS and OS in

HIV-positive patients with HL treated with response-adapted therapy. PFS and OS estimates (with 95% confidence intervals [CI]) were calculated using the Kaplan-Meier methods. Grade 3–4 toxicities were compared between HIV⁺ and HIV[−] patients using two-sided Fisher's exact test.

Among 13 HIV-HL patients enrolled, 12 were eligible and received study treatment. Median age was 45 years (range, 25 to 50 years), 84% were male. 50% of patients had poor risk IPS 4. Six of twelve (50%) manifested B-symptoms, 33% had bone marrow involvement by HL and 1/12 (8%) presented with bulky lymphadenopathy (≥ 10 cm in diameter or a mediastinal mass >1/3 chest diameter). 59% of patients had ECOG performance status (PS) 0, 33% had a PS of 1 and 8% had a PS of 2. Most (10/12, 82%) received concurrent HAART during chemotherapy. At registration, the median CD4 count was 165 cells/μL (range, 22–400) and <100 cells/μL in 5 of 12 patients (42%).

All HIV-HL patients successfully completed 2 initial cycles of ABVD on study. Grade 4 neutropenia and Grade 3 febrile neutropenia were common during this treatment (66% and 25%, respectively; see Table I). HIV-positive patients had a higher risk of developing febrile neutropenia than HIV-negative patients (Supplemental Table I). Ten of twelve (83.3%) patients achieved PET2-negative status and two of 12 remained PET2-positive with Deauville scores of 4 and 5. This result is comparable to non-HIV-HL patients in this Intergroup trial (82%).

All HIV-HL PET2-negative patients continued planned therapy with ABVD. Of those, 9 patients completed the planned 4 additional cycles of treatment and one discontinued early for progressive disease 4 months after registration on study. Among PET2-positive patients, one elected to receive ABVD therapy off the study protocol, while the other completed 6 cycles of BEACOPP. Both patients achieved a partial response (PR). Thus, following initial ABVD therapy, 75% of HIV-HL patients achieved CR and 25% a PR. This was somewhat inferior compared with HIV-negative patients enrolled on SWOG S0816, who had a CR rate of 96% after 6 cycles of ABVD [12]. Our results are consistent with findings in a retrospective analysis of 224 patients with advanced HIV-HL who did not receive response-adapted therapy, documenting an end-of-treatment CR rate of 77% [8]. The discrepancy with S0816 non-HIV outcomes could be due to the small size of this cohort.

With median follow-up of 39 months (range, 5–53 months) all study patients remain alive (Figure 1A). Three patients developed progressive disease, with the estimated PFS of 83% at 2 years (95% CI, 46.1 to 95.3%), similar to that in S0816 non-HIV-HL patients (79%) [12].

ABVD was well tolerated by HIV-positive patients. The most frequent grade 3–4 adverse events with continued therapy were neutropenia (70%) and febrile neutropenia (30%), consistent with previously reported data [13]. Other toxicities were uncommon (Table I). Eleven patients experienced at least one treatment-related grade 3–4 toxicity during study treatment. Four patients (33%) required dose reductions due to febrile neutropenia (vinblastine and doxorubicin, N=2), elevated bilirubin and LFT's (vinblastine and doxorubicin, N=1) and neuropathy (vinblastine, N=1). The frequency of febrile neutropenia was higher in HIV-HL, compared with non-HIV patients on this trial (Supplemental Table I).

Finally, the one patient who received BEACOPP experienced grade 4 neutropenia and lymphopenia, grade 3 anemia and grade 3 infection. CD4⁺ T-cell counts were monitored throughout the study in patients with HIV-HL. CD4 counts remained stable during treatment, were not associated with the development of febrile neutropenia and were not predictive of PFS (Fig. 1B and Supplemental Tables II–III).

Thus, ABVD is highly effective in patients with advanced stage poor-risk HIV-HL, resulting in PFS rates similar to those in non-HIV patients in a prospective trial setting. In the HAART era, survival of patients with HIV-HL may be compromised by withholding or attenuating chemotherapy [14], and our results support aggressive therapy in this group of patients. Furthermore, as response-adapted therapy evolves to be a standard approach for HIV-negative patients with advanced stage HL [10–12], the results of this S0816-subset study implicate that a similar approach should be tested in patients with HIV-HL. While stage-adapted therapy has been successfully evaluated in patients with HIV-HL [13], this is a first attempt to use a response-adapted approach in this patient population. Interpretation of PET study results was not confounded by reactive lymphadenopathy which may be present in patients with HIV. Therefore, patients with HIV-HL should continue to be included in further evaluation of response-adapted therapy with the goal of reducing long-term toxicity. The role of intensified chemotherapy regimens in patients with HIV-HL who do not achieve PET-negative status requires further study. Finally, this trial demonstrates the feasibility of including HIV + patients in a general population study with appropriate modifications.

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Figure 1.
A, Progression-free survival and B, CD4 counts in patients with A

Table I

Selected adverse events following therapy with ABVD in patients with HIV-HL.

Adverse event	ABVD cycles 1–2 (N = 12)		ABVD cycles 3–6 (N = 10)	
	Any grade, N (%)	Grade 3–4, N (%)	Any grade, N (%)	Grade 3–4, N (%)
Non-hematologic				
Alopecia	2 (16.6)	-	3 (30)	-
Anorexia	3 (25)	-	3 (30)	1 (10)
Constipation	4 (33.3)	-	2 (20)	-
Elevated creatinine	2 (16.6)	-	2 (20)	-
Diarrhea	3 (25)	-	5 (50)	-
Fatigue	5 (41.7)	1 (8.3)	7 (70)	1 (10)
Hyponatremia	1 (8.3)	1 (8.3)	2 (20)	-
Hypophosphatemia	1 (8.3)	1 (8.3)	1 (10)	1 (10)
Neuropathy, sensory	6 (50)	1 (8.3)	5 (50)	1 (10)
Nausea	4 (33.3)	-	6 (60)	-
Elevated transaminases	-	-	5 (50)	-
Vomiting	3 (25)	-	4 (40)	-
Weakness	2 (16.6)	1 (8.3)	-	-
Headache	4 (33.3)	-	2 (20)	-
Hematologic				
Anemia	5 (41.7)	1 (8.3)	7 (70)	3 (30)
Lymphopenia	4 (33.3)	1 (8.3)	6 (60)	2 (20)
Neutropenia	9 (75)	8 (66.6)	7 (70)	7 (70)
Thrombocytopenia	2 (16.6)	-	3 (30)	1 (10)
Febrile Neutropenia	3 (25)	3 (25)	3 (30)	3 (30)