Original Study

Safety and Preliminary Efficacy of Vorinostat With R-EPOCH in High-risk HIV-associated Non-Hodgkin's Lymphoma (AMC-075)

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Abstract

We performed a phase I trial of vorinostat (VOR) given on days 1 to 5 with R-EPOCH (rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride) in patients with aggressive HIV-associated non-Hodgkin lymphoma. VOR was tolerable at 300 mg and seemingly efficacious with chemotherapy with complete response rate of 83% and 1-year event-free survival of 83%. VOR did not significantly alter chemotherapy steady-state concentrations, CD4$^+$ cell counts, or HIV viral loads.

Introduction: Vorinostat (VOR), a histone deacetylase inhibitor, enhances the anti-tumor effects of rituximab (R) and cytotoxic chemotherapy, induces viral lytic expression and cell killing in Epstein-Barr virus-positive (EBV$^+$) or human herpesvirus-8-positive (HHV-8$^+$) tumors, and reactivates latent human immunodeficiency virus (HIV) for possible eradication by combination antiretroviral therapy (cART). **Patients and Methods:** We performed a phase I trial of VOR given with R-based infusional EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride) (n = 12) and cART in aggressive HIV-associated B-cell non-Hodgkin lymphoma (NHL) in order to identify safe dosing and schedule. VOR (300 or 400 mg) was given orally on days 1 to 5 with each cycle of R-EPOCH for 10 high-risk patients with diffuse large B-cell lymphoma (1 EBV$^+$), 1 EBV$^+$/HHV-8$^+$ primary effusion lymphoma, and 1 unclassifiable NHL. VOR was escalated from 300 to 400 mg using a standard 3 + 3 design based on dose-limiting toxicity observed in cycle 1 of R-EPOCH. **Results:** The recommended phase II dose of VOR was 300 mg, with dose-limiting toxicity in 2 of 6 patients at 400 mg (grade 4 thrombocytopenia, grade 4 neutropenia), and 1 of 6 treated at 300 mg (grade 4 sepsis from tooth abscess). Neither VOR, nor cART regimen, significantly altered chemotherapy steady-state concentrations. VOR chemotherapy did not negatively impact CD4+ cell counts or HIV viral loads, which decreased or remained undetectable in most patients during treatment. The response rate in high-risk patients with NHL treated with VOR(R)-EPOCH was 100% (complete 83% and partial 17%) with a 1-year event-free survival of 83% (95% confidence interval, 51.6%-97.9%). **Conclusion:** VOR combined with R-EPOCH was tolerable and seemingly efficacious in patients with aggressive HIV-NHL.

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AMC-075: A Phase I Study of Vorinostat-R-EPOCH in Patients With HIV-NHL

Introduction

Individuals infected with human immunodeficiency virus (HIV) are at an increased risk of developing highly aggressive non-Hodgkin lymphoma (NHL). Recent studies have demonstrated improved outcomes in patients with HIV-NHL approaching that of the general population after the introduction of combination antiretroviral therapy (cART) and newer chemotherapy paradigms.[1] A large retrospective pooled analysis describing the outcome of patients with HIV-NHL in the contemporary cART era reported 2-year survival rates of 67% for HIV-diffuse large B-cell lymphoma (DLBCL), as compared with 24% in the pre-cART era.[2] Recent advancements in the treatment of HIV-DLBCL might be attributed to the efficacy of infusional regimens, such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and the addition of rituximab (R) to standard curative NHL regimens.[3] R-EPOCH is the preferred regimen for treating HIV-DLBCL and HIV-primary effusion lymphoma (PEL) under current National Comprehensive Cancer Network guidelines based on multiple phase II clinical trials and retrospective studies.[3] Despite these advancements, treatment of HIV-NHL remains challenging in severely immune-compromised patients and aggressive NHL variants that carry poorer prognosis, such as plasmablastic lymphoma (PBL), PEL, and activated B-cell (ABC) type DLBCL.[4-7]

Differences in clinical spectrum and biology of HIV-NHL might be exploited therapeutically. For example, the high expression of the multidrug resistance (MDR-1) gene might be overcome by infusional regimens like EPOCH by prolonged continuous drug exposure.[8,9] Alternatively, despite their oncogenic potential, latent γ−herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus-8 [HHV-8]) can be targeted therapeutically, as doxorubicin and etoposide (EPOCH drugs), and histone deacetylase (HDAC) inhibitors disrupt viral latency.[10-13] Moreover, in preclinical B-cell lymphoma and hematologic malignancy models, the potent HDAC inhibitor vorinostat (VOR) was highly synergistic with R, anthracyclines, and etoposide.[14-16] VOR given with R, cyclophosphamide, etoposide, and prednisone was effective in elderly patients with relapsed/refractory DLBCL.[17] VOR induced HHV-8 lytic gene expression and p53 acetylation leading to apoptosis and increased survival in a PEL xenograft mouse model.[18] VOR also re-activates HIV, suggesting its potential role in eradicating latently infected reservoirs in human hosts via HIV cytopathic effects and immune-mediated mechanisms.[19-21]

Based on these concepts, the National Cancer Institute (NCI)-funded AIDS Malignancy Consortium (AMC) performed a phase I/II clinical trial (AMC-075) using VOR with R-EPOCH in aggressive, non-Burkitt, HIV-NHL. The primary objectives were to test the safety and the efficacy of VOR when combined with R-based chemotherapy and cART using complete response rate as the primary study endpoint. We report the phase I portion here. To evaluate toxicity, 2 VOR dose levels (300 mg or 400 mg given orally on days 1 through 5 during each chemotherapy cycle) were tested using a 3 + 3 design. This enabled us to compare directly the plasma steady-state concentrations of etoposide, doxorubicin, and vincristine achieved at the 2 VOR dose levels during cART. This trial is registered at http://clinicaltrials.gov as NCT01193842.

Patients and Methods

Eligibility Criteria

Twelve AMC sites in the United States enrolled patients after written informed consent according to the Declaration of Helsinki. Patients with HIV and absolute CD4+ count $\geq$ 50 cells/mm^3, with DLBCL or aggressive non-Burkitt NHL variants, were eligible. Patients were untreated or had received a maximum of 1 cycle of chemotherapy at time of enrollment.

Patients with any Ann Arbor stage (I-IV), age $\geq$ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, and adequate organ function were eligible. Non-zidovudine based cART was required. For antiretroviral-naive subjects at study entry, cART was started after cycle 1 to avoid confounding side effects. Patients who had active hepatitis B virus (surface antigen, core antigen, or viremia), or active hepatitis C infection were ineligible. Patients who were only hepatitis B core antibody-positive required prophylactic anti-hepatitis B virus therapy. Patients with known central nervous system involvement by lymphoma were ineligible.

Treatment Administration and Supportive Care

R was given at 375 mg/m^2 intravenously (IV) for CD20+ lymphomas on day 1. R-EPOCH was given to patients with high-risk NHL every 21 days for 6 cycles. Cyclophosphamide IV on day 5 was administered at initial dose of 375 mg/m^2 when baseline CD4+ count was 50 to 200 cells/mm^3, or 750 mg/m^2 if baseline CD4+ count was $>$ 200 cells/mm^3. For subsequent cycles, cyclophosphamide was dose-adjusted based on nadir counts according to specified guidelines (see Supplemental Tables 1 and 2 in the online version). Patients received VOR orally once on days 1 to 5. Treatment and supportive care options are summarized in Table 1.

Clinical and Response Assessments

Response was assessed by standard whole body computerized tomographic (CT) scan criteria[22] after cycle 4, and posttreatment (4-8 weeks, and months 6, 12, 18, and 24). Positive emission tomographic (PET) or CT-PET were required after the final treatment cycle to confirm a complete response (CR). Subjects with bone marrow involvement had a repeat biopsy to confirm CR. Subjects with CR after cycle 4 received up to 2 additional chemotherapy cycles (total, 6 cycles). Subjects who achieved only a partial response (PR) after cycle 4 had the option to continue at the discretion of the treating physician. Subjects were followed every 3 months for 2 years post-treatment, and then every 6 months for years 3 to 5.

Central Pathology Review, Immunohistochemistry, and EBV-encoded Small RNA (EBER) in Situ Hybridization

Central pathology review was conducted at Weill Cornell Medical College as previously described.[23] Cases with adequate tissue were categorized as germinal center (GC)-derived versus ABC (non−GC)-type according to the tissue microarray classification algorithm published by Hans et al.[24] Monoclonal antibodies to the following antigens were used: CD10 (56C6; Leica Microsystems), BCL-2 (124), BCL-6 (PG-B6p), MUM-1 (MUM1p) and Ki-67 (MIB-1) (DakoCytomation, Carpinteria, CA). EBV Probe ISH Kit (Leica Microsystems, Wetzlar, Germany; Vision BioSystems