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Brentuximab vedotin with AVD shows safety, in the absence of strong CYP3A4 inhibitors, in newly diagnosed HIV-associated Hodgkin lymphoma

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Abstract

Objective—Brentuximab vedotin (BV) is an FDA approved anti-CD30 antibody drug conjugate potently active in Hodgkin lymphoma (HL). Trials of BV with doxorubicin, vinblastine, and dacarbazine (AVD-BV) excluded patients with HIV. We studied the safety of (AVD-BV) in newly diagnosed HIV-associated classical Hodgkin lymphoma (HIV-cHL).

Design and Methods—Patients diagnosed with Stage II–IV HIV-cHL received AVD-BV on days 1 and 15 every 28 days for 6 cycles. Anti-HIV medications with strong CYP3A4 inhibition were excluded. This phase 1 trial followed a 3+3 dose de-escalation design started with BV at 1.2 mg/kg with standard dosing of AVD. Dose limiting toxicities (DLT) were defined in cycle one.

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Results—Seven patients were enrolled with 6 being evaluable: 5/6 stage III/IV, 3 with an international prognostic score 4. With no DLT identified, all 6 were treated at the 1.2 mg/kg dose. Only five grade (G) 3 non-hematological adverse events (AE) were noted in 3 patients: pulmonary infection, diarrhea, and peripheral neuropathy. No G4/5 AE occurred. PET/CT was negative in 5/6 after cycle 2 and 6/6 post therapy. Progression free survival was 100% at 25 months with all patients in remission. One patient was deemed ineligible for taking ritonavir, a strong CYP3A4 inhibitor, but developed G3/4 AE including febrile neutropenia, and pancreatitis and though consented was excluded from all evaluation.

Conclusions—AVD-BV was well tolerated at recommended phase II dose of 1.2mg/kg. Concurrent strong CYP3A4 inhibitors should be avoided. A phase II study of AVD-BV is currently enrolling (NCT01771107).

Keywords

HIV-associated Hodgkin Lymphoma; Targeted Therapy; Antibody Drug Conjugate

Introduction

Patients infected with HIV have an 8–20 fold increased risk of classical Hodgkin lymphoma (cHL) over the general population [1–3]. Currently cHL is the second most common non-AIDS-defining cancer and its incidence has increased since the implementation of combined anti-retroviral therapy (cART) in the mid 1990s [1,2,4]. HIV-associated classical Hodgkin lymphoma (HIV-cHL) presents typically in patients with CD4+ T cell counts above 200 cells/μl, and is dominated by the mixed cellularity histologic subtype in contrast to the nodular sclerosis in the non-HIV population [2,3,5,6]. HIV-cHL also presents with higher stages and higher international prognostic scores (IPS) [5,6]. Despite presenting more aggressively, the overall survival (OS) currently is similar to the non-HIV population when treated concurrently with cART [6–8]. Treatment in the upfront setting with anti-HIV therapy has improved the overall survival (OS) from 48% at 2 years to 78% at 5 years for advanced stage HIV-cHL when treated with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) [6–9].

An important aspect of HIV-cHL therapy is the identification of potential cART/chemotherapy interactions. Interactions with chemotherapy have become more pronounced as many cART inhibit or induce CYP450 enzymes or drug transporter like P-glycoprotein which are important mechanisms of drug distribution and excretion [10–14]. cART/chemotherapy interactions therefore increase toxicity or potentially decrease efficacy [2,3,10–12]. The protease inhibitor ritonavir, a CYP3A4 and P-glycoprotein inhibitor, increases vinblastine-related neuropathy and neutropenia which is a key component of HIV-cHL treatment [2,3,10–12]. Cobicistat has similar inhibitory effects on CYP3A4 and P-glycoprotein [15]. Newer chemotherapeutic agents are metabolized by the CYP3A4 enzyme or transported by P-glycoprotein [15]. The active chemotherapeutic component of brentuximab vedotin (BV), monomethyl auristatin E, is a sensitive CYP3A4 substrate [14]. In addition, antiretrovirals can have overlapping toxicities with chemotherapy. For example, zidovudine can cause severe neutropenia in 8% of patients with advanced AIDS which is a significant complication for cytotoxic chemotherapy and is thus excluded in multiple HIV-

cancer clinical trials including this trial [11]. These interactions emphasize the importance of cancer trials in patients with HIV not just to assess efficacy but also therapy-related toxicity in the presence of antiretroviral therapy.

Advanced stage cHL has a rate of relapse of up to 30% after treatment with front line chemotherapy, and 10% of newly diagnosed cHL patients will not achieve remission [16]. Thus, new treatments are needed, particularly in the HIV-infected population, as most patients present with higher stage cHL. Brentuximab vedotin (BV) is an anti-CD30 antibody drug conjugate attached to the anti-tubulin agent monomethyl auristatin E, specifically targeting CD30+ cancer cells including the Hodgkin Reed Sternberg cell (HRS) [17]. A phase II study of BV in 102 patients with refractory disease who relapse after autologous stem cell transplant achieved a 73% response rate with a complete remission (CR) rate of 33% and an acceptable safety profile leading to its FDA approval [18]. With a 5-year follow up, 9% of this high risk population has remained in remission, without any additional forms of therapy [18].

In the front line setting, a phase I trial of BV combined with ABVD in advanced stage HL, yielded a rate of overall pulmonary toxicity of 44%. However, when BV (1.2 mg/kg) was combined with AVD alone, the 3 year failure-free survival was 96% and OS was 100%, without pulmonary complications [19,20]. In addition, just released results from the phase III ECHELON-1 study, of ABVD vs AVD+BV, demonstrated a 2 year modified PFS benefit utilizing AVD+BV of 82.1 compared to 77.2% in the ABVD arm [21].

In light of the impressive efficacy in the HIV negative population, we designed a phase I/II study utilizing AVD-BV in the front line setting for HIV-associated cHL. Here we present the phase I portion of the trial to examine AVD-BV safety, evaluate preliminary efficacy, and define the recommended phase II dose (RP2D) and evaluate preliminary efficacy.

Patients and Methods

Study Population

Patients with untreated CD30-positive HIV-cHL stage II–IV were eligible for study. Diagnoses were confirmed by central pathology review and HIV by enzyme-linked immunosorbent assay (ELISA). Other key eligibility requirements included 18 years of age, and a Karnofsky Performance Status (KPS) > 30%. All patients were required to be on cART. Subjects had to change to a non-ritonavir or non-cobisistat -based HIV regimen 7 days prior to therapy, due to its strong CYP3A4 and P-glycoprotein inhibitory properties. Additionally, subjects have to change a non-zidovudine-based HIV regimen 7 days prior to therapy, due to the potential for profound neutropenia. In addition, patients had to meet the following criteria for eligibility: CD4+ T-cell count 50 cells/ μ l, serum creatinine of 1.5 mg/dl, absolute neutrophil count 1000 cells/ μ l, and AST and ALT 3 times the ULN, cardiac ejection fraction 50%, diffusing capacity of the lung for carbon monoxide (DLCO) adjusted for hemoglobin 70% and bilirubin 1.5 times the ULN unless thought to be secondary to cART, e.g. atazanavir, in which case the total bilirubin could be 3.5[11,20,22]. All patients with exposure to hepatitis B, C, or evidence of chronic infection

with or without immunity to hepatitis B were permitted on study provided subjects were taking anti-hepatitis B virus therapy and met parameters for hepatic function.

Study Design and Treatment

This was an open label phase I study. The latest assessment was approximately 2 years after the last patient was enrolled on the phase I portion of the study (ClinicalTrials.gov identifier NCT01771107). Patients for the Phase I were recruited from March 2013 through January 2015. Each site institutional review board approved the study and patients were provided written consent. All research was done in accordance with the precepts of the Helsinki declaration. BV was given sequentially just after AVD (AVD-BV) on days 1 and 15 on a 28 day schedule, for 6 cycles. The study was a 3+3 dose de-escalation design, where BV was to be studied at doses of 1.2 mg/kg, 0.9 mg/kg, and 0.6 mg/kg in combination with standard dosing of AVD. Prophylaxis for pneumocystis jiroveci with trimethoprim sulfamethoxazole or dapsone was required and granulocyte colony stimulating growth factor (or pegfilgrastim) was administered on days 2–10 and 16–24 of therapy of each cycle. Three participants began at a dose of 1.2 mg/kg. If 1 dose-limiting toxicities (DLT) in cycle 1 were encountered, 3 to 6 additional participants would be enrolled at the next lowest dose level. This would then be the RP2D as long as no more than 1/6th of the participants experienced a DLT. The DLT in the phase I portion of the study was defined as any adverse event (AE) resulting in a delay of AVD-BV therapy of 7 days during the first cycle of therapy.

Study Assessments

Baseline assessments included evaluation of disease-related signs and symptoms, physical examination, and bone marrow biopsy, CD4 + T-cell count, HIV-1 RNA viral load, sedimentation rate, and a multigated acquisition scan (MUGA) or echocardiogram. Imaging included computer tomography (CT) of the neck, chest abdomen, and pelvis and positron emission tomography (PET) at baseline, after cycle 2, and at treatment completion. Treatment evaluations included a history and physical, documentation of cART compliance, CBC and serum chemistries prior to each cycle. CD4 + T-cell count, HIV-1 RNA viral load analysis was performed at the start of cycle 2, 5, end of treatment, and every 3 months afterwards for 1 year. All AEs were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. CT scans were also done after study completion every 6 months for 5 years. Bone marrows showing HL were repeated to confirm complete remission. Magnetic resonance imaging (MRI) of the brain was required before treatment initiation to exclude progressive multifocal leukoencephalopathy. Staging and response evaluation followed the 2007 Cheson criteria [22]. PET/CT evaluation followed the Deauville criteria, where a score below 4 was considered to be complete radiographic remission.

Statistical Analysis

For the Phase I portion of the study, utilizing the 3+3 dose de-escalation design, a minimum of 6 and a maximum of 18 participants could be enrolled. The primary endpoint of the phase I study was the determination of the MTD. Secondary endpoints included progression free survival (PFS), overall survival (OS), and correlation of response with cycle 2 and post treatment PET/CT scan evaluation. Criteria for early study discontinuation included any

diagnosis of progressive multifocal leukoencephalopathy or if more than 30% of the first 10 patients enrolled on the study experienced a G3 neurotoxicity lasting more than 4 weeks. With an underlying probability of grade 3 neuropathy of no more than 10%, the probability of observing > 3 participants with grade 3 neuropathy was less than 5%.

Results

Patients

Patients for the phase I were recruited from March 2013 through January 2015. Patient baseline characteristics can be found in Table 1. Of the 6 patients enrolled, 5 were men, the median CD4 + T-cell count was 163 cells/ μ l, (132–289) and a median viral load was 25 copies/ μ l (20–77). Eighty-three percent of the patients had stage III/IV HIV-cHL, with 60% of the patients having an IPS of 4. Three of 6 subjects had stage IV disease, of which 2 out of 3 patients had bone marrow involvement. One ineligible patient excluded for concomitant ritonavir administration was excluded from all statistical analyses and was eventually replaced.

No DLTs occurred in cycle 1. Based on the 3+3 design, only 6 patients were required to complete phase I. The recommended phase II dose (RP2D) of BV was determined to be 1.2 mg/kg and is being utilized currently in the ongoing AVD-BV phase II portion of the study.

Safety

Treatment-related grade 3–5 AE are listed in Table 2 for all cycles. All AE are shown in the online supplement (supplement table 1). With respect to hematological toxicity, no patient experienced a G4 or G5 AE and only 1 patient developed a G3 neutropenia during treatment. Three patients experienced a G3 non-hematological AE: one lung infection after cycle 3, one diarrhea, and two with peripheral neuropathy. The neuropathy was a G3 peripheral motor and sensory neuropathy in one patient and a peripheral motor neuropathy in another, both after cycle 5. Per protocol, treatment was concluded with AVD alone in those patients, and in both cases the neuropathy decreased to a grade 2, 3 months after drug discontinuation. The study was amended to hold BV for $\geq$ G2 peripheral neuropathy. One patient had pneumonia after cycle 3 day 14, and due to a decrease of DLCO, the patient completed therapy with only AVD after cycle 4.

Effects of Chemotherapy on CD4 + T-cell count, Viral load, and cART interactions

The median CD4+ T-cell count and viral load for all subjects was 163 cells/ μ l and 25 copies/ μ l, respectively. Trends over time of both CD4+T cell count and viral load are shown in Tables 3 and 4 respectively. Four of five patients with entry CD4+ T-cell counts below normal, normalized CD4 counts by the start of cycle 2. Three of the five with available data maintained or improved the CD4+ T-cell count further by the end of therapy. The HIV-1 viral load was also stable over time. Only one patient, not compliant with cART had an elevation in his viral load, (Tables 3 and 4) and a persistently low CD4 count. One patient not reporting taking ritonavir from the onset of therapy developed G3 febrile neutropenia and G4 pancreatitis 7 days after treatment initiation and required admission to the intensive

care unit. This patient was excluded from all final analysis due to a violation of inclusion criteria.

Response

Per CT criteria, 100% of the patients were in complete remission by the end of therapy. Five of 6 patients (83%) were PET/CT negative after cycle 2, and one patient had a Deauville score of 4. All patients were PET/CT negative after cycle 6, defined as a Deauville score of less than or equal to 3. Progression-free survival with a median follow up of 25 months is 100%.

Conclusions

This phase I study is the first trial to study AVD-BV in the upfront setting of HIV-cHL. The primary endpoint was safety and determination of the RP2D for the ongoing phase II study, currently enrolling. The trial was a 3+3 dose de-escalation design starting at BV 1.2 mg/kg. With no DLT identified, 6 patients enrolled. The RP2D of BV was determined to be 1.2 mg/kg, and is the dose utilized in the ongoing phase II study. This dose is identical to BV dose utilized in the phase III ECHELON-1 study, in the non-HIV population (NCT01712490).

Five G3 non-hematological adverse events occurred to 3 patients. Two motor neuropathies and one sensory neuropathy presented by cycle 5 and decreased to G2 3 months after BV discontinuation. One of the patients with a neuropathy also had a G3 diarrhea. A third patient had a G3 lung infection. BV was held as the DLCO decreased after the lung infection, per protocol. This DLCO criterion has been since removed from the ongoing phase II study, as bleomycin was not included in the regimen. The same modification was made in the non-HIV AVD-BV vs. ABVD phase III, ECHELON-1 trial. Hematological AE were not frequent with only 1 G3 neutropenia reported.

The incidence of neuropathy in our study was higher than the non-HIV studies with AVD-BV [16,19]. However, ABVD studies in advanced stage HIV-cHL have shown a wide variance in G3/4 neuropathy as high as 27% [23,24]. The cART containing strong CYP3A4 inhibitors, like ritonavir or cobisat, were not excluded nor reported [23]. In a study excluding ritonavir, G3/4 neuropathy did not occur when given with ABVD [24]. The high incidence of neuropathy (2/6 patients) observed in this study could be due to the use of dual microtubule chemotherapeutic agents, vinblastine and MMAE, though this will be better defined in the ongoing phase II study. As a whole, all AE were manageable in the phase I portion of the trial with either with dose delays or dose modifications.

Response to treatment was also encouraging, with 83% of the patients achieving CR by PET/CT post cycle 2, and all in complete remission by end of therapy, with 100% PFS at a median follow up of 25 months.

The target of BV, CD30, has been indirectly associated with the potential mechanism of increased HIV viral replication. sCD30 expression in T cells correlated with high viral loads and clinical outcomes in the pre-cART era [24–27]. In addition, both agonistic anti-CD30

antibodies and CD30L-expressing, glutaraldehyde-fixed CD8+ human T cell clones significantly enhanced HIV expression in human CD4+ T cells obtained from HIV infected individuals [27]. Thus, it is notable that in our study the CD4+ T-cell count and viral load were not adversely affected over time during treatment. In fact, in four of five patients with entry CD4 T-cell counts below normal, normalized their CD4 count by the start of cycle 2. The low CD4 + T-cell counts at treatment onset could be due to Hodgkin lymphoma related lymphopenia, however historic CD4 + T-cell counts were not captured.

cART chemotherapy interactions are also important. One patient did not report taking CYP3A4 inhibitor ritonavir, violating the inclusion criteria, and was excluded from all analysis, and was replaced by another participant. This patient subsequently developed G3 febrile neutropenia and G4 pancreatitis, all before the initiation of cycle 2. The timing of pancreatitis was consistent with the data published by Winter et al. where 4 of 8 cases of pancreatitis reported during BV therapy presented before cycle 2 in this cohort [29]. In the ongoing phase II portion of the present study, two other patients were inadvertently exposed to ritonavir. One was admitted to intensive care for febrile neutropenia at the start of cycle 1. The second patient having discontinued ritonavir less than 48 hours before therapy initiation and continued the moderate CYP3A4 inhibitor fluconazole, developed a prolonged G3 neuropathy. In one instance, a primary HIV provider had changed the anti HIV medication without consultation of the treating oncologist. This emphasizes the importance of communication between the oncologist and primary care HIV physician. In the ongoing phase II portion, provider letters are now mandated and the protocol team reviews all cART prior to enrollment. We strongly recommend against the use of ritonavir, or any similar anti-HIV medication with strong CYP3A4 or p-glycoprotein inhibitory properties, e.g. cobisistat, in combination with BV or ABVD. Additionally, we also made recommendation for patients taking 2 moderate CYP3A4 inhibitors given the concern of additive CYP3A4 inhibition. For the moderate CYP3A4 inhibitors, one of the two drugs must be withheld 7 days prior to treatment initiation and not restarted. Lastly, we are assessing pharmacokinetics in the phase II portion to elucidate whether BV or the warhead (mono-methyl auristatin E) exposure is altered in the presence of CYP3A4 inducing and non-inducing cART regimens.

In conclusion, this phase I trial demonstrated safety of the AVD-BV regimen with standard BV 1.2 mg/kg dosing in HIV-cHL. In the general population, a 3 year OS of 100% was observed in a phase I trial [16]. AMC 085 has at 25 months, a PFS of 100% with manageable AE. The phase II trial, in conjunction with the French lymphoma study association, LYSA, is enrolling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient Baseline Characteristics

	N = 6	(%)	Median (IQR)
Demographics			
Male gender	5	83%	
Age, years			34.0 (32.0–53.0)
Ethnicity/Race			
Non-Hispanic/White	4	67%	
Non-Hispanic/African-American	1	17%	
Unknown	1	17%	
HIV Characteristics			
CDC Risk Group			
Homosexual/bisexual contact	1	17%	
Heterosexual contact	4	67%	
Homosexual contact and IVDU	0	0%	
Homosexual/bisexual and heterosexual contact	0	0%	
Homosexual and heterosexual contact, IV drug user and transfusion recipient	0	0%	
Time since HIV diagnosis (years)			3.2 (0.7–6.2)
CD4 absolute cell count, / μ L			163.0 (132.0–289.0)
200 / μ L	4	67%	
HIV viral load <50 copies/mL ^a	4	100%	
Lymphoma Characteristics			
Histologic subtype			
Nodular sclerosis	3	50%	
Mixed cellularity	2	33%	
Lymphocyte depleted	1	17%	
Ann-Arbor Stage			
I	0	0%	
II	1	17%	
III	2	33%	
IV	3	50%	
IPS ^b			
2	1	20%	
3	1	20%	
4	1	20%	
5	2	40%	

^a 2 missing baseline HIV viral load measurements

^b IPS calculated only for advanced stage Hodgkin lymphoma

Table 2

Grade 3/4/5 Treatment related adverse events for all cycles at the patient level

Adverse Event	Grade 3	Grade 4/5 ²
Hematological Adverse Events		0%
Lymphocyte Decrease	1 (16%)	
Neutrophil Decrease	1 (16%)	
Non-Hematological Adverse Events		0%
Diarrhea	1 (16%)	
Lung Infection	1 (16%)	
Peripheral Motor Neuropathy ¹	2 (33%)	
Peripheral Sensory Neuropathy ¹	1 (16%)	

¹One patient experienced both a Grade 3 peripheral motor and sensory neuropathy²No grade 4/5 AE were identified.

Table 3

CD4+ T-cell counts (cells/μl) over time during and post therapy.

Patient	Baseline	Start of cycle 2	Start of cycle 5	Early Treat discontinuation	6–8 weeks post	3 mo post	6 mo post	9 mo post	12 mo post
1	169	503	777	602	637	170	419	362	477
2	132	386	289	273	259	356	541	495	390
3	157	499	361		466	490	396	402	382
4 ^I	53	86	28		25	17	7	6	4
5	530	530			616	420	557	507	571
6	289	784	395	594	430	492	637		594

* blank cells=not available.

^I Patient not compliant with cART

Table 4

HIV viral loads (copies/ml) over time counts over time during and post therapy.

Patient	Baseline	Start of cycle 2	Start of cycle 5	6–8 weeks post	3 mo post	6 mo post	9 mo post	12 mo post
1	<20		<20	<20	<20	<20	<20	<20
2	<20	<20	<20			<20	<20	0
3	<20	77	63	54	26	48	<20	<20
4 ^I	25	44		45091	146249	173645	76174	74741
5			<20	<20	<20	<20	<20	<20
6			<20	<20	<20	<20		

* blank cells=not available.

^I Patient not compliant with cART