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A Phase 1 study of Vorinostat Maintenance after Autologous Transplant in High Risk Lymphoma

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Abstract

Only a minority of patients with high risk lymphoma will be cured with autologous transplant, so maintenance with Vorinostat, an oral agent with activity in relapsed lymphoma, was studied starting day +60 for 21 consecutive days followed by a week off for up to 11 cycles. Twenty-three lymphoma patients were treated. Ten patients completed the full 11 cycle treatment plan per protocol, 4 patients were removed due to progressive disease, 7 withdrew or were removed from the study due to toxicities. Despite Prevnar vaccine administration every 2 months for 3 injections, the mean antibody concentration never reached protective levels (>0.35 mcg/mL). Fatigue and functional well-being measured by BFI and FACT-G improved significantly from cycle 1 to cycle 7, but the depression scores from the CES-D did not change. Given the toxicities observed, this broad spectrum deacetylase inhibitor at this schedule is not optimal for prolonged maintenance therapy.

Keywords

Chemotherapeutic approaches; lymphoma and Hodgkin disease; vaccines

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INTRODUCTION

High-dose chemotherapy and autologous hematopoietic stem cell transplantation (AH SCT) is a potentially curative therapy for relapsed and aggressive lymphomas[1,2]; unfortunately fewer than half of the patients with high risk disease will be cured[3,4]. Patients with relapsed and/or refractory NHL often achieve a minimal residual disease state following AH SCT, providing a unique opportunity to administer an immunomodulatory therapy that promotes apoptosis in residual tumor cells while sensitizing the recovering host effector cells to lymphoma.

Suberoylanilide hydroxamic acid (SAHA, Vorinostat) is a reversible deacetylase inhibitor (DAC-I) that has demonstrated single agent activity in patients with cutaneous T cell lymphoma[5] and patients with other relapsed lymphomas in phase I trials[6-8]. Although the mechanisms for immunomodulation of DAC-I's remain unclear, there is preclinical evidence that DAC-I's can increase lymphoma cell sensitivity to NK-cell mediated killing[9,10], increase MHC class II expression on lymphoma cells thus decreasing immune evasion[11-14], and decrease Th1-mediated inflammatory responses without affecting Th2-mediated responses[15].

In this phase 1 trial we explored different dose levels of Vorinostat administered daily as a maintenance agent in high risk lymphoma patients three weeks out of four for 12 months after transplant with close follow-up of toxicities, lymphoma status, and immune activity as measured by circulating leukocyte subsets and pneumococcus vaccine response. We hypothesized that this dosing schedule would result in lower peak Vorinostat concentrations and that a non-continuous dosing schedule would be less toxic.

METHODS

Clinical Trial

This study was approved by the Ohio State University Cancer Institutional Review Board and informed consent was obtained from all enrolled patients (NCT00561418). Patients had recently received an AH SCT conditioned with the BEAM regimen (BCNU, Etoposide, Ara-C, Melphalan) for high risk lymphoma with adequate marrow function as defined by absolute neutrophil count $\geq 1000/\mu\text{L}$ and platelet count $\geq 75,000/\mu\text{L}$. Risk for relapse was defined for each lymphoma entity as follows: 1) Diffuse large B-cell lymphoma (DLBCL): failing induction but with response to salvage therapy, relapse less than one year after completion of induction therapy, elevated LDH at relapse, stage III/IV at relapse, positive PET scan after induction or salvage, and 60 $\leq$ age < 75 y.o.; 2) Follicular lymphoma progressed after 2+ prior regimens or transformed disease; 3) Primary refractory Hodgkin's (HL), relapse less than one year after induction, PET positive disease after salvage; 4) Chemotherapy sensitive mantle cell lymphoma (MCL); 5) Peripheral T-cell lymphoma (T-cell NHL) with high LDH at diagnosis, marrow involvement at diagnosis, age > 60 y.o. at diagnosis, low platelet count at diagnosis, relapsed chemotherapy sensitive disease; and 6) Other T- and NK-cell lymphomas.

Beginning day+60 post transplant, Vorinostat was given orally for 21 consecutive days followed by a week off for a 28 day cycle. Patients continued study treatment for up to 11 cycles of Vorinostat until death, disease progression, unacceptable toxicity, patient refusal, or treatment delay greater than 4 weeks. Patients had blood drawn for correlative studies pre-treatment and then post-transplant corresponding to days +30, +60, +90, +120, +180, +230, +290, and +365. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0..

In this phase I cohorts-of-3 dose escalation trial, four dose levels were explored. Standard rules for dose escalation were followed for this design, where the maximum tolerated dose level (MTD) was defined as the dose level where at most one patient out of 6 had a dose-limiting toxicity (DLT). DLT was defined as any of the following during cycle 1 of experimental therapy: 1) any grade 3-4 nonhematologic toxicity that did not resolve or decrease to grade 1-2 within 2 weeks, or 2) any grade 4 hematologic toxicity that caused more than a one week delay in administration of therapy. Granulocyte colony stimulating factor (G-CSF) was used at the discretion of the treating physician. There was a planned expansion at the maximum dose level to obtain additional safety data and samples for correlative studies.

Vaccination

Response to vaccination was assessed using a heptavalent vaccine (PCV-7, Prevnar, manufactured by Wyeth-Lederle) against *Streptococcus pneumoniae* with a protein conjugate (carrier protein CRM-197). Each dose contained 2 mcg each of capsular polysaccharides (4, 9V, 14, 19F, 23F, and 18C), 4 mcg of 6B, and each was conjugated to inactivated diphtheria toxin (20 mcg). This vaccine was selected as it was found to be more immunogenic than a single dose of polysaccharide vaccine administered one year after AHSCT[16,17], and Rapoport et al.[18] used PCV-7 vaccine to evaluate the effectiveness of T-cell infusions post-transplant in patients with multiple myeloma. Vaccinations occurred at 2 (day+60), 4 (day+120), and 6 (day+180) months after transplant (mimicking the schedule in infants) and assessment of B cell response occurred at 3, 4, 6, 9, and 12 months. We measured antibody concentrations specific for immunogenic antigens (14 & 18C) and the less immunogenic antigen 23F using a standardized ELISA. The assay was performed with preabsorption of test sera by using pneumococcal C polysaccharide and pneumococcal polysaccharide from the nonvaccine 22F serotype to enhance specificity of the assay for serotype-specific antibody[19,20] with a criteria for adequate antibody response at >0.35 mcg/mL[21].

Flow Cytometry

Detailed immunophenotypic evaluation of subsets and activation status of T and NK cells and enumeration of T regulatory cells were performed in the Clinical Flow Cytometry Laboratory using whole blood staining method with panels of directly conjugated antibodies at 1, 2, 3, 4, 6, and 8 months after transplant using antibodies and methods described in detail in Supplementary table 1.

Patient Reported Outcomes

At 1, 2, 3, 4, 6, and 8 months after transplant, patients were asked to complete the Functional Assessment of Cancer Therapy-General (FACT-G, v4.0)[22], a 27-item questionnaire that measures four domains of quality of life (physical well-being, functional well-being, social/family well-being, emotional well-being) using a five-point Likert scale where the score is the mean in the relevant domain. This was followed by the 9-item Brief Fatigue Inventory (BFI)[23] assessing the severity of fatigue and the impact of fatigue on daily function. A global fatigue score was obtained by taking the mean of all nine items on the BFI. Clinically significant fatigue was defined when the worst fatigue was greater than 4. Finally patients answered questions from the Center for Epidemiologic Studies Depression (CES-D) Scale-short form[24] with the score as the sum of the 10 items with weights starting at 0 for items rated rarely to up to 3 for items listed as “all of the time.”

Statistics

Toxicities were defined as those thought to be at least possibly related to study treatment, and were tabulated by dose level, type, and severity. The primary endpoint of this trial was toxicity and tolerability and any patients who received any study treatment were included in toxicity analyses even if they were replaced and not used for dose escalation decision-making. Progression-free survival (PFS) and overall survival (OS) were also assessed for patients across all dose levels. Progression-free survival was defined as the time from study entry to the time of progression and/or death, and overall survival was defined as the time from study entry to death due to any cause. Patients who were event-free at their last evaluation were censored at that timepoint. Kaplan-Meier methods were used to characterize survival outcomes for the overall study cohort. In analyzing quality of life survey results, descriptive statistics summarizing means and standard deviations were performed within dose levels and at specific time points. In order to test whether different dose levels and cycles influenced the patients' FACT-G functional well-being score, global fatigue score from the BFI, and overall CES-D score across multiple timepoints, linear mixed effect models were utilized using dose and cycle number as the fixed effects variables and patients as random effects to account for correlation over time. All statistical analyses were conducted using the R statistical program (version 2.15.2). All p-values are reported based on two-sided tests, where $p < 0.05$ was used to determine statistical significance.

RESULTS

Patients

A total of 23 patients were enrolled on this phase 1 trial; while each had different chemotherapy exposure from diagnosis to stem cell mobilization (see Supplementary table 2, detailed therapeutic history), all patients were enrolled between 54 and 66 days after AH SCT. The median age was 55 years (range 25 – 75 years); histology across all doses included: 1 patient with follicular lymphoma, 6 with DLBCL, 6 with MCL, 6 with HL, and 4 with T-cell NHL divided into one with ALK-negative anaplastic lymphoma, one with angioimmunoblastic lymphadenopathy, and two with peripheral T-cell lymphoma NOS and a high LDH (Table 1). The median number of prior therapies was 2 (range 1-5) with the

most prior therapies in follicular lymphoma and Hodgkin's and the least number of prior therapies for mantle cell lymphoma and T-cell NHL.

Accrual

A total of 23 patients were accrued to this phase I trial across four dose levels. Three patients were treated at dose level 1, 6 at dose level 2, 5 at dose level 3, and 9 at dose level 4. Two DLTs were observed across all dose levels, both grade 3 anorexia (one at dose level 2, one at dose level 4). The patient on dose level 2 was evaluated 2 weeks into the first cycle and was found to have grade 3 anorexia and after cessation of study drug, the appetite recovered. The DLT patient on dose level 4 was admitted three weeks into cycle 1 with grade 3 anorexia and fatigue having completed all doses of cycle 1; cycle 2 was held for 4 weeks, but the patient had not recovered sufficiently to restart study drugs after this break. Two of the patients on dose level 3 were replaced after coming off treatment within the first cycle for non-DLT reasons.

Ten patients completed the full 11 cycle treatment plan per protocol, 4 patients were removed from the study early due to progressive disease, 7 withdrew or were removed from the study due to toxicities, and 2 patients were removed from the study because of unrelated complications: lung cancer (1) and infection (1).

Toxicities

In reviewing adverse events that were deemed possibly, probably, or definitely related to Vorinostat (Figure 1), the most frequent adverse events were fatigue (4 grade 2, 8 grade 1), lymphopenia (2 grade 1, 6 grade 2, 2 grade 3, and 1 grade 4), thrombocytopenia (5 grade 1, 5 grade 2, and 1 grade 3), leukopenia (3 grade 1, 5 grade 2, and 2 grade 3), and anemia (6 grade 1, 3 grade 2, and 1 grade 3).

At the 300 mg cohort, a patient with Hodgkin's was taken off treatment during cycle 1 due to grade 2 mental status changes, she did not meet criteria for DLT, and the patient was replaced in that cohort. Also in the 300 mg cohort, the patient with AILD withdrew consent midway through cycle 1 for both treatment and follow-up and was replaced.

There were no grade 3 or 4 infectious complications related to Vorinostat – there was 1 grade 3 infection unrelated to Vorinostat, and only 2 of the 8 episodes of grade 1 or 2 infection reported were deemed possibly related to study drug. There were three drug-related episodes of grade 4 neutropenia (none were dose-limiting) and one grade 3. In regards to gastrointestinal side effects, there was 1 grade 3, 2 grade 2, and 5 grade 1 instances of diarrhea with 2 episodes of grade 2 nausea and 5 episodes of grade 1 nausea. AST elevation occurred in four patients (grade 1) and grade 2 in one patient.

Disease response and survival

13 patients entered into a CR following AHSCT, 3 patients were in a partial response, 2 stable disease, and the remainder were not evaluable. Median follow-up of living patients was 23.2 months (range: 8.7 to 58.8 months) after beginning maintenance therapy; to date, a total of 7 patients died and/or had disease progression. Four patients who had previously

been in remission progressed at 7, 10, 12, and 14 months after starting maintenance Vorinostat for 6, 1, 9, and 11 cycles of therapy, respectively. One patient who was not evaluable after transplant progressed after approximately 1.5 cycles of therapy. The median PFS and OS had not yet been reached; 1- and 2-year estimated PFS rates were 78% and 66% (Figure 3A), respectively. Similarly, the 1- and 2-year estimated OS rates were 87% and 74%, respectively (Figure 3B).

Flow Cytometry

At 30 days post-transplant (n=17), prior to starting Vorinostat, the median percentage of leukocyte subsets was quantified. These patients were generally CD19+ B cell depleted (0.1%), most leukocytes were CD3+ T cells (78%) of which most were CD8+ T cells (60%), and NK cells (17% CD3-/CD16+/CD56+) made up most of the remainder of leukocytes of which most were CD314+/CD56+/CD3- NK cells (15%). After approximately one cycle of Vorinostat therapy (n=12), CD19+ B cells remained rare (0.35%), the distribution of CD3+, CD4+, and CD8+ T cells, NK cells, and percentages of activated T and NK cells were remarkably similar even though patients were two months farther out from receipt of BEAM conditioning.

Prevnar Responses

Despite Prevnar vaccine administration every two months for three injections, the mean antibody concentration never reached adequate levels (>0.35 mcg/mL) when testing for antigens 14 and 23 (figure 2).

Quality of Life

Over time, patients' fatigue (p=0.0012) as measured by the Brief Fatigue Inventory scale and functional well-being from the FACT-G (p=0.0007) improved significantly from cycle 1 to cycle 7, but the depression scores from the CES-D did not change significantly during the first 7 months of protocol therapy (Table 2). Variability of the scores in the three scales decreased over time in only the fatigue scale but not in the FACT-G or the CES-D. Descriptive statistics showed that fatigue, functional well-being, and the CES-D depression scale did not appear to differ significantly between dose levels, however, we recognize the limitations of strict comparisons between dose levels given the limited numbers of patients involved.

DISCUSSION

In this phase I trial we demonstrate that deacetylase inhibition with Vorinostat is generally tolerable up to 400 mg daily in three week intervals. While it seems to suppress circulating regulatory T cells, it is globally immunosuppressive as demonstrated by minimal antibody response to Prevnar and decreased activated B and T cell subsets in the blood. Its efficacy for maintenance was not an endpoint tested in this phase 1 trial and would require a randomized trial in a more homogeneous population of lymphoma patients known to be sensitive to deacetylase inhibition.

Vorinostat caused primarily grade 1 & 2 anorexia, diarrhea, and nausea on this schedule that caused 7 of 23 (30%) to discontinue therapy because of side effects. Despite this, the quality of life measures demonstrated improving fatigue and functional well-being for those patients receiving treatment with no worsening in the depression scale over the 11 cycles of treatment. More recent studies with Vorinostat when given alone or in combination have transitioned to a week on and week off (NCT 01266031) regimen or even weekly dosing[25], limiting side effects.

Deacetylase inhibition in maintenance after autologous transplant also includes Panobinostat. Because of a phase 2 trial showing tumor regressions in 74% of patients with relapsed Hodgkin's lymphoma and median duration of response of 6.9 months[26], a phase 3 trial of panobinostat was undertaken with a goal of recruiting 367 Hodgkin's lymphoma patients who achieved a CR following ASCT. Unfortunately only 41 patients were accrued with panobinostat treated patients reporting frequent diarrhea (88%), nausea (57%), vomiting (46%), and fatigue (35%) while the most frequently reported grade 3/4 AEs were neutropenia (26.9%), thrombocytopenia (15.4%), and diarrhea, vomiting and fatigue (all 11.5%)[27].

Maintenance after transplant in lymphoma continues to be of interest. Rituximab maintenance for patients with follicular lymphoma after upfront therapy[28], in relapsed non-transplant patients[29], or after AHSCT[30] prolonged progression free survival but not overall survival. Unlike patients who underwent autologous transplant without rituximab maintenance[31], in whom B-cell recovery occurred between 3 and 6 months, Rituxan maintenance delays immunoglobulin recovery (primarily IgM)[32] and obliterates vaccine response[33]. We observed little response to vaccination in our trial population even though CD19+ B-cells returned to normal levels 3-6 months from transplant.

Outside of follicular lymphoma where time to event limits the pace of interventions, another trial with maintenance Rituximab after AHSCT for relapsed diffuse large B-cell lymphoma (DLBCL) showed no difference in either event-free survival at 4 years (52% vs 53%) and an increased number of deaths in the Rituximab arm[34].

With toxicities such as anorexia, fatigue, and nausea in this phase 1 population, this broad deacetylase inhibitor at this schedule is not optimal for prolonged maintenance therapy. Alternatives such as a lower dose, a different schedule, or a different pan deacetylase inhibitor could be considered, but a randomized maintenance trial is unlikely until a more tolerable inhibitor with a higher response rate in the relapsed setting is proven.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authorship roles: CCH: Designed the study, analyzed the data, wrote the manuscript. GL: Designed the study, analyzed the data. NW, CTE, CQ, SG, MAB, KH, AB: analyzed the data, wrote the manuscript. EMH: Designed the study. SP, JF, KB, PP, SJ, DMB: enrolled patients. LAA, SMD: Designed the study, enrolled patients, wrote the manuscript. All authors revised the manuscript for intellectual content and approved the final version.

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Figure 1. The ten most frequent adverse events

The ten most frequent worst grade toxicities experienced per patient, as determined by the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), with attributions of possible, probable and definite in regards to relationship to treatment. A count of each adverse event grade lies within each bar on the graph. There were two DLTs of Grade 3 anorexia, though anorexia was not among the most frequent adverse events experienced.

Figure 2. Prevnar responses

The mean concentration of antibody levels in patients treated with Vorinostat. Patients in this study showed no clinically significant responses for antigens 14 (sample size at each time point ranged from 4 – 9 for each time point measured) and 23 with the clinically relevant threshold of 35 µg/mL.

Figure 3. Overall and progression free survival curves

Progression-free survival and overall survival curves as determined by Kaplan-Meier methods. Hashed lines reflect 95% confidence bounds for the survival distributions. Vertical tick marks reflect censored observations. After a median follow-up of 23.2 months, the median overall and progression free survival have not been reached and the 95% confidence intervals are shown as the hashed lines.

Table 1

Demographics of treated patients

Age	Lymphoma	Priors *	High Risk Feature	Disposition	Cycles Received
100 mg Vorinostat (3 patients)					
65	Follicular	5	Progressive disease after 2+ prior regimens	✓ Treatment completed	11
11	Mantle Cell	1	Chemotherapy sensitive after induction		11
25	Hodgkin's	2	Primary refractory		11
200 mg Vorinostat (6 patients)					
58	Mantle Cell	1	Chemotherapy sensitive after induction	✓ Treatment completed	11
75		4	Chemotherapy sensitive, relapsed	✗ Progressed on Vorinostat	9
63		3		Stopped - grade 3 anorexia (DLT)	1
54	T-Cell NHL	1	Peripheral T-Cell Lymphoma NOS and high LDH	✗ Progressed on Vorinostat	3
60		3		✗ Progressed on Vorinostat	1.5
52		1	ALK-negative anaplastic lymphoma	✓ Treatment completed	11
300 mg Vorinostat (5 patients)					
58	T-Cell NHL	1	Angioimmunoblastic lymphadenopathy	Stopped because of side effects	0.5
27	Hodgkin's	2	PET positive after salvage		1
26		2			1.5
36		3		✓ Treatment completed	11
31		3		✓ Treatment completed	11
400 mg Vorinostat (9 patients)					
55	DLBCL	2	Relapse less than one year after induction	Stopped because of lung cancer	6
55		2		Stopped because of side effects	1.5
35	Hodgkin's	4	Primary refractory	✓ Treatment completed	11
61	Mantle Cell	1	Chemotherapy sensitive after induction	Stopped because of unrelated infection	1
67	DLBCL	2	PET positive after induction	Stopped because of side effects	1
32		2	Relapse less than one year after induction	✗ Progressed on Vorinostat	6
67	Mantle Cell	1	Chemotherapy sensitive after induction	Stopped - grade 3 anorexia (DLT)	1
32	DLBCL	2	Induction failure. chemotherapy sensitive	✓ Treatment completed	11
51		2	Relapse less than one year after induction	✓ Treatment completed	11

Abbreviations: Diffuse Large B-cell Lymphoma (DLBCL), Angioimmunoblastic lymphadenopathy (AILD), Anaplastic Lymphoma Kinase (ALK), Not otherwise specified (NOS), lactate dehydrogenase (LDH), dose limiting toxicity (DLT)

* In addition to the number of prior therapies denoted here, all patients also underwent mobilization and autologous hematopoietic stem cell transplant (HSCT) with BEAM conditioning.

Table 2

Fatigue, Quality of Life and Depression scales over time

	BFI			FACT-G FWB			CES-D		
Timepoint	n	$\bar{x}(s)$	<i>p</i>	n	$\bar{x}(s)$	<i>p</i>	n	$\bar{x}(s)$	<i>p</i>
C1D1 (+60)	23	2.8 (2.1)	-0.0012	23	81.1 (12.6)	-0.0007	23	7.4 (4.5)	-0.13
C2D1 (+90)	18	2.1 (1.6)		18	82.0 (13.0)		19	6.4 (5.0)	
C3D1 (+120)	15	1.7 (1.6)		15	83.4 (13.4)		15	5.5 (5.0)	
C5D1 (+180)	13	1.4 (1.9)		13	85.1 (10.9)		13	6.6 (5.7)	
C7D1 (+230)	11	1.3 (1.0)		11	87.6 (12.0)		11	6.3 (4.9)	

Abbreviations: CXDY represents cycle X and day Y. $\bar{x}$ = sample mean, s = standard deviation, BFI = Brief Fatigue Inventory: Mean scores represent a global fatigue score, with a score of 10 being the worst fatigue possible. FACT-G FWB = Functional Assessment of Cancer Therapy - General Functional Well-Being Domain (GF1-GF7) with higher scores meaning better function. CES-D = Center for Epidemiologic Studies Short Depression Scale graded as the sum of all items, with a score of 10 or greater being indicative of depression. P-value is the statistical comparison between the first and seventh cycle in the relevant domain obtained from the linear mixed effects model.