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A Phase I Study of Intermittently Dosed Vorinostat in Combination with Bortezomib in Patients with Advanced Solid Tumors

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Abstract

Background—Accumulating evidence shows evidence of efficacy with the combination of vorinostat and bortezomib in solid tumors. We previously examined a once-daily continuous dosing schedule of vorinostat in combination with bortezomib which was well tolerated in cycles 1 and 2; however, there was concern regarding the tolerability through multiple cycles. This study was conducted to evaluate an intermittent dosing schedule of vorinostat with bortezomib.

Methods—Vorinostat was initially administered orally twice daily on days 1–14 with bortezomib IV on days 1, 4, 8, and 11 of a 21 day cycle. Two DLTs (elevated ALT and fatigue) were observed at dose level 1, thus the protocol was amended to administer vorinostat intermittently twice daily on days 1–4 and 8–11.

Results—29 patients were enrolled; 13 men and 16 women. Common cancer types included sarcoma, pancreatic, colorectal, GIST, and breast. The most common Grade 3–4 toxicities at any dose level included thrombocytopenia, fatigue, increased ALT, elevated INR, and diarrhea. DLTs in the intermittent dosing schedule included thrombocytopenia and fatigue. The C_{max} and AUC for the intermittent dosing regimen were similar to those observed in the daily dosing. In this heavily pretreated population, stable disease was observed in patients with sarcoma, colorectal adenocarcinoma and GIST.

Conclusions—The MTD was established at vorinostat 300 mg BID on days 1–4 and 8–11 and bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 of a 21 day cycle. Tolerability was not improved with the intermittent dosing schedule of vorinostat when compared to continuous dosing.

Keywords

SAHA; vorinostat; PS-341; bortezomib; phase I

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Disclosures

No potential conflicts of interest were disclosed.

INTRODUCTION

Over the past 10 years, epigenetic regulation of gene expression has been shown to play an important role in the biology of multiple hematologic malignancies and solid tumors (1–3). Histone deacetylation is a critical regulatory mechanism of gene expression and promotes transcriptional activity by allowing access of transcription factors to exposed (4,5). In contrast to histone acetyltransferases, histone deacetylases (HDACs) cause chromatin condensation and silencing of various genes, including those involved in cell survival, proliferation, differentiation, and apoptosis (6). HDACs also have many non-histone protein targets such as tumor suppressor genes and proteins that control proliferation, migration, death, and angiogenesis (5).

Accumulating evidence suggests that HDAC inhibitors and proteasome inhibitors may act synergistically in malignancies. Vorinostat (suberoylanilide hydroxamic acid (SAHA), MK-0683, Zolinza, Merck, Whitehouse Station, NJ) is a small molecule inhibitor of class I and II HDAC enzymes and is currently approved by the Food and Drug Administrations (FDA) for use in refractory cutaneous T-cell lymphoma (7–9). Bortezomib (Velcade, PS341, Millenium, Cambridge, MA) is a modified dipeptidyl boronic acid that reversibly inhibits the 26S proteasome. It is currently approved by the FDA for use in multiple myeloma. Several preclinical studies have demonstrated efficacy for the treatment of solid tumors with this combination including hematologic malignancies, renal cell carcinoma, sarcoma, and non-small cell lung cancer (10–12).

We had previously conducted a study of once-daily vorinostat administered on a continuous dosing (CD) schedule with bortezomib (13). Two patients had partial responses indicating potential clinical efficacy, but there was concern about late cycle toxicities preventing prolonged administration. This study was conducted to evaluate twice daily dosing of vorinostat on an intermittent dosing (ID) schedule along with bortezomib to determine safety and efficacy, pharmacokinetics, and activity this alternate regimen.

MATERIALS AND METHODS

Patient Selection

Patients with histologically documented, advanced solid malignancy refractory to standard therapy or for which no curative standard therapy was available were considered eligible. Other key eligibility criteria included: > 18 years, Eastern Cooperative Oncology Group performance status of 0 to 2, adequate hematologic, hepatic and renal functions (WBC > 3,000/ μ l, absolute neutrophil count > 1,500/ μ l, platelets > 100,000/ μ l, total bilirubin within institutional normal limit, AST/ALT $\leq$ 2.5 $\times$ the institutional upper limit of normal, creatinine $\leq$ 1.5 mg/dl or measured creatinine clearance $\geq$ 60 ml/min/1.73m² for patients with creatinine levels about institutional normal); and life expectancy greater than 12 weeks.

Patients were excluded if they had untreated brain metastasis, were treated within 4 weeks with chemotherapy or radiation therapy, had a history of myocardial infarction or had severe pulmonary disease requiring oxygen. All patients were required to practice effective birth control.

The protocol was approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison. Informed consent was obtained from each patient before participating in the study.

Study Design and Patient Treatment

This open-label, dose escalation, phase 1 trial was designed to determine the safety and tolerability of an alternate dosing schedule of vorinostat in combination with bortezomib. Initially, a fixed dose of vorinostat was administered orally twice daily on days 1–14. As a result of two dose limiting toxicities (DLTs) (elevated ALT and fatigue) at dose level 1, the protocol was amended to administer vorinostat twice daily on days 1–4 and 8–11. The starting dose (level 1°) was vorinostat (200 mg) and bortezomib (1 mg/m²). Increasing doses of bortezomib were administered as an IV bolus over 15 minutes on day 1, 4, 8 and 11. Two dose levels of bortezomib were evaluated: 1 mg/m², and 1.3 mg/m². Treatment was repeated every 21 days. Dose escalation of bortezomib followed the traditional 3 + 3 design, and the MTD was defined as the dose level in which one or fewer of six patients developed a DLT.

Dose Modification

For dose-escalation to occur, three evaluable patients had to complete their first cycle without a DLT. As stated previously, two DLTs (elevated ALT and fatigue) were observed at dose level 1, cycle 1, and the protocol was amended. With each DLT thereafter, 3 additional evaluable patients had to be accrued, and further escalation could occur if no more DLTs were observed. Patients who experienced any DLT were delayed by 1-week intervals until recovery and then allowed to continue on study with dose reduction in either vorinostat or bortezomib. Patients were removed from study following a treatment delay of more than 2 weeks due to delayed recovery from toxicity related to treatment with vorinostat or bortezomib. In addition, patients were required to have an absolute neutrophil count 1000/mm³ a platelet count 50,000/mm³ on day 8 of each cycle.

Patient Evaluations and Follow-up

History, physical examination, weight, evaluation of ECOG performance status, and routine laboratory studies were obtained from all patients at baseline and at the beginning of subsequent cycles. Tumor assessment was obtained at baseline and every cycle if measured by physical examination, or every other cycle if measured by imaging, utilizing, whether clinically or radiographically, identical methods. Other pre-registration studies included measurement of height, serum pregnancy testing for women of childbearing age and an EKG. In addition, a CBC with differential was obtained on days 8 and 15 of each cycle.

Adverse events were evaluated using the National Cancer Institute Common Toxicity Criteria (CTC), version 3.0 guidelines. DLTs were defined as adverse events occurring during the first cycle of vorinostat and bortezomib administration and fulfilling one of the following criteria: absolute neutrophil count 500 > 7 days or longer; febrile neutropenia or grade 3 neutropenic infection; platelets 25,000 or thrombocytopenic bleeding; any nonhematologic toxicity grade 3 except nausea, vomiting, or diarrhea associated with suboptimal premedication and/or management; AST/ALT elevations of grade 3 or higher for > 7 days; any toxic effect leading to missing two or more doses per cycle; and any toxic effect resulting in the delay of the subsequent cycle by > 7 days.

All patients who completed at least one treatment course followed by 2 weeks of observation were considered evaluable. The determination of antitumor efficacy was based on objective tumor assessments made according to the Response and Evaluation Criteria in Solid Tumors (RECIST) criteria. Baseline imaging-based tumor assessments were performed within 28 days prior to the start of treatment, and all tumor assessments were re-evaluated every 6 weeks thereafter. All patients with responding tumors (CR and PR) were required to have response confirmed 4 weeks after the first documented response.

Duration of Study Treatment

Patients with objective response or stable disease were allowed to remain on study until disease progression. Otherwise, study treatment continued until disease progression, unacceptable adverse event, patient's decision to withdraw, or changes in the patient's condition necessitating discontinuation of study treatment, including intercurrent illness.

Pharmacokinetic Analysis

Blood samples for vorinostat PK analysis were collected on cycle 1, day 1, in the absence of bortezomib, and on days 2 and 12, with bortezomib for the first cohort of patients. The day 12 sample collection was changed to day 11 after intermittent dosing was introduced. PK sampling was performed before and 0.25, 0.5, 0.75, 1, 2, 4, 6, and 8 hours following vorinostat administration. Concentrations of vorinostat and its metabolites (vorinostat glucuronide and 4-anilino-4-oxobutanoic acid) were quantitated with a liquid chromatography-electrospray ionization tandem mass spectrometric method as previously described (14).

Statistical Methods

The primary outcome measure of this study was assessment of toxicity. The number and severity of toxicity incidents determined the level of tolerance for vorinostat and bortezomib in the treatment of advanced cancer. Hematologic toxicity measures were assessed using continuous variables as the outcome measures (primarily nadir and percent change from baseline values), as well as categorization via CTC standard toxicity grading. Nonhematologic toxicities were evaluated via the ordinal CTC standard toxicity grading only. Frequency distributions and other descriptive measures formed the basis of analysis of these variables. The number of treatment anti-tumor responses served as the secondary outcome measure. Treatment efficacy was summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease.

Pharmacokinetic analysis for vorinostat and metabolites was performed by noncompartmental methods using the WinNonlin program, version 5.2 (Pharsight, Cary, NC), and data were summarized using means $\pm$ standard deviations. Day 1 pharmacokinetic parameters were compared to day 2 and day 3 pharmacokinetic parameters with the Wilcoxon Signed Rank Test.

RESULTS

Patient Characteristics

29 patients, 13 male and 16 female, with a median age of 59 were enrolled and received a total of 53 courses of therapy (median, 2; range 1 to 5). The majority of patients were pretreated, having received 2 or more prior chemotherapy regimens. Baseline characteristics are outlined in Table 1.

Dose Escalation and MTD

Four dose levels ranging from bortezomib 0.7 to 1.3 mg/m² with vorinostat 200mg to 300mg BID days 1–4 and 8–11 were evaluated (Table 2). Dose level 1 was initiated with vorinostat 200 mg orally twice daily on days 1–14. Due to two DLTs of elevated ALT and fatigue at dose level 1 cycle 1, an amendment was written to change the dosing interval to vorinostat BID on days 1–4 and 8–11 for cycles 1° to 3°. No DLTs were observed at dose level 1° (vorinostat 200 mg BID and bortezomib 1 mg/m²), and three patients were unevaluable due to elevated ALT and fatigue preventing completion of cycle 1. An

additional three patients were enrolled at this dose level without initial toxicity. Dose-limiting grade 3 (and one grade 4) thrombocytopenia was observed in dose level 3° (vorinostat 300 mg and bortezomib 1.3 mg/m²). Two patients were unevaluable in dose level 3° due to symptoms of progressive disease. Based on these findings, the MTD was established at vorinostat 300 mg BID on days 1–4 and 8–11 and bortezomib 1.3 mg/m² days 1, 4, 8 and 11.

Safety and Tolerability

The most frequent adverse events (with attribution at least related to vorinostat or bortezomib) are described by dose level in Tables 3 and 4. Thrombocytopenia and anemia were the most common hematologic toxicities reported with this combination. Most hematologic events were grade 1 or 2, but grade 3 thrombocytopenia was seen during 1 course of treatment with bortezomib dosed at 1.0 mg/m² and 2 were seen at bortezomib at 1.3mg/m², with one grade 4 thrombocytopenia at that level. Grade 1 or 2 nausea, vomiting, fatigue, constipation, anorexia, and diarrhea were the most common non-hematologic toxicities encountered.

One of the primary objectives of this study was to determine whether the ID schedule was more tolerable than the CD schedule. After the amendment was implemented to change the dosing interval to vorinostat BID on days 1–4 and 8–11, treatment was better-tolerated. In those patients that received more than two cycles of therapy, the most common reason for discontinuation of the treatment was disease progression. Treatment was discontinued in only one patient who received more than two cycles of therapy due to progressive thrombocytopenia. Fatigue, nausea, and sensory neuropathy were common, especially with prolonged administration. However, the fatigue was less common that was observed with once daily dosing of vorinostat on the CD schedule.

Efficacy

Although not a primary endpoint of this trial, patients underwent disease assessment prior to every even numbered cycle. There was stable disease found in heavily pre-treated sarcoma, colorectal carcinoma, and GIST. Two patients had heavily pre-treated soft tissue sarcoma, including one with leiomyosarcoma, who had stable disease on their first disease evaluation but progressed after cycle 4. Treatment was discontinued in these patients for eventual disease progression. One of these patients required a dose reduction due to elevated ALT that required the amended protocol.

Vorinostat Pharmacokinetics

Pharmacokinetics are presented in Table 5. The twice daily continuous and intermittent dosing schedules were compared and since there were no significant differences in PK parameters between the dosing schedules observed, data was combined. Evaluation of day 1 pharmacokinetic parameters compared with day 2 pharmacokinetic parameters to assess the influence of bortezomib on vorinostat PKs showed a statistically significant increases in C_{max} on day 2 compared to day 1 for vorinostat (ratio 1.28 ± 0.46 , $p < 0.001$), the acid (ratio 1.51 ± 0.54 , $p < 0.001$) and the glucuronide metabolite (ratio 1.27 ± 0.46 , $p = 0.002$); however, this is more likely related to twice daily dosing than an interaction with vorinostat. As expected, C_{max} for vorinostat and its metabolites significantly increased between Day 1 after a single dose and Day 12 after continued dosing (ratio 1.30 ± 0.55 , $p = 0.039$).

DISCUSSION

The combination of vorinostat and bortezomib is an intriguing combination as evidence of efficacy has been demonstrated, including 2 partial responses in patients treated with the CD

schedule (1 patient with chemotherapy-refractory malignant fibrous histiocytoma and 1 patient with previously-treated advanced squamous cell carcinoma of the lung) (13). Although the patients treated on the CD schedule tolerated that dosing regimen fairly well in early cycles, there was significant concern about potential cumulative toxicities with prolonged administration, including myelosuppression, fatigue, and sensory neuropathy. In this study, an alternate dosing schema was investigated to determine if this regimen would have an improved toxicity profile.

Treatment with ID vorinostat in combination with bortezomib on the alternate dosing schema was well-tolerated. The MTD was established at vorinostat 300 mg PO BID on days 1–4 and 8–11 and bortezomib 1.3 mg/m² IV on days 1, 4, 8 and 11 of a 21 day cycle. The DLTs observed included thrombocytopenia, increased ALT, and fatigue. The most common grade 1 and 2 toxicities included nausea, diarrhea, fatigue, diaphoresis, and anorexia. These toxicities are consistent with documented side effects of these agents in prior studies and did not appear to be increased in severity or frequency when given in combination. The most common hematologic toxicities included anemia and thrombocytopenia, which are commonly seen in other studies with bortezomib. There may be an increased occurrence of thrombocytopenia with the combination of these two agents that appears to be independent of dose. Although not a primary endpoint of this trial, five patients had evidence of stable disease after the cycle two disease evaluation. Stable disease was seen in three patients with soft tissue sarcoma, including one with gastrointestinal stromal tumor, and one with colorectal cancer.

Pharmacokinetic analysis showed no significant difference in PK parameters between the twice daily continuous and intermittent dosing schedules evaluated in this study. The twice daily dosing of vorinostat resulted in an increase in C_{max} on day 2 compared to day 1 for vorinostat, the acid and the glucuronide metabolite. In addition, C_{max} for vorinostat and its metabolites significantly increased between Day 1 after a single dose and Day 12 after chronic dosing. An increase in C_{max} has been described previously with chronic dosing (15). In comparison to CD schedule of vorinostat, where the MTD was 400 mg daily for 14 days of a 21 day cycle, for a total dose of 5600 mg per cycle, the MTD on the ID schedule was 300 mg twice a day, with intermittent dosing (8 days of dosing out 21) for a total of 4800 mg per cycle. The C_{max} and AUC were similar between CD and ID, despite the lower overall dose administered in the ID schedule, which may explain why an improvement in tolerability was not observed with the dosing schedule in this study when compared to the previous study examining CD vorinostat.

In summary, the combination of vorinostat and bortezomib remains an interesting combination for the patients with treatment refractory solid tumors. The MTD was established at vorinostat 300 mg PO BID on days 1–4 and 8–11 and bortezomib 1.3 mg/m² IV on days 1, 4, 8 and 11 of a 21 day cycle. Multiple patients with treatment refractory cancer achieved stable disease with this dosing regimen. Although fewer patients stopped treatment for cumulative toxicities after receiving two cycles of therapy when compared to once daily dosing of vorinostat administered continuously, the toxicity profile in the first two cycles was similar between the two dosing schedules.

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Table 1**Baseline characteristics**

Total, <i>n</i>	29
Median age, years (range)	59 (30–81)
Gender, <i>n</i>	
Male	13
Female	16
ECOG performance status, <i>n</i>	
0	5
1	22
2	2
Primary tumor type, <i>n</i>	
Sarcoma	7
Pancreatic	6
Colorectal	3
Breast	2
GIST	2
Other ^a	1
Prior cytotoxic therapy ^b , <i>n</i>	
0	2
1	3
2	7
3 or more	17
Average number of Tx	3.3

^aOne each of prostate, mesothelioma, neuroendocrine, biliary, cervical, lung, ovarian, thymus, head and neck.

^bIncludes conventional chemotherapy, cytokine-based immunotherapy, and experimental cytotoxic chemotherapy.

Table 2

Dose escalation schema and frequency of dose limiting toxicities

Dose Level ^a	<i>n</i>	Vorinostat (mg) ^b	Bortezomib (mg/m ²) ^c	Courses, <i>n</i>	<i>N</i> of patients with DLTs (cycle 1)	Description of DLTs (cycle 1)
-1	6	100	0.7	19	0	
1	4	200	1	7	2	Fatigue, ALT
1 ^o	6	200	1	5 ^d	0	
2 ^o	3	200	1.3	8	0	
3 ^o ^e	10	300	1.3	14 ^f	1	Thrombocytopenia

^aDue to 2 DLTs at Dose Level 1, an amendment was written to change dosing interval to Vorinostat for cycles 1^o–3^o.^bAdministered orally twice daily days 1–14 for Dose Levels 1 and –1; twice daily on days 1–4 and 8–11 for Dose Levels 1^o–3^o.^cAdministered i.v. on days 1, 4, 8 and 11 of a 21 day cycle.^dThree patients were unevaluable.^eMTD.^fTwo patients were unevaluable.

Table 3

Drug-related adverse events

Toxicity	Step B (n = 53)	
	Grade 1/2, n (%)	Grade 3/4, n (%)
Hematologic		
Thrombocytopenia	3 (5.7)	6 (11.3) ^a
Anemia	7 (13.2)	1 (1.9)
Pulmonary		
Dyspnea	3 (5.7)	0
Gastrointestinal		
Nausea	20 (37.7)	1 (1.9)
Vomiting	6 (11.3)	1 (1.9)
Anorexia	9 (17)	1 (1.9)
Diarrhea	15 (28.3)	3 (5.7) ^a
Dyspepsia	3 (5.7)	0
ALT elevation	0	2 (3.8)
Renal/FEN		
Hypotension	2 (3.8)	0
Urinary frequency	0	0
Hyponatremia	0	0
Miscellaneous		
Fatigue	29 (54.7)	4 (7.5) ^a
Diaphoresis/flushing	0	0
Fever / chills	5 (9.4)	0
Elevated INR	0	1 (1.9)
Sensory neuropathy	5 (9.4)	0
Altered taste	1 (1.9)	0
Mucositis	1 (1.9)	0
Rash / pruritis	3 (5.7)	0
Dizziness	5 (9.4)	1 (1.9)

^aDose Limiting Toxicity (DLT)

Table 4

Drug-related adverse events, worst grade per patient during cycle 1

Selected toxicities	Bortezomib (mg/m2); Vorinostat (mg)											
	0.7; 100			1.0; 200			1.0; 200			1.3; 200		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
Hematologic												
Thrombocytopenia				1	1				1			2*
Anemia	1			1						2		4 (7.5)
Non-hematologic												
Nausea	3			2		2				7		15 (28.0)
Fatigue	2			1		2			2	5	1	15 (28.0)
Diarrhea				1					1	3		7 (13.2)
Anorexia	1			1		1			1	3	1	10 (18.9)
Dizziness	1			1		1			1	1		6 (11.3)
Vomiting				1						5		7 (13.2)
Constipation	2			2					1			5 (9.4)
Sensory neuropathy	2			1								3 (5.7)

Abbreviations: G, Grade

* One Grade 4 thrombocytopenia

Table 5

Pharmacokinetic parameters in plasma and in patients receiving vorinostat or one of its metabolites in combination with bortezomib

	Ratio	N	C _{max} (ng/mL/dose)	T _{max} (hr)	AUC _{0-∞} (ng/mL × hr/dose)	T _{1/2} (hr)	Cl/F (L/hr)	V/F (L)
Vorinostat	CID2/CID1	23	1.28 ± 0.46 [*]	1.44 ± 1.09	1.03 ± 0.32	0.87 ± 0.41	1.26 ± 1.13	1.10 ± 1.51 [*]
	CID11 ^a /CID1	18	1.30 ± 0.55 [*]	1.87 ± 1.55 [*]	1.12 ± 0.39	0.90 ± 0.51	1.11 ± 0.75	0.84 ± 0.44
Vorinostat glucuronide	CID2/CID1	23	1.27 ± 0.46 [*]	1.18 ± 0.92	1.00 ± 0.26	1.90 ± 1.13	0.88 ± 0.32	1.07 ± 1.06
	CID11 ^a /CID1	18	1.15 ± 0.45	1.60 ± 1.47	0.93 ± 0.32	2.36 ± 1.25	0.96 ± 0.53	1.05 ± 0.53
Vorinostat acid	CID2/CID1	23	1.51 ± 0.54 [*]	0.90 ± 0.68	1.07 ± 0.28	0.77 ± 0.29	1.00 ± 0.28	0.73 ± 0.27 [*]
	CID11 ^a /CID1	18	1.55 ± 0.60 [*]	1.00 ± 0.81	1.07 ± 0.42	0.71 ± 0.46	1.05 ± 0.37	0.67 ± 0.28 [*]

Abbreviations: C_{max}, concentration maximum; Cl, clearance; AUC_{0-∞}, area under the plasma concentration time curve from 0 to infinity; T_{1/2}, half-life; T_{max}, time of maximum concentration.

^{*} p < 0.05.

^a Patients with continuous dosing were sampled on day 12.