

Vorinostat in Advanced Prostate Cancer Patients Progressing on Prior Chemotherapy (National Cancer Institute Trial 6862)

Trial Results and Interleukin-6 Analysis: A study by the Department of Defense Prostate Cancer Clinical Trial Consortium and University of Chicago Phase 2 Consortium

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BACKGROUND: This phase 2 trial was designed to evaluate the efficacy of vorinostat in chemotherapy-pre-treated patients with metastatic castration-resistant prostate cancer. **METHODS:** Patients with disease progression on 1 prior chemotherapy, a prostate-specific antigen (PSA) ≥ 5 ng/mL, and adequate organ function were treated with 400 mg vorinostat orally daily. The primary endpoint was the 6-month progression rate. Secondary endpoints included safety, rate of PSA decline, objective response, overall survival, and effects of vorinostat on serum interleukin-6 (IL-6) levels. **RESULTS:** Twenty-seven eligible patients were accrued. The median number of cycles delivered was 2 (range, 1-7). All patients were taken off therapy before 6 months. The best objective response in the eligible patient was stable disease in 2 (7%) patients. No PSA decline of $\geq 50\%$ was observed. There was 1 grade 4 adverse event (AE), and 44% of patients experienced grade 3 adverse events. The most common adverse events were fatigue (81%), nausea (74%), anorexia (59%), vomiting (33%), diarrhea (33%), and weight loss (26%). Median time to progression and overall survival were 2.8 and 11.7 months, respectively. Median IL-6 levels (pg/mL) were higher in patients removed from the protocol for toxicity compared with progression at all time points, including baseline (5.2 vs 2.1, $P=.02$), Day 15 Cycle 1 (9.5 vs 2.2, $P=.01$), Day 1 Cycle 2 (9.8 vs 2.2, $P=.01$), and end of study (11.0 vs 2.9, $P=.09$). **CONCLUSIONS:** Vorinostat at this dose was associated with significant toxicities limiting efficacy assessment in this patient population. The significant association between IL-6 levels and removal from the study for toxicities warrants further investigation. *Cancer* 2009;115:5541-9. © 2009 American Cancer Society.

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With the establishment of docetaxel as standard first-line chemotherapy for castration-resistant prostate cancer,^{1,2} a clinical research priority in this disease is to identify second-line therapy. Histone deacetylases regulate cell signaling and gene transcription through removal of acetyl groups from histone and nonhistone proteins.³⁻⁵ Inhibition of histone deacetylase activity leads to accumulation of acetylated proteins, which in turn lead to alterations in transcription, mitosis, and protein stability, with resultant inhibition of tumor cell proliferation and survival.³⁻⁶ In preclinical studies, histone deacetylase inhibitors have been shown to induce tumor cell cytostasis, differentiation, and apoptosis, and to inhibit tumor angiogenesis in various hematologic and solid malignancies. In prostate cancer, histone deacetylase inhibition has resulted in decreased proliferation in cell lines,⁷⁻⁹ and decreased tumor growth in preclinical models,⁹⁻¹⁵ suggesting that histone deacetylase inhibition is of potential therapeutic benefit in this disease.

Vorinostat is a small molecule inhibitor of class I and II histone deacetylases that has been approved by the Food and Drug Administration for treatment of cutaneous T-cell lymphoma.¹⁶⁻¹⁸ In early testing, vorinostat showed significant antitumor activity in a broad range of cancers,¹⁹⁻²² including preclinical activity in prostate cancer.^{23,24} Specifically, vorinostat suppressed the growth of the LNCaP, PC-3, and TSU-Pr1 cell lines at micromolar concentrations.²³ In mice with transplanted CWR222 human prostate tumors, vorinostat treatment at 50 mg/kg/day resulted in significant suppression of tumor growth. At this dose, there was no detectable toxicity, as evaluated by change in weight and necropsy examination.²³ Kulp and colleagues have similarly shown growth inhibition of PC-3, DU-145, and LNCaP human prostate cancer cell lines and suppression of PC-3 xenograft tumors with vorinostat treatment.⁹ These biologic, preclinical, and phase 1 data collectively provided the rationale for testing vorinostat in patients with castration-resistant prostate cancer failing prior chemotherapy.

Interleukin-6 (IL-6) is a pleiotropic cytokine that stimulates the progression of a variety of cancers. Multiple studies have demonstrated that IL-6 is elevated in the sera of patients with metastatic prostate cancer.²⁵⁻²⁷ Drachenberg and colleagues²⁸ reported elevated serum IL-6 levels in men with hormone-refractory prostate cancer compared with normal controls, benign prostatic hyperplasia, prostatitis, and localized or recurrent disease, suggesting that IL-6 may be a surrogate marker of the androgen-independent phenotype. IL-6 has also been associated with disease progression and has been implicated as a potential marker of response to therapy.²⁹⁻³¹ Histone deacetylase inhibition has also been shown to be associated with decreased expression of IL-6 and other proinflammatory mediators.³²⁻³⁴ These findings, along with the observations that vorinostat can down-regulate the IL-6 signaling cascade,³⁵ portend a possible role for the evaluation of IL-6 as an indicator of response to vorinostat. We hypothesized that vorinostat-mediated down-regulation of IL-6 activity would be associated with a favorable outcome.

MATERIALS AND METHODS

This Cancer Therapy Evaluation Program-sponsored trial was conducted by the Department of Defense Prostate Cancer Clinical Trials Consortium and the National Cancer Institute (NCI)-sponsored University of Chicago Phase 2 Consortium. The protocol was reviewed and approved by the institutional review board at each participating institution, and all patients provided informed consent before initiation of any study procedures. Eligible patients had metastatic prostate cancer with measurable and/or bony disease that had progressed despite androgen deprivation therapy and 1 prior chemotherapy regimen for castration-resistant prostate cancer. All patients were required to have prostate-specific antigen (PSA) progression defined as at least 2 rises in PSA documented over a reference value, no less than 7 days apart, with a minimum value of 5 ng/mL. Patients had to have an Eastern Oncology Cooperative Group performance status of

0-2 and adequate hematological, renal, and hepatic function defined by a white blood count of $\geq 3000/\mu\text{L}$, absolute neutrophil count $\geq 1500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, creatinine $< 2\text{mg/dL}$, bilirubin within normal limits, and aspartate aminotransferase and alanine transaminase $\leq 2.5\times$ the upper limits of normal. Patients with significant cardiovascular disease including congestive heart failure (New York Heart Association class III or IV), active angina pectoris, or recent myocardial infarction (within the last 6 months) were excluded. Patients requiring diuretics for reasons other than hypertension, digoxin for reasons other than atrial fibrillation, or with a history of mild to moderate congestive heart failure, or patients with electrocardiogram results of 1) significant q waves, 2) ST elevation or depressions of > 2 mm, 3) the absence of a regular sinus rhythm, or 4) the presence of a bundle block were required to undergo additional cardiac testing. Patients with known brain metastases were excluded, but those with treated and controlled epidural disease were eligible. Patients on luteinizing hormone-releasing hormone (LHRH) agonists were required to continue therapy. Discontinuation of all nonsteroidal antiandrogens (28 days for flutamide and 42 days for bicalutamide) was required. Patients taking valproic acid (a histone deacetylase inhibitor) must have stopped therapy at least 2 weeks before registration. No investigational or commercial agents (other than LHRH analogues) or therapies including other hormonal agents such as steroids, megestrol acetate (unless low dose given for hot flashes), antiandrogens, or herbal medications were permitted to be administered with the intent to treat the patient's malignancy. Patients with a currently active second malignancy other than nonmelanoma skin cancers were not eligible. Patients were not considered to have a currently active malignancy if they had completed therapy and were considered by their physician to show no evidence of disease.

Treatment Plan

Patients received open-label oral vorinostat 400 mg daily continuously. All patients completed a medication diary to monitor compliance. Toxicity was assessed using NCI Common Toxicity Criteria for Adverse Events version 3.0, and dose reductions to 300 mg/day and 100 mg/day were specified for grade 3 or 4 toxicities. Patients were

evaluated clinically and by laboratory tests every 21 days. A maximum 4-week break in treatment for toxicity resolution was permitted.

Duration of Therapy, Monitoring, and Response Assessment

Patients were monitored by history and physical exam, toxicity assessment, and PSA every 3 weeks. Response assessment by bone scan and computed tomography scan and/or other appropriate imaging was performed every 12 weeks. Patients were removed from the protocol if there was evidence of progression by PSA or Response Evaluation Criteria in Solid Tumors criteria, or symptomatic progression. Patients with progression by bone scan only at first assessment continued treatment with reassessment after 6 additional weeks of therapy. Patients with confirmed progression were removed from the protocol. Patients with stable disease or better were permitted to continue protocol therapy. Patients demonstrating progression by bone scan or other measures at the 24-week or subsequent scheduled assessments were considered as having progressive disease, and a confirmation of progression was not required. All patients were followed for survival.

Response and Progression Definition

Progression for the purpose of the study was defined by any 1 or more of the following parameters: 1) PSA progression—25% increase over baseline or nadir, whichever is lower, and an increase in the absolute value of PSA by 5 ng/mL that is confirmed by another PSA at no less than a 4-week interval; 2) measurable disease progression—progression of target lesions by Response Evaluation Criteria in Solid Tumors criteria³⁶; 3) nonmeasurable disease progression—worsening of bone scan defined as development of ≥ 2 new lesions, appearance of new metastatic lesions outside of the bone, unequivocal progression of existing nontarget lesions, or development of an indication for radiation therapy or other change in cancer therapy based on a change in a disease manifestation while on therapy.

Objective responses were defined using Response Evaluation Criteria in Solid Tumors criteria.³⁶ PSA response was defined based on the PSA Working Group Consensus Criteria.³⁷ Bone disease was evaluated by bone

Table 1. Patient Characteristics, N = 27

Characteristic	No. of Patients
Age, median y (range)	68 (54-80)
Race	
White	21 (78%)
Nonwhite	6 (22%)
Performance status	
0	7 (26%)
1	19 (70%)
2	1 (4%)
PSA, median ng/mL (range)	95 (5.8-1526)
Disease progression at registration	
PSA	100%
Soft tissue	56%
Bone	81%
Prior chemotherapy for CRPC	
Docetaxel	25 (92%)
Paclitaxel	1 (4%)
Cyclophosphamide	1 (4%)

PSA indicates prostate-specific antigen; CRPC, castration-resistant prostate cancer.

Two patients were ineligible (total 29 patients registered). Patients were registered between May 2006 and February 2007.

scan, with disease characterized as complete response if there was disappearance of all osseous lesions as evaluated by scans, stable or improved if there were no new lesions and no new pain in an area where uptake was previously observed, and progression if there was the appearance of 2 or more new skeletal lesions. An increase in the size or intensity of lesions was not considered progression.

Endpoints and Statistical Design

The primary objective of this phase 2 trial was to evaluate the activity of oral vorinostat in patients with metastatic prostate cancer that had progressed on 1 prior chemotherapy regimen. The primary endpoint was the proportion of patients who did not demonstrate disease progression at 6 months. On the basis of a published retrospective analysis of second-line chemotherapy in men with metastatic castration-resistant prostate cancer,³⁸ the expected progression rate by criteria used in this protocol in this patient population at 6 months is 84% (nonprogression rate of 16%). Therefore, if the progression-free rate was 10% or less, there would be little interest in pursuing this therapy further, whereas with a progression-free rate of 30% or more, further study would be proposed.

Given the late time point for measuring progression, a single-stage design was used. By using Fisher exact test, 29 patients were to be accrued. If 7 or more of these 29 patients were progression-free at 6 months, this agent would be felt to be worthy of further evaluation. This design provided for 80% power at the 5% significance level.

Secondary endpoints were to evaluate the safety of vorinostat and to determine the objective response rate in patients with bidimensionally measurable disease, the rate of PSA decline of $\geq 50\%$, and progression-free and overall survival.

Correlative Biology Studies

When designing this trial, we hypothesized that vorinostat-mediated down-regulation of IL-6 activity would be associated with a favorable outcome. However, because all eligible patients were taken off the study before 6 months, this analysis was not possible. Given that IL-6 is associated with the systemic immune response,³⁹ we performed an exploratory analysis to determine whether patients with higher levels of serum IL-6 were more likely to be removed from the protocol for toxicity versus progression.

Pretreatment and on-treatment peripheral blood samples for IL-6 were collected 2 hours after the most recent dose of vorinostat on Day 15 of Cycle 1, Day 1 of Cycle 2, the last week of Cycle 4, and at the time of removal from the study. Quantitative levels of IL-6 were measured using a human IL-6 immunoassay (Quantikine HS, R&D Systems, Minneapolis, Minn) according to the manufacturer's instructions. IL-6 levels were compared between patients removed from the protocol for progression versus toxicity using the Wilcoxon rank sum test.

RESULTS

Between May 2006 and February 2007, 29 patients were registered to the protocol. Two patients were ineligible (because of noncastration testosterone levels or previous treatment with a radiopharmaceutical). Table 1 lists baseline patient characteristics of the 27 eligible patients. The median age was 68 years (range, 54-80 years). Seventy percent of patients had a performance status of 1. Previous chemotherapy treatment for metastatic castration-resistant prostate cancer included docetaxel (92%),

Table 2. Treatment-Related Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue (81%)	7	8	7	0
Nausea (74%)	11	7	2	0
Anorexia (59%)	5	8	3	0
Diarrhea (33%)	9	0	0	0
Vomiting (33%)	8	0	1	0
Dehydration (26%)	4	3	0	0
Weight loss (26%)	7	0	0	0
↓ Platelet count (22%)	4	1	1	0
Taste alteration (22%)	4	2	0	0
↑ Creatinine (19%)	2	3	0	0
Dry mouth (15%)	3	1	0	0
Leukopenia (15%)	3	1	0	0
Urinary frequency (15%)	4	0	0	0
↑ AST (11%)	2	1	0	0
Edema limbs (11%)	3	0	0	0
↓ Hemoglobin (11%)	1	1	1	0
Mucositis oral (11%)	2	1	0	0
Muscle weakness (11%)	3	0	0	0
Thrombosis*	0	0	0	1
Hematuria*	0	0	1	0
Abdominal pain*	0	0	1	0
Pain*	0	0	1	0

AST indicates aspartate aminotransferase.

Grades are based on the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

*All grade 3 and 4 treatment-related adverse events are listed.

paclitaxel (4%), and cyclophosphamide (4%). All patients are off protocol therapy, with a median number of cycles given of 2 (range, 1-7). Seventy percent of patients required dose reduction.

Adverse Events

Forty-eight percent of patients experienced grade 3 or 4 toxicities. There were no grade 5 (treatment-related deaths) adverse events. Table 2 describes in detail toxicities by type and grade, for which 70% of patients required dose reductions. The most common adverse events were fatigue (81%), nausea (74%), anorexia (59%), vomiting (33%), diarrhea (33%), and weight loss (26%). Eleven (41%) patients discontinued therapy because of toxicity (Table 3).

Response and Survival

All eligible patients were off therapy before 6 months (Table 3); 13 (48%) were removed because of progression, 11 (41%) secondary to toxicity, and 3 (11%) for other reasons. The best objective response obtained was stable disease in 2 patients (7%). Duration of stable disease was 84 and 135 days, respectively. No PSA declines of $\geq 50\%$

were observed (Fig. 1). Median time to progression was 2.8 months (range, 0.5-5.3 months), with a median overall survival of 11.7 months (2.3-14 months, with 1 patient censored at 15.1 months). Of note, the 2 additional ineligible patients not included in the final analysis also achieved a best objective response of stable disease.

Correlative Studies

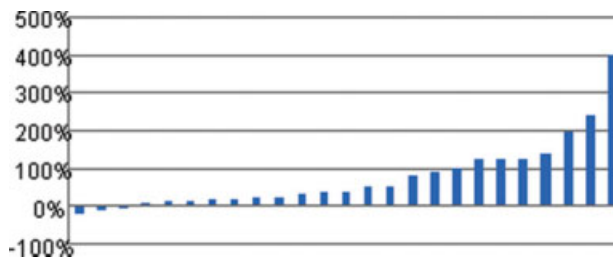
Median IL-6 levels (pg/mL) were higher in patients removed from the protocol for toxicity versus progression at all time points, including baseline (5.2 vs 2.1, $P = .02$), Day 15 Cycle 1 (9.5 vs 2.2, $P = .01$), Day 1 Cycle 2 (9.8 vs 2.2, $P = .01$), and end of study (11.0 vs 2.9, $P = .09$) (Fig. 2).

DISCUSSION

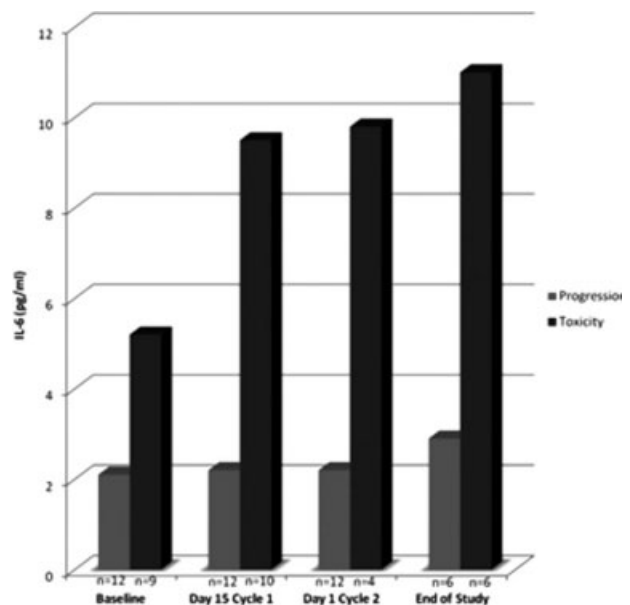
To date there is no established second-line systemic therapy for patients with castration-resistant prostate cancer. Histone deacetylase inhibitors are attractive agents, particularly in prostate cancer, because of a demonstrated effect in vitro on proliferation, differentiation, apoptosis, and angiogenesis coupled with antitumor effects in preclinical prostate cancer models.

Table 3. Treatment Discontinuation by Cycle, N = 27

	Progression	Toxicity	Other	Cumulative No.
Cycle 1	1	3	2	6
Cycle 2	3	6	0	15
Cycle 3	1	0	1	17
Cycle 4	6	1	0	24
Cycle 5	1	0	0	25
Cycle 6	1	0	0	26
Cycle 7	0	1	0	27

**FIGURE 1.** The best percentage prostate-specific antigen (PSA) change from baseline is shown. A PSA waterfall plot represents the best percentage PSA change from baseline for all evaluable patients. No PSA declines of $\geq 50\%$ were observed.

Recognizing that tumor regressions are difficult to quantify objectively in patients with bone metastases, the clinical importance of delaying progression, and the available preclinical data on the antitumor effect of vorinostat, this trial was designed with a primary objective of assessing the effect of vorinostat on 6-month progression rates. Although the most optimal design would have included a control arm, the progressive nature of this disease and the availability of published historical institutional data, at the time of study design, on second-line chemotherapy in a similar population indicating that the expected 6-month progression rate is 84%³⁸ led us to choose a single-arm design. Although 41% of patients were taken off the study because of toxicity, thus making it difficult to assess the true efficacy of vorinostat at this dose and schedule, it is reasonable to assume that, had there been clinically meaningful antitumor activity, better results would have been expected. There was only 1 grade 4 adverse event, and grade 3 adverse events were predominantly constitutional in nature and not significantly different from dose-limiting toxicities observed in phase 1 testing.²¹ However, despite dose reduction in 70% of patients in this trial,

**FIGURE 2.** Serum interleukin-6 (IL-6) values are shown by reason for removal from treatment. Median IL-6 levels (pg/mL) were higher in patients removed from the protocol for toxicity versus progression at all time points, including baseline (5.2 vs 2.1, $P = .02$), Day 15 Cycle 1 (9.5 vs 2.2, $P = .01$), Day 1 Cycle 2 (9.8 vs 2.2, $P = .01$), and end of study (11.0 vs 2.9, $P = .09$)

41% of patients discontinued therapy because of toxicity. Our experience is in contrast to other reports using this agent both as monotherapy and in combination with other systemic therapies in other studies. In the phase 1 trials, once on a tolerable dose, patients could be treated for prolonged periods of time^{21,22,40} with chronic adverse effects of fatigue, renal insufficiency, and weight loss reversible upon discontinuation of the drug.²¹ Dose-limiting toxicities reported in phase 1 trials were not related to prior therapy or type of underlying malignancy and remained unpredictable within treatment cohorts.²¹ They

were also rapidly reversible, suggesting a readily reversible metabolic process.²¹

Safety data from 86 patients with cutaneous T-cell lymphoma treated with vorinostat led to Food and Drug Administration approval of the drug, with only 9.3% of patients removed because of toxicity and 10.5% requiring dose reductions using the same dose/schedule as used in this trial, also in patients who had failed prior systemic therapies.¹⁶ Similar results were recently reported on safety data from 476 patients who participated in the vorinostat clinical trial program, receiving vorinostat as single-agent therapy and in combination with other systemic therapies.⁴¹

The key question is whether our observed results are a function of the patient population studied, lack of significant antitumor activity, or both. Given the toxicity seen in this trial, leading to dose reductions in 70% of patients, it is possible that suboptimal cell inhibitory plasma concentrations of vorinostat may explain why less clinical activity was seen than expected. Without pharmacokinetics data and data from other prostate cancer settings, it is difficult to conclude whether the preclinical models were poor predictors of clinical activity or whether this agent would be more efficacious in an alternative patient population or dosing schedule. One interesting observation from this population is that patients who came off the study because of toxicity had significantly higher serum IL-6 levels at all time points (baseline, Day 15 Cycle 1, Day 1 Cycle, and end of study) as compared with patients removed from the study for progression. It is possible that, because IL-6 is associated with the inflammatory response and regulation of the systemic immune response,³⁹ higher levels of serum IL-6 at baseline that were not modulated by the drug predisposed patients to adverse side effects, leading to treatment discontinuation. IL-6 has been associated with nonresponsiveness to drug therapy.²⁹⁻³¹ However, of the 11 patients taken off the protocol because of toxicity in this study, 9 patients recovered, suggesting drug effect and not disease progression.

Toxicities were also prominent, with no significant clinical activity, in the only other reported clinical trial of histone deacetylase inhibition in prostate cancer.⁴² In this phase 2 trial (n = 31) investigating romidepsin, a bicyclic depsipeptide that inhibits histone deacetylase, as front-line therapy for patients with metastatic castration-resistant prostate cancer, constitutional toxicities were

common, with a 6-month disease control rate of 14% and PSA response rate of 7%. Observations from this trial and ours raise questions regarding the impact of an androgen-suppressed state as it relates to predisposing to toxicities to this class of drugs.

It is not clear why outcomes from clinical investigation of histone deacetylase inhibitors in metastatic castration-resistant prostate cancer have not matched the promising preclinical activity and scientific rationale. However, based on the current data, further investigation of vorinostat at this dose and schedule is not recommended. The lack of significant clinical activity in this trial, coupled with a comparable outcome reported with romidepsin,⁴² raises concerns regarding further study of this class of drugs as single-agent therapy for treatment of castration-resistant prostate cancer, unless newer agents with a more favorable toxicity profile with substantial supportive preclinical data are introduced. Our observation of the association of IL-6 levels and removal from the study for toxicities warrants further investigation.

Conflict of Interest Disclosures

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