A Study to Determine the Effects of Food and Multiple Dosing on the Pharmacokinetics of Vorinostat Given Orally to Patients with Advanced Cancer

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Abstract

Purpose: This phase I study, conducted in advanced-stage cancer patients, assessed the safety and tolerability of oral vorinostat (suberoylanilide hydroxamic acid), single-dose and multiple-dose pharmacokinetics of vorinostat, and the effect of a high-fat meal on vorinostat pharmacokinetics.

Experimental Design: Patients ($n = 23$) received single doses of 400 mg vorinostat on day 1 (fasted) and day 5 (fed) with 48 hours of pharmacokinetic sampling on both days. Patients received 400 mg vorinostat once daily on days 7 to 28. On day 28, vorinostat was given (fed) with pharmacokinetic sampling for 24 hours after dose.

Results: The apparent $t_{1/2}$ of vorinostat was short ($\sim$1.5 hours). A high-fat meal was associated with a small increase in the extent of absorption and a modest decrease in the rate of absorption. A short lag time was observed before detectable levels of vorinostat were observed in the fed state, and T_{max} was delayed. Vorinostat concentrations were qualitatively similar following single-dose and multiple-dose administration; the accumulation ratio based on area under the curve was 1.21. The elimination of vorinostat occurred primarily through metabolism, with <1% of the given dose recovered intact in urine. The most common vorinostat-related adverse experiences were mild to moderate nausea, anorexia, fatigue, increased blood creatinine, and vomiting.

Conclusions: Vorinostat concentrations were qualitatively similar after single and multiple doses. A high-fat meal increased the extent and modestly decreased the rate of absorption of vorinostat; this effect is not anticipated to be clinically meaningful. Continued investigation of 400 mg vorinostat given once daily in phase II and III efficacy studies is warranted.

Histone deacetylases (HDAC) are enzymes that regulate gene transcription and cell signaling pathways through removal of acetyl groups from histone and nonhistone (e.g., p53, α-tubulin, and HSP90) proteins (1). Numerous changes in the structure or expression of HDACs or histone acetyltransferases resulting in aberrant gene transcription and cell signaling have been identified in cancer cells (1, 2). Further-more, decreased levels of acetylated histones in tumor samples have been correlated with a poor clinical outcome (3). HDAC inhibition may correct the transcriptional dysregulation associated with decreased levels of histone acetylation, ultimately benefiting patients with cancer (1).

A number of HDAC inhibitors are currently being developed as antineoplastic agents derived synthetically or from natural sources. These compounds can be divided into several structurally diverse classes, including hydroxamic acids, cyclic tetrapeptides, aliphatic acids, benzamides, carboxylic acids, and electrophilic ketones (4). Individual HDAC inhibitors may preferentially inhibit distinct classes of HDACs and have intrinsically different pharmacokinetic and pharmacodynamic properties (5).

Vorinostat (suberoylanilide hydroxamic acid) is a small-molecule inhibitor of class I and II HDAC enzymes (2) that has shown preclinical activity in numerous cancer models both *in vitro* and *in vivo* (6–9). Vorinostat is currently in clinical development for the treatment of solid and hematologic malignancies, and clinical activity has been achieved in patients with a variety of malignancies, including cutaneous T-cell lymphoma (10–14). The most common adverse experiences associated with oral vorinostat in phase I and II trials have included fatigue, nausea, vomiting, and diarrhea (10, 11, 13, 14).

Table 1. Patient disposition

Characteristic	N = 23
Male, *n* (age range), median age, y	11 (39-84), 63
Female, *n* (age range), median age, y	12 (41-74), 62
Cancer diagnosis	
Lung	5
Breast	4
Colon	3
Mesothelioma	3
Prostate	2
Bladder	1
Ovarian	1
Gastric	1
Osteogenic sarcoma	1
Testicular germ cell	1
Renal cell	1
Prior systemic anticancer therapies, *n*	
1	0
2	3
≥3	20
Prior radiation therapies, *n*	
1	3
2	4
≥3	4
Discontinued, *n*	9
Clinical adverse experience	7
Progressive disease	1
Withdrew consent	1
Completed trial, *n*	14*

*Patients who completed Day 28 dosing and pharmacokinetics.

The primary objectives of this study were (*a*) to obtain serum pharmacokinetic data of vorinostat after single-dose and multiple-dose administration in patients with advanced cancer and (*b*) to obtain single-dose serum pharmacokinetic data of vorinostat in the fasted state and following a standard high-fat meal. A secondary objective was to evaluate the urinary excretion of intact drug and two inactive metabolites (vorinostat glucuronide and 4-anilino-4-oxobutanoic acid), both thought to be important human metabolites, following administration of oral vorinostat. In preclinical studies, these metabolites did not inhibit HDAC1 activity or cell proliferation at concentrations ≤10 μmol/L.[3]

Materials and Methods

This open-label, nonrandomized phase I trial was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School, and written informed consent was obtained from all patients before enrollment.

Eligibility criteria. Patients ≥18 years of age with histologically confirmed malignancies (including solid tumors, hematologic malignancies, and lymphoma) that were metastatic or unresectable and for which standard curative or palliative measures did not exist or were no longer effective were eligible for enrollment. Patients must also have had an Eastern Cooperative Oncology Group performance status of ≤2 and a life expectancy of >3 months. Patients must not have had received

tumor directed immunologic therapy, radiation therapy, surgery, chemotherapy, or other investigational agents within 4 weeks of the study (except thyroid replacement or gonadotropin-releasing hormone therapy). Patients must not have received other experimental HDAC inhibitors, high-dose chemotherapy with stem cell rescue, or radiation to >25% of total bone marrow. Other exclusion criteria included the following: history of unstable anemia, gastrointestinal resection, leukemia or lymphoma with central nervous system or testicular involvement, active central nervous system involvement of disease, uncontrolled intercurrent illness, active hepatitis B or C infection, HIV or known HIV-related malignancy, pregnancy, lactation, abnormal bone marrow function [leukocyte count <3,500/μL, absolute neutrophil count <1,500/μL (solid tumor) or <500/μL (leukemia), and platelets <100,000/μL (solid tumor) or <50,000/μL (leukemia)], hepatic insufficiency (total bilirubin >1.5 times the upper limit of normal, aspartate aminotransferase/alanine aminotransferase >2.5 times the upper limit of normal, prothrombin time/activated partial thromboplastin >1.2 times the upper limit of normal), or renal insufficiency (creatinine >2 times the upper limit of normal or creatinine clearance ≤60 mL/min).

Treatment schema and study design. Single-dose pharmacokinetics were assessed in the fasted state and after a high-fat meal. The standard high-fat meal contained ∼900 to 1,000 total calories, including 500 to 600 calories of fat, 150 calories of protein, 250 calories of carbohydrates. Following continuous dosing for 22 days, multiple-dose pharmacokinetics were assessed after administration of a high-fat meal. Patients received a single oral dose of 400 mg vorinostat in the fasted state on the morning of day 1 and following a standard high-fat meal on the mornings of days 5 and 28. Patients received single daily oral doses of 400 mg vorinostat on days 7 through 27 and were advised to take these doses with food. Anti-emetics were not given prophylactically but were permitted for symptomatic relief of nausea and vomiting. Blood and/or urine samples for pharmacokinetic assays were collected before dose and at various times/intervals after dose on days 1, 5, 15, and 28 as described below. Completion of the study was defined as having completed day 28 dosing and pharmacokinetics. If not contraindicated, patients continued to receive vorinostat as part of an extension phase of the parent study or in a separate continuation protocol.

Treatment with vorinostat was allowed to be held for grade 3/4 drug-related adverse experiences (except grade 3 anemia or grade 3 thrombocytopenia without bleeding) and/or grade 3/4 non–drug-related adverse experiences at the investigator's discretion. Patients who required any dose interruption or reduction, or discontinuation during the first 28 days of drug administration were not included in subsequent pharmacokinetic analyses. Upon resolution of an adverse experience, treatment with oral vorinostat was allowed to be restarted
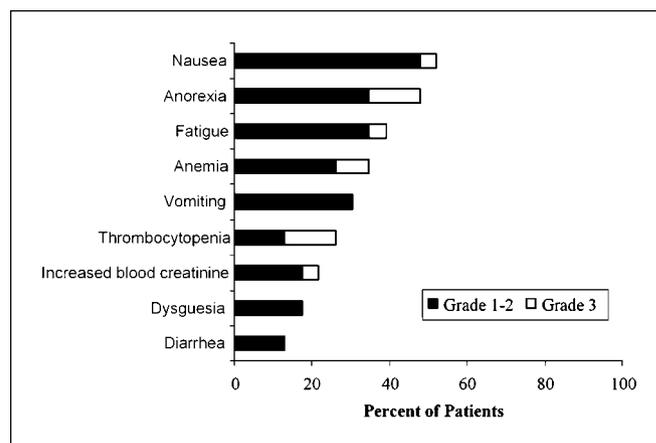

Fig. 1. Most common vorinostat-related adverse experiences.

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[3] V. Richon, personal communication.

Table 2. PK parameters of vorinostat following oral administration of single or multiple doses of 400 mg

Dose	Single dose	Single dose	Multiple doses*	GMR	*P*
Diet	Fasted	Fed	Fed	—	—
N	23	20	14		
$AUC_{0-\infty}$, µmol/L h[†] (range)	3.87 (2.33-9.86)	5.33 (3.41-9.34)	—	1.38[‡]	<0.001[‡]
$AUC_{0-24\ h}$, µmol/L h[†] (range)	3.82 (2.31-9.85)	5.33 (3.51-9.24)	6.46 (4.06-10.47)	1.21[§,‖]	0.019[§]; 0.010[‖]
C_{max}, µmol/L[†] (range)	1.12 (0.56-1.76)	1.02 (0.43-2.98)	1.13 (0.46-2.64)	0.91[‡]	0.451[‡]
T_{max}, h[¶] (range)	1.50 (0.5-1.52)	4.00 (2.0-10.0)	4.21 (0.5-14.0)	—	<0.001[‡]; 0.869**
Apparent $t_{1/2}$, h[††] (range)	1.74 (0.93-18.44)	1.44 (0.79-3.77)	1.34 (0.83-3.88)	—	0.036[‡]
f_e[‡‡] (range)	0.0021 (0.0001-0.0051)	0.0030 (0.0008-0.0089)	0.0037 (0.001-0.0092)	—	—

Abbreviation: GMR, geometric mean ratio.
*Once daily for 22 days.
[†] Geometric mean.
[‡] Single dose fed/single dose fasted.
[§] Accumulation ratio: $AUC_{0-24\ h}$ multiple dose fed/$AUC_{0-24\ h}$ single dose fed.
[‖] Linearity ratio: $AUC_{0-24\ h}$ multiple dose fed/AUC_{0-8} single dose fed.
[¶] Median.
**Multiple dose fed/single dose fed.
[††] Harmonic mean.
[‡‡] f_e = fraction of dose excreted unchanged in urine; data are arithmetic mean (single dose fasted, *n* = 22; single dose fed, *n* = 21; multiple dose fed, *n* = 12).

at either the original dose (400 mg, once daily) or a reduced dose of 300 mg once daily. A second reduction to 300 mg once daily for 5 days out of 7 was also allowed. The maximal number of dose reductions allowed per patient was two. Patients could continue on treatment until disease progression, intolerable toxicity, withdrawal of consent, or for other reasons related to the patient's best interests, or at the investigator's discretion.

Evaluation. Safety and tolerability were assessed by measurements of vital signs, performance status, 12-lead electrocardiograms, and routine laboratory safety tests (complete blood count, serum chemistries, coagulation profiles, and urinalyses). Electrocardiogram QTc interval changes were assessed by comparing pretreatment baseline values with those during treatment (at 2, 6, and 24 hours after dose on day 1; 2 hours after dose on day 5; before dose on day 15; and 2 and 24 hours after dose on day 28). All clinical adverse experiences were evaluated by the investigator with respect to intensity (National Cancer Institute Common Terminology Criteria, version 3.0), seriousness, action taken, and relationship to vorinostat.

The primary serum pharmacokinetic variables of vorinostat that were calculated included area under the curve (AUC), maximum concentration (C_{max}) and its time of occurrence (T_{max}), apparent terminal half-life ($t_{1/2}$), and accumulation ratio. These pharmacokinetic variable values were also calculated for two inactive metabolites of vorinostat (*O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid), and the total recovery of vorinostat and these two metabolites in urine was determined.

Pharmacokinetic assay. Five milliliters of blood samples were collected in red-top vacutainer tubes (no anticoagulant) for pharmacokinetic assays before dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, and 48 hours after dose on days 1 and 5; before dose on day 15; and before dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose on day 28. Blood samples were allowed to clot at room temperature for 30 minutes, centrifuged at 2,000 × *g* for 15 minutes at 4°C, and stored at −70°C until analysis.

Urine samples were obtained before dose and at the intervals of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after dose on days 1, 5, and 28. Urine collected within each interval was pooled for each patient; total volume was measured (to the nearest 5 mL); and a 4-mL aliquot was removed and stored at −70°C until analysis.

Serum and urine vorinostat and two of its inactive metabolites (*O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid) were analyzed using a turbulent flow on-line extraction format for analyte

isolation followed by reversed-phase high-performance liquid chromatography with tandem mass spectrometric detection (15).

Pharmacokinetic analysis. Individual serum concentrations were used to estimate vorinostat, *O*-glucuronide of vorinostat, and 4-anilino-4-oxobutanoic acid pharmacokinetic variables, AUC_{0-8}, $AUC_{0-24\ h}$, C_{max}, T_{max}, apparent terminal $t_{1/2}$, and accumulation ratio, as appropriate. The software package WinNonlin Enterprise version 5.0.1 was used for the calculations. The apparent terminal $t_{1/2}$ was estimated from the best-fit variables of a single exponential to the log-linear portion of the serum concentration/time curve using unweighted linear regression. AUC_{0-8} was calculated using the linear up/log down method up to the last measured concentration and the additional area estimated from that concentration and the value of apparent terminal $t_{1/2}$ estimated for that administration. $AUC_{0-24\ h}$ was calculated using the linear up/log down method. C_{max} and T_{max} were obtained by inspection of the concentration/time data. The accumulation ratio following multiple dosing was calculated from the ratio of $AUC_{0-24\ h}$ values from the last dose of multiple dosing in the fed state to the single dose in the fed state. The geometric mean ratio of the AUC during a dosing interval at steady state (following the last daily dose) in the fed state to AUC_{0-8} following a single dose in the fed state was calculated for vorinostat to assess pharmacokinetic linearity.

Urinary concentrations of vorinostat, the *O*-glucuronide of vorinostat, and 4-anilino-4-oxobutanoic acid from individual collection intervals were used to calculate the total recovery of vorinostat and these two metabolites in urine, expressed as percentage of the dose.

Statistical analysis. The individual values of vorinostat AUC and C_{max} were natural log-transformed and evaluated in mixed effect models, which contained day as a fixed effect and subject as a random effect. The day effect had three levels (days 1, 5, and 28), corresponding to single dose fasted, single dose fed, and multiple dose fed treatments, respectively. For AUC_{0-8} analysis, only day 1 and 5 data were included in the model because day 28 data were not available. For $AUC_{0-24\ h}$ and C_{max} analyses, all data (days 1, 5, and 28) were included in the model. For the linearity ratio of $AUC_{0-24\ h}$ multiple dose fed/AUC_{0-8} single dose fed, AUC_{0-8} on day 1 and day 5 and $AUC_{0-24\ h}$ on day 28 data were included.

Two-sided 95% confidence intervals for the true means of log AUC and log C_{max} were calculated using the least-squares means and the mean square error from the mixed models. These limits were exponentiated to obtain the corresponding 95% confidence intervals for the true geometric means for AUC and C_{max}. The least-squares means for

log AUC and log C_{max} were exponentiated to obtain the estimated geometric means. Similarly, the two-sided 90% confidence intervals for the true mean differences in log AUC or log C_{max} were calculated based on the mixed models. These limits were exponentiated to obtain the corresponding 90% confidence intervals for the true geometric mean ratio (AUC_{0-8} single dose fed/AUC_{0-8} single dose fasted, $AUC_{0-24 h}$ multiple dose fed/AUC_{0-8} single dose fed, $AUC_{0-24 h}$ multiple dose fed/$AUC_{0-24 h}$ single dose fed, C_{max} single dose fed/C_{max} single dose fasted). The least-squares means for the differences in log AUC or log C_{max} were exponentiated to obtain the estimated geometric mean ratios. Ps were also obtained from the models.
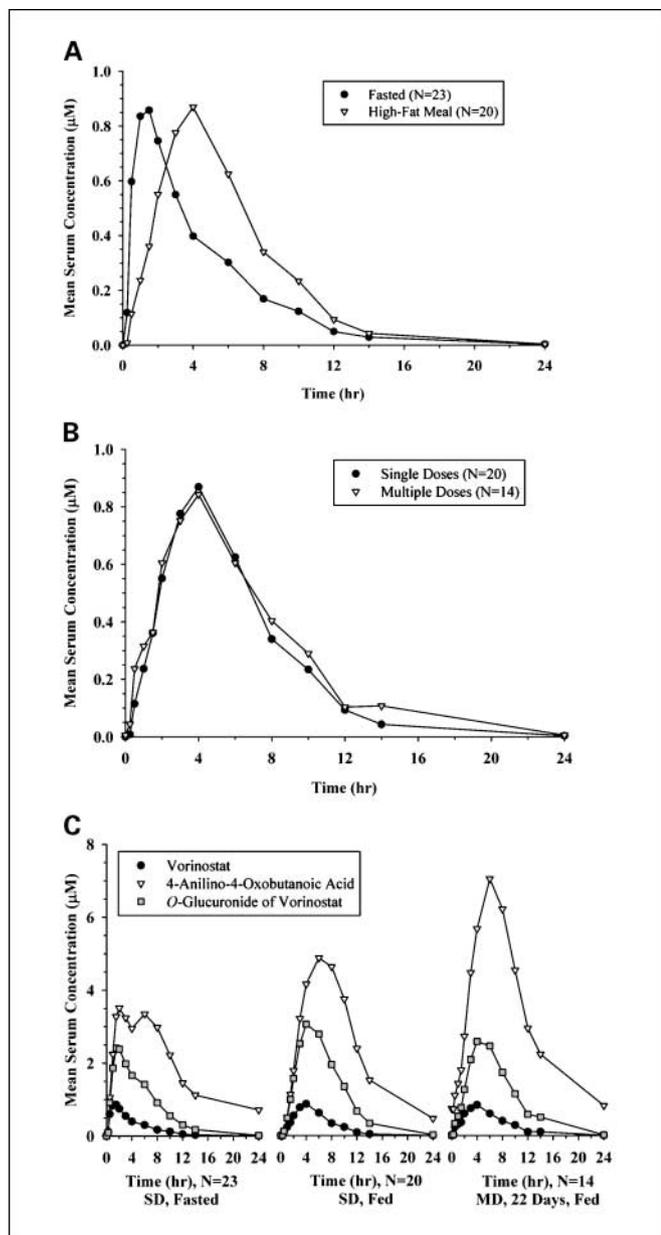
Fig. 2. Serum concentration time profiles. *A,* mean serum concentrations of vorinostat following administration of a single 400 mg oral dose in the fasted state and following administration a high-fat meal. *B,* mean serum concentrations of vorinostat following oral administration of single or multiple 400 mg doses after a high-fat meal. *C,* mean serum concentrations of vorinostat and two inactive metabolites following oral administration of single or multiple 400 mg doses in the fasted state and after a high-fat meal.

The individual values of T_{max} on days 1, 5, and 28 were given ranks. Ps of the comparisons (single dose fed/single dose fasted and multiple dose fed/single dose fed) were obtained by applying the same mixed effect model used for C_{max} to the ranks of T_{max}. The individual values of apparent $t_{1/2}$ on days 1, 5, and 28 were inverse transformed. Harmonic mean on each day was obtained from data only on that day. Ps for the comparison (single dose fed/single dose fasted) were obtained by applying the same mixed effect model used for C_{max} on the inverse-transformed $t_{1/2}$. No missing values were imputed for the pharmacokinetic analyses.

Results

The study was initiated on November 18, 2004 and completed on July 29, 2005.

Patient disposition. The baseline characteristics of the 23 patients enrolled in this study are shown in Table 1. Seventy-eight percent of the patients had a study diagnosis of stage IV cancer, and only one did not have metastatic disease at baseline. All had received at least two prior systemic anticancer therapies, and almost half had received prior radiation therapy. Fourteen patients completed the study and continued on vorinostat treatment in the continuation phase of this study or in a separate continuation protocol. Nine patients were discontinued from the study before completing day 28 pharmacokinetics for one of the following reasons: progressive disease ($n = 1$), clinical adverse experiences ($n = 7$), and withdrawal of consent ($n = 1$).

Adverse experiences. The most common vorinostat-related adverse experiences included nausea (52%), anorexia (48%), and fatigue (39%; Fig. 1). These experiences were mostly mild to moderate in severity. Anorexia (13%) and thrombocytopenia (13%) were the most commonly reported grade 3 vorinostat-related adverse experiences and typically resolved upon dose reduction, dose interruption, or no action taken with a median time to resolution of 8 days. There were no grade 4 adverse experiences attributed to vorinostat in this study. There were no deaths on study.

Interruptions, discontinuations, and dose reductions due to adverse experiences. Seven patients had treatment with vorinostat interrupted and discontinued from the study due to adverse experiences. Five of these patients had treatment interrupted due to vorinostat-related adverse experiences (grade 3 thrombocytopenia, grade 3 thrombocytopenia and grade 3 asthenia, grade 3 thrombocytopenia and grade 2 increased creatinine, grade 2 thrombocytopenia and grade 3 anorexia, and grade 3 increased blood creatinine). Although two of these interruptions were not necessary per protocol, vorinostat treatment was interrupted in the best interest of these patients. Two patients had treatment interrupted due to non–vorinostat-related adverse experiences (grade 3 nausea and grade 3 vomiting and grade 3 bacteremia).

There were a total of three dose reductions. Two of the seven patients described above had their dose of study drug reduced to 300 mg once daily because of vorinostat-related grade 3 thrombocytopenia, and one patient was dose reduced because of non–vorinostat-related grade 3 bacteremia.

Pharmacokinetics. A summary of the pharmacokinetic variables for vorinostat across all treatments is presented in Table 2. A high-fat meal was associated with a small increase in the extent of vorinostat absorption (AUC_{0-8} increased 38%; $P < 0.001$) and a modest decrease in the rate of vorinostat

Table 3. Mean urinary recovery of vorinostat and two inactive metabolites following oral administration of single or multiple oral of 400 mg

Dose	Diet	N	Analyte	Urinary recovery, mean % dose (SD)	Total recovery (% dose)
400 mg single dose	Fasted	22	Vorinostat	0.2 (0.1)	34.9
			OG-V	10.7 (5.9)	
			4A4OA	24.0 (8.6)	
400 mg single dose	Fed	21	Vorinostat	0.3 (0.2)	50.5
			OG-V	18.2 (6.2)	
			4A4OA	31.9 (10.6)	
400 mg once daily × 22 d	Fed	12	Vorinostat	0.4 (0.2)	52.3
			OG-V	15.9 (5.9)	
			4A4OA	36.0 (8.6)	

Abbreviations: 4A4OA, 4-anilino-4-oxobutanoic acid; OG-V, *O*-glucuronide of vorinostat.

absorption (2.5-hour delay in T_{max}; Fig. 2A). However, these small effects are not expected to be clinically meaningful. C_{max} was not statistically different following vorinostat dosing in the fed and fasted states.

Trough concentrations following multiple dosing were below the limit of quantification in most patients, which is consistent with the observed short apparent $t_{1/2}$. Multiple-dose pharmacokinetic data showed that vorinostat plasma concentration time profiles following 22 days of daily dosing were similar to those observed following a single dose. The AUC accumulation ratio (multiple dose $AUC_{0-24\ h}$/single dose $AUC_{0-24\ h}$) was 1.21 (P = 0.019). No accumulation was expected with once daily dosing; however, it is possible that intraindividual variability contributed to a slightly higher ratio. The T_{max} after single and multiple doses were comparable (Table 2; P = 0.869; Fig. 2B).

Regarding the two inactive metabolites of vorinostat, mean serum exposures (AUC) of the *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid metabolites were on average 3- to 4-fold and 10- to 13-fold higher, respectively, than that of vorinostat (Fig. 2C). The apparent terminal half-life of the *O*-glucuronide of vorinostat metabolite (∼1.8 hours) was similar to that of vorinostat, whereas that of the 4-anilino-4-oxobutanoic acid metabolite was much longer (∼6 to 9 hours). Consistent with its longer half-life, 4-anilino-4-oxobutanoic acid accumulated to some extent with multiple dosing, whereas the *O*-glucuronide of vorinostat did not (Fig. 2C).

Recovery of vorinostat unchanged in urine was low (<1% of the dose; Table 3). Recovery of the two inactive vorinostat metabolites in urine was more substantial: ∼10% to 18% as the *O*-glucuronide of vorinostat and ∼24% to 36% as 4-anilino-4-oxobutanoic acid. Total recovery of vorinostat and these two inactive metabolites was ∼35% to 52% of the dose.

Exploratory analyses. An analysis of electrocardiograms at baseline and at various times during vorinostat treatment suggested that vorinostat did not increase QTc intervals to a clinically meaningful extent. The maximum QTc change from baseline was ≤30 ms in 18 patients and >30 to ≤60 ms in 5 patients. None of the 23 patients had a QTc change >60 ms, and there were no QTc prolongation adverse experiences during the study. No patient had a QTc interval of ≥500 ms. Two patients had a maximum QTc interval of ≥480 to <500 ms occur on day 1 at 6 hours after dose; neither patient had cardiac-related adverse experiences.

Another analysis compared the frequency of the most commonly reported grade ≥2 drug-related adverse experiences with vorinostat AUC. The patients with $AUC_{0-\infty}$ below the median at day 5 experienced five grade ≥2 vorinostat-related adverse experiences, whereas those with $AUC_{0-\infty}$ above the median at day 5 experienced 19 grade ≥2 vorinostat-related adverse experiences. Furthermore, five of the six patients with the highest day 5 $AUC_{0-\infty}$ required a dose interruption or reduction due to a drug-related adverse experience that prevented them from completing the study. The most frequent of these experiences were thrombocytopenia and anorexia.

There were no significant associations between AUC or C_{max} and gender, race, age, body surface area, or weight. Therefore, normalization of dosing based on these factors may not be necessary.

Activity. Fourteen patients who completed this study continued on vorinostat treatment in an extension phase of the study or in a separate continuation trial. One of these patients (with stage IV granulosa cell ovarian cancer) achieved a partial response by the Response Evaluation Criteria in Solid Tumors (16) as shown by a substantive reduction in abdominal disease. Response was noted after 11 months of treatment with current treatment duration of ≥18 months (Fig. 3). Before receiving vorinostat, the patient had received bleomycin with cisplatin and etoposide, doxorubicin, tamoxifen, carboplatin, leuprolide, topotecan, paclitaxel, and an experimental medication. Another patient (with stage IV breast cancer) has maintained stable disease for ≥15 months. A third patient (with stage IV non–small cell lung cancer) maintained stable disease for 10.8 months.

Discussion

Consistent with the results of previous trials with oral vorinostat (10, 11, 13, 14), short-term administration of 400 mg vorinostat given once daily was generally well tolerated with the most common vorinostat-related adverse experiences being nausea, anorexia, fatigue, increased blood creatinine, and vomiting. Overall, these experiences were generally mild to moderate in severity. Unlike certain other HDAC inhibitors (17–22), vorinostat was not associated with clinically significant cardiac or neurologic toxicity in this study.

Multiple-dose pharmacokinetic data showed that vorinostat plasma concentration time profiles following 22 days of daily
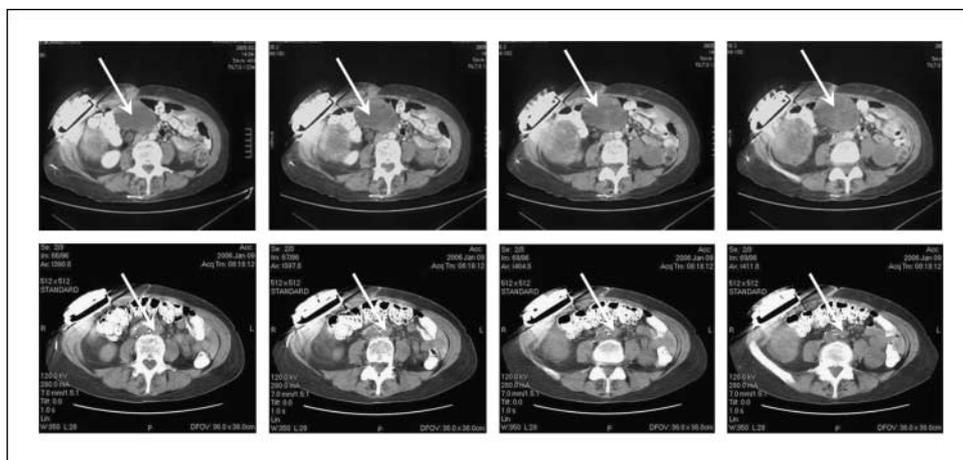
Fig. 3. Computerized tomography images at baseline (*top*) and at 11 months (*bottom*) after initiation of vorinostat therapy in a patient with stage IV granulosa cell ovarian cancer. The arrows indicate a large anterior abdominal mass that decreased in size significantly during the 11-month interval. The patient achieved a partial response by the Response Evaluation Criteria in Solid Tumors.

dosing were similar to those observed following a single dose. Compared with a single dose, there was a slight accumulation of vorinostat after administration of multiple doses (once-daily dosing) with an average $AUC_{0-24 \, h}$ accumulation ratio of 1.21. With regard to the effect of taking vorinostat with food, a high-fat meal was associated with a small increase in the extent of absorption of vorinostat (AUC_{0-8} increased 38%) and a modest decrease in the rate of absorption (2.5-hour delay in T_{max}). Because the small effect of food on the pharmacokinetics of vorinostat is not expected to be clinically meaningful, these data support the schedule of once daily dosing with food, which was a recommended schedule and administration method in other studies (10, 13).

The elimination of vorinostat occurred primarily through metabolism, with <1% of an given dose recovered intact in urine. Two inactive metabolites (*O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid) circulated to a substantially greater extent than vorinostat and accounted for up to ~50% of the dose of vorinostat recovered in urine.

Pharmacokinetic analyses indicated an ~3- to 4-fold variability in systemic exposure in patients given a 400-mg oral dose of vorinostat in the presence or absence of food. An exploratory analysis comparing vorinostat day 5 AUC_{0-8} with the frequency of specific drug-related grade ≥2 adverse experiences provided some evidence that higher vorinostat exposures were associated with an increased incidence of drug-related adverse experiences. Patients with a day 5 AUC_{0-8} above the median had a nearly four times greater incidence of grade ≥2 adverse experiences than patients whose day 5 AUC_{0-8} fell below the median. Moreover, five of the six patients with the highest day 5 exposures required either a dose interruption or reduction due to drug related adverse experiences and did not complete the study. The three patients with the longest duration of vorinostat treatment had day 5 AUC_{0-8} below the median.

Although antitumor activity was not an end point of the study, there was evidence of anticancer activity of vorinostat shown in one patient with metastatic ovarian cancer who achieved and maintained a partial response and has been receiving vorinostat for >1.5 years. Two other patients, one with stage IV breast cancer and one with stage IV non–small cell lung cancer, have maintained stable disease for >10 months.

In conclusion, a high-fat meal has a small but statistically significant effect on vorinostat pharmacokinetics. However, this effect is not anticipated to be clinically relevant. Additionally, the concentration/time profiles of this drug are qualitatively similar after single and multiple doses. The results of this study support continued investigation of 400 mg vorinostat given daily. The efficacy and safety of oral vorinostat in advanced cancer patients are being further evaluated in ongoing phase II and III trials.

References

1. Bhalla KN. Epigenetic and chromatin modifiers as targeted therapy of hematologic malignancies. J Clin Oncol 2005;23:3971–93.
2. Marks P, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. Nat Rev Cancer 2001;1:194–202.
3. Seligson DB, Horvath S, Shi T, et al. Global histone modification patterns predict risk of prostate cancer recurrence. Nature 2005;435:1262–6.
4. Marks PA, Richon VM, Kelly WK, Chiao JH, Miller T. Histone deacetylase inhibitors: development as cancer therapy. Novartis Found Symp 2004;259:269–81.
5. Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 2006;6:38–51.
6. Glick RD, Swendeman SL, Coffey DC, et al. Hybrid polar histone deacetylase inhibitor induces apoptosis and CD95/CD95 ligand expression in human neuroblastoma. Cancer Res 1999;59:4392–9.
7. He LZ, Tolentino T, Grayson P, et al. Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia. J Clin Invest 2001;108:1321–30.
8. Heider U, Kaiser M, Sterz J, et al. Histone deacetylase inhibitors reduce VEGF production and induce growth suppression and apoptosis in human mantle cell lymphoma. Eur J Haematol 2006;76:42–50.
9. Mitsiades N, Mitsiades CS, Richardson PG, et al. Molecular sequelae of histone deacetylase inhibition in human malignant B cells. Blood 2003;101:4055–62.
10. Duvic M, Talpu R, Zhang C, Goy A, Richon V, Frankel SR. Phase II trial of oral suberoylanilide hydroxamic acid (SAHA) for cutaneous T-cell lymphoma (CTCL) unresponsive to conventional therapy. J Clin Oncol 2005;23:577s.
11. Garcia-Manero G, Yang H, Sanchez-Gonzalez B, et al. Final results of a phase I study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with leukemia and myelodysplastic syndrome. Blood 2005;106:785a.
12. Kelly WK, Richon VM, O'Connor O, et al. Phase I clinical trial of histone deacetylase inhibitor: suberoylanilide hydroxamic acid administered intravenously. Clin Cancer Res 2003;9:3578–88.
13. Kelly WK, O'Connor OA, Krug LM, et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. J Clin Oncol 2005;23:3923–31.
14. O'Connor OA, Heaney ML, Schwartz L, et al. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. J Clin Oncol 2005;24:166–73.
15. Du L, Musson DG, Wang AQ. High turbulence liquid chromatography online extraction and tandem mass spectrometry for the simultaneous determination of suberoylanilide hydroxamic acid and its two

metabolites in human serum. Rapid Commun Mass Spectrom 2005;19:1779–87.

16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92: 205–16.

17. Gore SD, Weng LJ, Figg WD, et al. Impact of prolonged infusions of the putative differentiating agent sodium phenylbutyrate on myelodysplastic syn-dromes and acute myeloid leukemia. Clin Cancer Res 2002;8:963–70.

18. Pilatrino C, Cilloni D, Messa E, et al. Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid. Cancer 2005;104:101–9.

19. Raffoux E, Chaibi P, Dombret H, Degos L. Valproic acid and all-trans retinoic acid for the treatment of elderly patients with acute myeloid leukemia. Haematologica 2005;90:986–8.

20. Rowinsky EK, Pacey S, Patnaik A, et al. A phase I, pharmacokinetic (PK) and pharmacodynamic (PD) study of a novel histone deacetylase (HDAC) inhibitor LAQ824 in patients with advanced solid tumors. J Clin Oncol 2004;22:3022.

21. Sandor V, Bakke S, Robey RW, et al. Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res 2002;8:718–28.

22. Shah MH, Binkley P, Chan K, et al. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. Clin Cancer Res 2006;12:3997–4003.

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