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ORIGINAL REPORT

Pediatric Phase I Trial and Pharmacokinetic Study of Vorinostat: A Children's Oncology Group Phase I Consortium Report

Maryam Fouladi, Julie R. Park, Clinton F. Stewart, Richard J. Gilbertson, Paula Schaiquevich, Junfeng Sun, Joel M. Reid, Matthew M. Ames, Roseanne Speights, Ashish M. Ingle, James Zwiebel, Susan M. Blaney, and Peter C. Adamson

From the St Jude Children's Research Hospital, Memphis, TN; Seattle Children's Hospital, Seattle, WA; Children's Oncology Group Operations Center, Arcadia, CA; Mayo Clinic College of Medicine, Rochester, MN; Baylor College of Medicine; Texas Children's Cancer Center/Baylor College of Medicine, Houston, TX; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; and the Children's Hospital of Philadelphia, Philadelphia, PA.

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Corresponding author: Maryam Fouladi, MD, Division of Hematology-Oncology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH, 45229; e-mail: maryam.fouladi@cchmc.org.

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ABSTRACT

Purpose
The purpose of this study was to determine the maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetics of vorinostat administered as a single agent and in combination 13-cis retinoic acid (13cRA) in children with refractory solid tumors; to evaluate the tolerability of the solid tumor MTD in children with refractory leukemias; and to characterize the pharmacokinetics of a vorinostat suspension in children.

Patients and Methods
Vorinostat was administered orally daily starting at 180 mg/m^2/d with escalations planned in 30% increments. Pharmacokinetic studies were performed with the initial dose. Acetyl-histone (H3) accumulation was assessed by Western blotting of peripheral blood mononuclear cells (PBMC).

Results
Sixty-four patients were enrolled on this multipart trial. In patients with solid tumors, the MTD was 230 mg/m^2/d with dose-limiting neutropenia, thrombocytopenia, and hypokalemia at 300 mg/m^2/d. DLTs observed with the combination of 13cRA and vorinostat included thrombocytopenia, neutropenia, anorexia, and hypertriglyceridemia, resulting in a MTD of vorinostat 180 mg/m^2/d 4 times per week and 13cRA 80 mg/m^2/dose twice per day, days 1 through 14 every 28 days. Wide interpatient variability was noted in vorinostat disposition, with area under the concentration-time curves at 230 mg/m^2/d for the capsule (range, 1,415 to 9,291 ng/mL × hr) and oral suspension (range, 1,186 to 4,780 ng/mL × hr). Significant accumulation of acetylated H3 histone in PBMC was observed after administration of vorinostat, particularly at higher doses. One patient with neuroblastoma experienced a complete response to the combination.

Conclusion
In children with recurrent solid tumors, vorinostat is well-tolerated at 230 mg/m^2/d, with a modest dose reduction being required when combining vorinostat with 13cRA. Drug disposition is similar to that observed in adults.

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INTRODUCTION

Deregulation of histone acetylation plays an important role in the pathogenesis of many malignancies by altering chromatin structure and gene transcription.[1-7] Thus, histone deacetylase (HDAC) inhibition leads to histone acetylation, an open chromatin structure, and expression of previously silenced genes.[8] In preclinical studies, HDAC inhibitors induce growth arrest, activate apoptotic pathways, autophagic cell death, and cell death through induction of reactive oxygen species.[9] Vorinostat, an oral HDAC inhibitor of class I and II HDACs, has antitumor activity in vitro[7] and in vivo[10] and can alter vascular endothelial growth factor signaling.[11,12] When evaluated in the Pediatric Preclinical Testing Program, activity was observed in an in vitro panel of tumors and significant differences in event-free survival were noted in 16 of 30 solid tumor xenografts.[10] Additive or synergistic preclinical and/or clinical activity of vorinostat has also been reported in combination with antiangiogenic agents,[13] 5-aza-2′-deoxycytidine,[14,15] and 13-cis-retinoic acid (13cRA).[7,16-18] Vorinostat, indicated for the treatment of cutaneous T-cell lymphoma,[19,20] is well-tolerated by adults at daily doses of 400 mg.[4,20] Dose-limiting toxicities (DLTs) include fatigue, anorexia, diarrhea, nausea, vomiting, and

thrombocytopenia. Recent trials have demonstrated activity in acute myeloid leukemia[4] and B-cell lymphoma.[21]

We report the results of a phase I trial of vorinostat alone and in combination with 13cRA in children with recurrent or refractory malignancies. The primary objectives were (part A) to estimate the maximum-tolerated dose (MTD), determine the DLTs, and characterize the pharmacokinetics of single-agent vorinostat in children with solid tumors; (part B) to assess the tolerability of vorinostat administered at the solid tumor MTD in patients with recurrent or refractory leukemia; (part C) to estimate the MTD and determine the DLTs of vorinostat administered in combination with 13cRA in patients with recurrent neuroblastoma, medulloblastoma, CNS primitive neuroectodermal tumor (PNET) or atypical teratoid rhabdoid tumor (ATRT); and (part D) to characterize the pharmacokinetics of vorinostat when administered as a suspension at the solid tumor MTD for the capsule formulation. The secondary objectives were to assess the biologic activity of vorinostat by measuring histone acetylation status in peripheral blood mononuclear cells (PBMCs) and to preliminarily evaluate its antitumor activity.

PATIENTS AND METHODS

Patient Eligibility

Patients older than 12 months and younger than 22 years with measurable or evaluable tumors refractory to therapy were eligible. Histologic verification of malignancy was required except for patients with intrinsic brainstem glioma. Eligible diagnoses included patients with recurrent or refractory solid tumor (parts A, D); leukemia with more than 25% blasts in the bone marrow (part B); neuroblastoma, medulloblastoma, CNS PNET or ATRT (part C). Other eligibility criteria included: Lansky or Karnofsky score ≥ 60; body-surface area of ≥ 0.5 m^2; recovery from the acute toxic effects of prior therapy; ≥ 3 months since total-body irradiation, craniospinal or hemi-pelvic radiation and ≥ 2 months since a stem-cell transplant; adequate bone marrow function for patients with solid tumors (peripheral absolute neutrophil count $\geq 1{,}000/\mu$L, platelets $\geq 100{,}000/\mu$L [transfusion independent], hemoglobin ≥ 8.0 g/dL), for patients with leukemia (part B) platelets $\geq 20{,}000/\mu$L, hemoglobin ≥ 8.0 g/dL; adequate renal function (age-adjusted normal serum creatinine or a glomular filtration rate ≥ 70 mL/min/1.73 m^2), adequate liver function (total bilirubin $\leq 1.5\times$ institutional upper limit of normal for age, ALT $\leq 5\times$ institutional upper limit of normal for age and albumin ≥ 2 g/dL). Patients who were to receive 13cRA (part C) had to have $\leq$ grade 1 skin toxicity, serum triglycerides lower than 300 mg/dL, a negative urine dipstick for protein, or lower than 1,000 mg/24 hour urine collection, and no gross hematuria. Patients were excluded if they had received valproic acid in the previous 2 weeks, were on enzyme-inducing anticonvulsants, or other noncytotoxic anticancer agents, were pregnant or lactating or had uncontrolled infections. Patients with solid tumor with bone marrow involvement and patients with active CNS leukemia were excluded. Patients with CNS malignancies receiving dexamethasone had to be on a stable or decreasing dose for ≥ 7 days before study enrollment.

The institutional review boards of participating institutions approved the protocol. Informed consent and assent, as appropriate, were obtained according to local institutional guidelines.

Drug Administration and Study Design

Vorinostat was supplied by the Cancer Therapy Evaluation Program (National Cancer Institute, Bethesda, MD) as a white, opaque gelatin capsule, containing 100 mg of vorinostat. A dosing nomogram was used to minimize interpatient dosing variability. For part D, a suspension was prepared locally by the investigational pharmacists by mixing 20 mL of OraPlus (Humco, Texarcana, TX) with the contents of twenty 100 mg vorinostat capsules in a 4 ounce glass bottle. After shaking for up to 3 minutes to disperse, an additional 20 mL of OraSweet (Paddock Lab, Minneapolis, MN) was added. The container was again shaken to disperse, resulting in a final concentration of 50 mg/mL. The suspension was stored at room temperature and based on manufacturer's recommendation was stable for a maximum of 2 weeks. Vorinostat was administered orally each day, preferably with food.

The starting vorinostat dose for part A (patients with recurrent or refractory solid tumor) was 180 mg/m^2/d (approximately 80% of the adult recommended dose of 400 mg daily) with dose escalations in 30% increments. Once the MTD for vorinostat was defined, vorinostat was administered to six patients with recurrent or refractory leukemia to assess its tolerability at the solid tumor MTD (part B). In part C, additional cohorts of patients with recurrent neuroblastoma, medulloblastoma, PNET, or ATRT were enrolled to determine the MTD of vorinostat administered in combination with standard

Table 1. Patient Characteristics for Eligible Patients (n = 63)

Characteristic	Patients No.	Patients %
Age, years		
Median	11	
Range	2.6-22	
Sex		
Male	40	63.5
Female	23	36.5
Diagnosis part A		
CNS tumors		
Malignant glioma	7	23.3
Medulloblastoma	3	10.0
Astrocytoma, mixed glioma	2	6.6
Ependymoma, NOS	2	6.7
Atypical teratoid/rhabdoid tumor	1	3.3
Non-CNS tumors		
Soft tissue sarcomas	6	19.9
Ewing's sarcoma	2	6.7
Neuroblastoma	2	6.7
Osteosarcoma	2	6.7
Rhabdomyosarcoma,	3	9.9
Diagnosis part B		
Acute lymphoblastic leukemia	4	66.6
Acute promyelocytic leukemia	1	16.7
Acute lmyeloid leukemia FAB M1	1	16.7
Diagnosis part C		
CNS tumor		
Medulloblastoma	5	35.7
Primitive neuroectodermal tumor	4	28.5
Pineoblastoma	2	14.3
Atypical teratoid rhabdoid tumor	1	7.1
Non-CNS tumor		
Neuroblastoma	2	14.29
Diagnotic part D		
CNS tumor		
Malignant glioma	3	23.1
Ependymoma	2	15.4
Medulloblastoma	1	7.7
Pineoblastoma	1	7.7
Non-CNS tumor		
Rhabdomyosarcoma	3	23.1
Endodermal sinus tumor	1	7.7
Osteosarcoma	2	15.4
Prior therapy		
Median No. prior regimens	2	
Range	1-7	
Prior radiation therapy	45	

Abbreviations: NOS, not otherwise specified; FAB, French-American-British.

neuroblastoma dosing of 13cRA (80 mg/m^2/dose twice per day for 14 days).[22] The starting dose for vorinostat in part C was 180 mg/m^2/dose daily. In part D, patients with recurrent or refractory solid tumor received vorinostat as a 50-mg/mL suspension at the part A MTD in order to characterize the pharmacokinetics of the suspension compared with the capsule.

In the absence of disease progression, and if laboratory parameters as defined in the eligibility section were met, each 28-day course was repeated without interruption for up to 12 courses. In parts A and C, a minimum of three evaluable patients were treated at each dose level. If one of three patients at a given dose level experienced a DLT, up to three more were accrued at the same dose level. If $\geq$ two patients experienced DLT, then the MTD was exceeded and three more patients were treated at the next lower dose level. The MTD was defined as the dose level at which at most one patient experienced DLT with at least two of three to six patients experiencing a DLT at the next higher level. If observed DLTs were different classes of adverse effects, then expansion of the cohort to 12 patients was considered if the following conditions were met: one of the DLTs did not appear to be dose related; the toxicity was readily reversible; the study chair, statistician, Children's Oncology Group Developmental Therapeutics Chair, and investigational new drug sponsor all agreed that cohort expansion was acceptable. If fewer than one third of patients in the expanded cohort experienced DLT at the dose, further dose escalation could proceed.

In part B, six patients with recurrent or refractory leukemia received vorinostat at the solid tumor MTD to assess its tolerability.

To study the pharmacokinetics of an oral suspension formulation in part D, 12 patients with recurrent or refractory solid tumors (six patients $<$ 12 years, six $>$ 12 years) were enrolled. The suspension was administered on day 1 of course 1 at the solid tumor MTD; after day 1, patients could continue their course using either capsules or suspension.

Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0. Hematologic DLT was defined as grade 4 neutropenia or thrombocytopenia (children with leukemia were not considered evaluable for hematologic toxicity). Nonhematologic DLT was defined as grade 3 or 4 nonhematologicatoxicity with the specific exclusion of: grade 3 nausea and vomiting of fewer than 5 days duration responsive to antiemetic therapy, grade 3 transaminase elevations that met eligibility criteria within 7 days of interruption and did not recur on rechallenge with study drug, grade 3 fever or infection fewer than 5 days, any grade 2 nonhematologic toxicity that persisted for $\geq$ 7 days and was considered sufficiently medically significant or sufficiently intolerable by patients that it required treatment interruption, grade 2 allergic reactions that necessitated discontinuation of study drug, or any adverse event requiring interruption of study drug for longer than 7 days or which recurred on drug rechallenge. Before opening part D of the study, the protocol was amended to exclude grade 3 hypokalemia, hypophosphatemia, hypocalcemia, and hypomagnesemia responsive to oral supplementation from the definition of DLT.

Pretreatment evaluations included a history, physical examination and CBC, electrolytes, renal and liver function tests, serum protein and albumin, triglycerides (part C only). CBCs were obtained twice weekly during the first course and weekly thereafter. History, physical examinations, and laboratory studies were obtained weekly in course 1 and before each subsequent course. Disease evaluations were obtained at baseline, at the end of course 1 and after every other course. Tumor response was reported using the Response Evaluation Criteria in Solid Tumors (RECIST).[23]

Pharmacokinetics Studies

Participation in pharmacokinetic studies in parts A, B, and C was voluntary[24] whereas all subjects enrolled in part D had to agree to participate in pharmacokinetics studies before enrollment. Blood samples (2 mL) were collected in heparinized tubes before the vorinostat dose, and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 24 ($\pm$ 2) hours after the first dose. The plasma concentrations of vorinostat and its metabolite, 4-anilio-4-oxobutanoic, acid were determined using a previously described validated liquid chromatography, tandem mass spectrometry method.[25] The lower limit of quantitation was 2 ng/mL for vorinostat and 10 ng/mL for 4-anilio-4-oxobutanoic acid. The within-day and between-day precision (coefficient of variation) values and accuracy values for both analytes met standard assay validation criteria.[26]

Pharmacokinetic parameters for vorinostat and 4-anilio-4-oxobutanoic acid were calculated using noncompartmental methods. For each patient, the maximum concentration and time to maximum concentration were the observed values. The area under the plasma concentration-time curve ($AUC_{0\rightarrow t}$ where t was the last measured time point) was calculated by the trapezoidal rule.

Biologic Assays

PBMC protein lysates were isolated as described previously[27] from patients' whole blood drawn before, and at 1, 6, and 24 hours ($\pm$ 2 hours) after the first vorinostat. Ten to 25 micrograms of each lysate was analyzed by Western blotting using a purified rabbit polyclonal antiacetyl-H3 antibody

Table 2. Summary of Dose-Limiting Toxicities

Stratum	Dose Level	No. Entered	No. Evaluable	No. With DLT	DLT Type (No.)
Part A	Vorinostat 180 mg/m^2	10	6	1	Thrombosis (1)
	Vorinostat 230 mg/m^2	6	6	1	Hypokalemia (1)
					Hypokalemia (1)
	Vorinostat 300 mg/m^2	14	12	4	Platelets (2)
					Neutropenia (1)
Part B	Vorinostat 230 mg/m^2	6	5	2	AST (1)
					Hyperbilirubinemia (1)
					GGT (1)
					Hypokalemia (1)
Part C	Vorinostat 180 mg/m^2 daily, cis retinoic acid 80 mg/m^2/dose bid	7	6	2	Platelets (2)
					Neutropenia (1)
					Anorexia (1)
					Hypertriglyceiremia (1)
					Hypophosphatemia (1)
	Vorinostat 180 mg/m^2 4 times per week, cis retinoic acid 80 mg/m^2/dose bid	7	6	0	
Part D suspension	Vorinostat 230 mg/m^2	13	12	4	ALT (1)
					Platelets (3)
					Hyponatremia (1)

(Upstate Biotechnology, Lake Placid, NY) and chemiluminescence. The level of acetyl-H3 in each sample was determined relative to the expression of the housekeeping gene *HPRT* (Abcam, Cambridge, MA).

RESULTS

Of the 64 patients enrolled on study, one patient was ineligible (only 1 month had elapsed since stem-cell transplant) and 10 were not fully evaluable for toxicity: five never received vorinostat, four experienced disease progression during course 1, one patient received a single dose of vorinostat but no 13cRA, developed thrombocytopenia and was taken off therapy due to parental withdrawal of consent. Patients received a median of two courses (range, 1 to 12) of therapy (Table 1).

Toxicity

Table 2 summarizes the DLTs observed. In part A, at 180 mg/m^2, one patient on oral contraceptives who had a vascular anomaly developed a deep vein thrombosis of the iliac vein. No DLTs occurred at 230 mg/m^2/d dose level (n = 3). At 300 mg/m^2/d dose-limiting hypokalemia (n = 1) and thrombocytopenia (n = 1) occurred in two of six patients. Since these adverse events were of different classes, the cohort was expanded to six additional evaluable patients. In this expanded cohort, one patient each had dose-limiting neutropenia and thrombocytopenia thereby exceeding the MTD. Three additional patients were subsequently enrolled at the 230 mg/m^2; only one experienced a DLT of grade 3 hypokalemia, defining 230 mg/m^2/d as the MTD and recommended phase II dose for children with solid tumors. Two of the first five patients with relapsed or refractory leukemia receiving vorinostat at 230 mg/m^2/d experienced DLTs: elevated AST (n = 1), hyperbilirubinemia (n = 1), elevated gamma-glutamyl transferase (n = 1), and hypokalemia (n = 1). The solid tumor MTD thus did not appear tolerable in children with refractory leukemia; no other dose finding was attempted in this population.

For the combination of vorinostat with 13cRA, two of the six patients treated at the starting dose of vorinostat 180 mg/m^2/dose and 13cRA 80 mg/m^2/dose twice per day for 14 days every 28 days, developed DLT. DLTs in one patient included anorexia and thrombocytopenia and in the other patient included thrombocytopenia, neutropenia, hypertriglyceridemia, and hypophosphatemia. When the vorinostat dosage was de-escalated to 180 mg/m^2/d four times per week, none of the six patients experienced DLTs.

In part D, of 13 patients who agreed to participate in pharmacokinetic studies, 12 had adequate samples for analysis. Six received the suspension throughout the first course and six received it as a single dose before changing to the capsule formulation. Four (two who received suspension throughout) experienced grade 3 or 4 toxicities: increased ALT (n = 1), thrombocytopenia (n = 3), and hyponatremia (n = 1).

Table 3 summarizes non–dose-limiting hematologic toxicities ≥ grade 2 at least possibly attributable to vorinostat in 24 evaluable patients in part A and 13 evaluable patients in part C, respectively. Appendix Table A1 (online only) summarizes all non–dose-limiting,

Table 3. Non–Dose-Limiting Hematologic Toxicities (≥ grade 2), Independent of Frequency and Attribution, Observed in Evaluable Patients Enrolled on Part A (24 evaluable patients) and Part C (12 evaluable)

	Course 1 by Grade (total, 24 courses)				Courses 2 to 8 by Grade (total, 31 courses)			
Toxicity Type	1	2	3	4	1	2	3	4
Part A								
Hemoglobin	5	4			4	5		
Leukopenia	7	5	3	1	6	3	2	
Lymphopenia	3	2	3		3	1		
Neutropenia	2	4	4		1	5	1	1
Platelets	8	3	4		7		2	1
	Course 1 by Grade (total, 12 courses)				Courses 2 to 12 by Grade (total, 26 courses)			
	1	2	3	4	1	2	3	4
Part C								
Hemoglobin	2	3			4	2		
Leukopenia	2	3	2		2	3		
Lymphopenia	3	2	3		2	1		
Neutropenia		2	1		3	1		
Platelets	4		1		1		2	

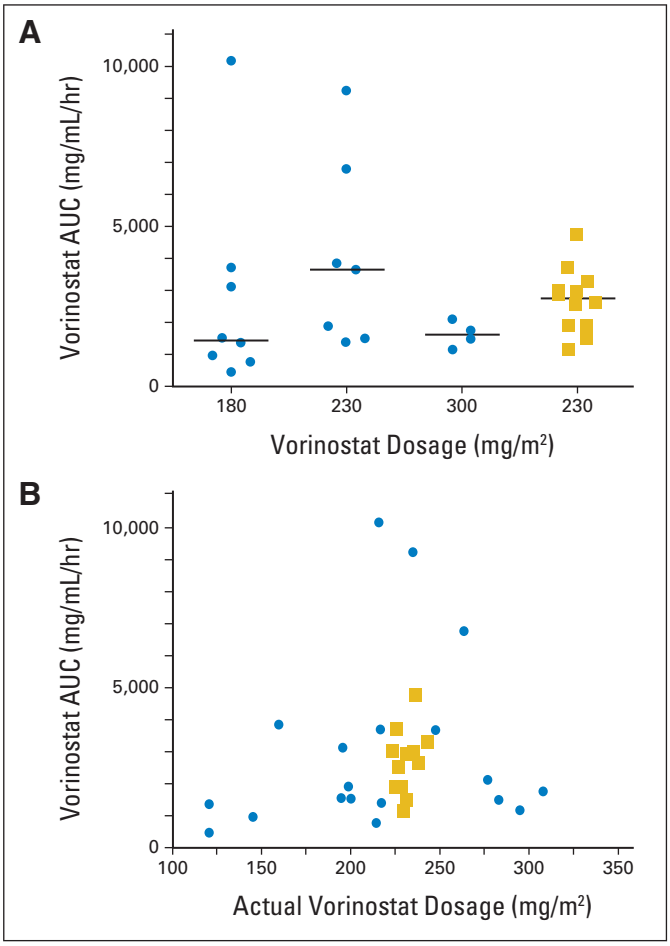

Fig 1. Vorinostat area under the curve (AUC) 0→∞ does not increase with (A) vorinostat dosage level or (B) actual dosage (mg/m^2/d). Patients in parts A, B, or C (blue circle) on the dosage level were combined. Gold box represents vorinostat AUC of patients in part D (suspension). Horizontal line represents median for each group.

nonhematologic toxicities that were at least possibly attributable to vorinostat in parts A and C. Similar Tables for parts B and D are included as Appendix Tables A2-A4 (online only).

Responses

No objective responses were observed to single-agent vorinostat. Prolonged stable disease (median, 4; range, 4 to 8 cycles) was observed in five patients (one each with osteosarcoma, spindle cell sarcoma, diffuse intrinsic pontine glioma, low-grade glioma, and synovial cell sarcoma). One patient with neuroblastoma treated with the combination of vorinostat and 13cRA experienced a complete response and completed 12 courses of therapy. The patient had evaluable disease detected by iodine-123 metaiodobenzylguanidine at study entry and after course 9 had no abnormal radiotracer uptake. Two additional patients (medulloblastoma, pineoblastoma) treated with the combination had stable disease for 5 and 7 courses, respectively.

Pharmacokinetics

After the first vorinostat dose on course 1, pharmacokinetic studies were obtained in 21 subjects after administration of the capsule formulation and from 11 subjects after administration of the suspension formulation (Appendix Table A5, online only). Wide interpatient variation in drug disposition was noted such that there did not appear to be a clear relationship between dose and drug exposure (Fig 1). Similarly, no relationship was noted between drug exposure, toxicity, or prolonged stabilization. After administration of the capsule formulation, the median apparent oral vorinostat clearance was 171 L/h/m^2

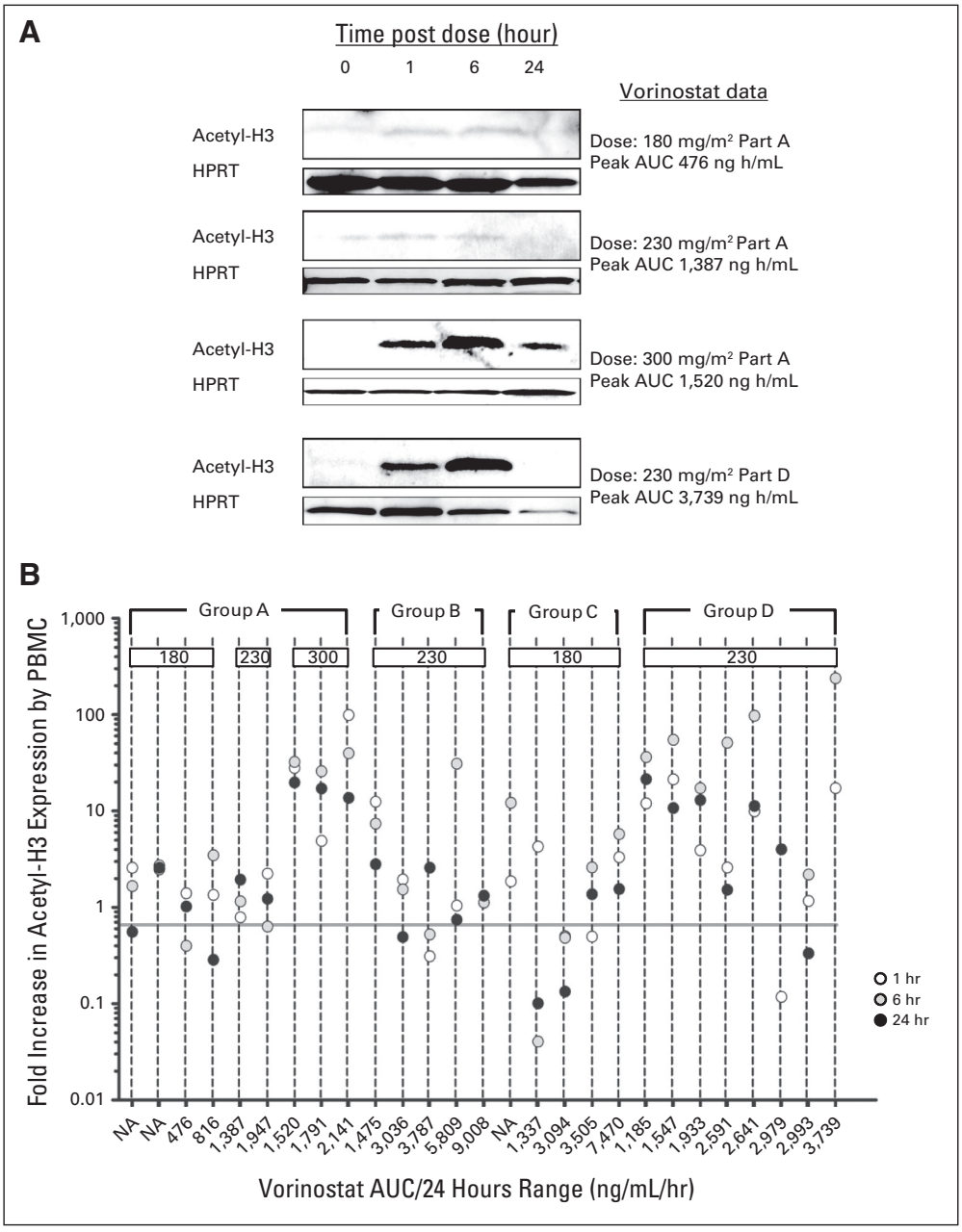

Fig 2. (A) Western blot analysis of acetyl-H3 (and HPRT loading control) in peripheral blood mononuclear cells (PBMC) isolated from trial patients. (B) Graph reporting the fold induction of acetyl-H3 (relative to pretreatment levels) at 1, 6, and 24 hours post-treatment in PBMC isolated from 27 trial patients. AUC, area under the curve.

(range, 102 to 263 L/h/m^2) with a median vorinostat half-life of 2.4 hours (range, 1.1 to 8.0 hours).

Histone Acetylation

One hundred five adequate PBMC samples were obtained from 27 patients. Patients receiving 180 mg/m^2/d of vorinostat capsules alone or 180 mg/m^2/d in combination with 13cRA showed little evidence of acetyl-H3 accumulation in PBMC (Figs 2A and Fig 2B). In contrast, patients receiving 300 mg/m^2/d of vorinostat capsules alone demonstrated significant induction of acetyl-H3 in PBMC at 1, 6, and 24 hours after dose (group A, $P < .05$; Figs 2A and Fig 2B). Wide interpatient variability in PBMC acetyl-H3 accumulation was observed among patients receiving the intermediate dose of 230 mg/m^2/d vorinostat either as capsules or suspension (parts B and D). A significant induction of PBMC acetyl-H3 accumulation was observed at 6 hours after dose among patients in part D ($P < .01$) and in two patients in part B, suggesting 230 mg/m^2/d may produce a more transient inhibition of HDAC relative to 300 mg/m^2.

DISCUSSION

This pediatric phase I trial established the MTD of vorinostat as 230 mg/m^2/d administered orally in patients with recurrent or refractory solid tumors. Patients with refractory leukemia did not appear to tolerate this dose due to liver dysfunction. The combination of vorinostat with standard neuroblastoma dosing of 13cRA (80 mg/m^2/dose twice per day, days 1 through 14) required a reduced dose/schedule of vorinostat (180 mg/m^2/dose 4 times per week). Our single-agent DLTs for vorinostat (ie, neutropenia, thrombocytopenia, and hypokalemia) were similar to those observed in adult studies. Frequent adverse events included nausea, vomiting, anorexia, increased transaminases, and hyperbilirubinemia. The vorinostat suspension was generally tolerable at the MTD of 230 mg/m^2 in patients with solid tumor, with four of 12 patients experiencing toxicities that required dose modifications during course 1. A detailed toxicity comparison between formulations was not possible as six of these 12 patients chose to switch to the capsule formulation following the day 1 pharmacokinetic study. Our pharmacokinetic and toxicity data suggest that the 230 mg/m^2 dose of vorinostat with either formulation is generally well-tolerated; however, dose de-escalation for toxicity may be required in some patients. Further study of the toxicity and pharmacokinetics of the suspension formulation is recommended.

The disposition of vorinostat in children was similar to that observed in adults.[28-30] The parent drug is absorbed relatively slowly with a time to maximum concentration ranging from 1.3 to 3.1 hours, (1.5 hours in adults[28-30]). Although in adults, the maximum plasma concentration increased with dosage, the wide interpatient variability observed in our study obscured any relationship between vorinostat dosage and maximum plasma concentration or AUC. Similarly, no correlation was noted between pharmacokinetic, pharmacodynamic, toxicities, or response data. However, at the MTD of 230 mg/m^2/d, the AUCs of parent drug[28-30] and the inactive vorinostat 4-anilino-4-oxobutanoic acid metabolite[18] were similar to those previously reported in adults.

Accumulation of acetyl H3 histones in PBMCs was detected in patients receiving the highest vorinostat dosages and particularly in patients treated with 300 mg/m^2/dose in whom accumulation of acetyl-H3 persisted for 24 hours. Evidence of more transient (6 hours) PBMC acetyl H3 accumulation was observed in patients receiving 230 mg/m^2/dose. No significant accumulation was seen at the 180 mg/m^2/d dosage. Acetyl-H3 accumulation did not appear to correlate with drug exposure as measured by the AUC.

Overall, vorinostat drug disposition and tolerance in children was similar to that observed in adult patients. Additional studies will be needed to understand the basis for the wide interpatient variation in drug disposition that was observed. Future trials include the combination of 13cRA and vorinostat in children with neuroblastoma or select CNS malignancies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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