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Safety, Pharmacokinetics, and Pharmacodynamics of Panobinostat in Children, Adolescents, and Young Adults with Relapsed Acute Myeloid Leukemia

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Abstract

Background: Novel therapies are urgently needed for pediatric patients with relapsed acute myeloid leukemia.

Methods: To determine if the histone deacetylase inhibitor panobinostat could be safely given in combination with intensive chemotherapy, we performed a phase I trial in which 17 pediatric patients with relapsed or refractory acute myeloid leukemia received panobinostat (10 mg/m^2, 15 mg/m^2, or 20 mg/m^2) prior to and in combination with fludarabine and cytarabine.

Results: All dose levels were tolerated, with no dose-limiting toxicities observed at any dose level. Pharmacokinetic studies demonstrated that exposure to panobinostat was proportional to the

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Authorship Contributions

TMC and JER designed the study; SEK, TMC, TBA, JWT, NJL, KMH, DJK, DES, DB, RCR, HI, C-HP, and JER participated in patient care and in the collection, analysis, and interpretation of clinical data; PEM, KRC, JCP, YG, and JMK performed the biological correlative studies; SEK wrote the first draft of the manuscript; and all authors participated in the critical review of the manuscript and approved of the manuscript for submission.

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dose given, with no associations between pharmacokinetic parameters and age, weight, or body surface area. Among the nine patients who had sufficient (>2%) circulating blasts on which histone acetylation studies could be performed, seven demonstrated at least 1.5-fold increases in acetylation. Although no patients had a decrease in circulating blasts after single-agent panobinostat, eight of the 17 patients (47%) achieved complete remission, including five of six patients treated at dose level 3. Among the 8 complete responders, 6 (75%) attained negative minimal residual disease status.

Conclusions: Panobinostat can be safely administered with chemotherapy and results in increased blast histone acetylation, suggesting that it should be further studied in acute myeloid leukemia. This trial is registered with ClinicalTrials.gov (NCT02676323).

Precis

The combination of panobinostat with fludarabine and cytarabine is safe and active in children with relapsed AML. Panobinostat results in increased histone acetylation in leukemic blasts of children with relapsed AML.

Keywords

acute myeloid leukemia; relapse; childhood

Introduction

Although survival rates for children with acute myeloid leukemia (AML) are greater than 60%, the outcome for patients with relapsed or refractory disease remains poor, with less than 40% of them becoming long term survivors.[1] Because epigenetic dysfunction plays a pathogenic role in AML and may contribute to relapse and resistance, histone deacetylase (HDAC) inhibitors may be particularly active in this disease.[2] The antileukemic effects of several HDAC inhibitors, including valproic acid, vorinostat, and panobinostat, have been examined alone and in combination with chemotherapy.[3] Panobinostat, a potent inhibitor of both class I and class II HDACs, has single-agent activity against a variety of AML cell lines and primary samples, suppresses the expression of *BRCA1*, *CHK1*, and *RAD51*, induces DNA double-strand breaks and apoptosis, and abrogates cell cycle checkpoints induced by cytarabine or daunorubicin.[4,5] Furthermore, treatment of mice bearing AML xenografts with the combination of panobinostat and cytarabine significantly increased survival compared to treatment with either agent alone.[5] Recently, panobinostat was shown to be tolerable when given prior to standard induction therapy in older adults with AML.[6] However, little is known about the tolerability or activity of panobinostat when combined with chemotherapy in pediatric patients. Here we describe the safety, pharmacokinetics, pharmacodynamics, and activity of panobinostat in combination with fludarabine and cytarabine in pediatric patients with relapsed or refractory AML.

Methods

Patients 24 years old with relapsed (5% bone marrow disease) or refractory (to at least 2 lines of induction therapy) AML with adequate organ function, no evidence of graft-versus-

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host disease, and no uncontrolled infections, were eligible for enrollment in this multi-institutional study. The protocol was approved by each site's institutional review board and registered at ClinicalTrials.gov (NCT02676323). Informed consent, and assent when appropriate, was obtained from all patients or their legal guardians.

Patients received a single cycle of panobinostat orally on days 1, 3, 5, 8, 10, and 12, while fludarabine (30 mg/m^2/dose IV over 30 minutes) and cytarabine (2 g/m^2/dose IV over 4 hours) were each given for 5 days (days 8-12). Granulocyte-colony stimulating factor was not given. All patients received intrathecal methotrexate, hydrocortisone, and cytarabine prior to day 1. Patients with central nervous system leukemia received weekly triple intrathecal therapy until the cerebrospinal fluid became clear of leukemia. The starting dose of panobinostat was 10 mg/m^2 (dose level 1), with planned dose escalations to 15 mg/m^2 (dose level 2), and 20 mg/m^2 (dose level 3) using a rolling-six design.[7]

Toxicities were graded according to the CTEP Common Terminology Criteria for Adverse Events version 4.0. Dose-limiting toxicity (DLT) was based on toxicities that were deemed to be possibly attributable to panobinostat and were defined as any grade 5 event or any grade 3 or 4 non-hematologic event that occurred within 28 days of the first dose of panobinostat, except for grade 3 nausea, vomiting, mucositis, diarrhea, weight loss, electrolyte abnormalities, infection, or elevation in amylase, lipase, bilirubin, or transaminases that returned to Grade 2 within 14 days. Failure to recover counts by day 56 in the absence of persistent leukemia was considered a hematologic DLT.

Pharmacokinetic and pharmacodynamic studies

Plasma samples were collected prior to and at 0.5, 1, 6, 24, and 48 hours after the first dose of panobinostat and prior to and at 1, 6, and 24 hours after the fourth dose. The population pharmacokinetic and individual post-hoc estimates of panobinostat were determined using non-linear mixed effects modeling via Monolix (version 5.0.0, www.monolix.org) using the Stochastic Approximation Expectation-Maximization approach. A linear 2-compartment model, with first-order absorption and elimination was used to model the data. Parameters estimated included oral absorption; ka (1/hr), absorption lag time; Tlag (hrs), CL/F ($L/hr/m^2$), the panobinostat clearance; V_1/F (L/m^2), the volume of panobinostat; Q ($L/hr/m^2$), the intercompartmental clearance; and V_2 (L/m^2), the volume of the peripheral compartment. In addition, the individual post-hoc parameter values were used to estimate the area under the concentration curve (AUC) for each individual. The inter-individual variability of the parameters was assumed to be log normally distributed. A proportional residual error model was used with assumed normal distribution of the residuals. The covariates age, BSA, and weight were evaluated to determine their significance in explaining pharmacokinetic variability. These covariates were considered significant in a univariate analysis if their addition to the model reduced the objective function value at least 3.84 units ($p < 0.05$, based on the χ^2 test for the difference in the −2 log-likelihood between 2 hierarchical models that differ by 1 degree of freedom), and the covariate term was significantly different than zero ($p < 0.05$, t-test).

Blood samples for histone acetylation studies were collected prior to and at 6, 24, and 48 hours after the first dose and prior to the fourth dose of panobinostat. Peripheral blood

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samples were treated with a mild fixative [50 μL Transfix (Cytomark) per 1 mL of EDTA blood] and assayed within 72 hr. For patients with adequate peripheral blasts (>2%), flow cytometry for surface markers (including CD45, CD34, CD117, CD33) was used to identify the leukemic blast population, followed by intranuclear staining with monoclonal antibodies specific for acetylated histone H3 to measure changes in H3 acetylation.[8] Briefly, following staining with surface markers, washed cells were fixed, permeabilized, and stained using the BD Cytofix/CytoPerm system according to the manufacturers recommendations (BD Biosciences). Primary anti-acetyl-histone H3 (Lys14) antibody (Millipore Sigma) was followed by secondary goat anti-rabbit IgG H&L Alexa Fluor 488 (abcam). Data were collected on a BD LSR Fortessa cytometer and analyzed using BD FACSDiva version 8.0 software.

Response Assessment

Response was assessed by central review using morphologic and flow cytometric examination of bone marrow aspirates obtained between days 28 and 42 of therapy. For flow cytometric studies of minimal residual disease (MRD), leukemia-associated immunophenotypes were identified in diagnostic bone marrow specimens and marker combinations that allowed detection of 10 leukemia cells per 10,000 (0.1%) mononuclear bone marrow cells were applied to subsequent samples. Complete remission was defined as < 5% blasts, absolute neutrophil count 500/μl, platelet count 75,000/μl without transfusions, and no evidence of extramedullary disease; partial response as bone marrow with 5% to 25% blasts and a decrease of at least 50% in blast percentage; all other patients were considered to have no response.

Results and Discussion

Seventeen patients with relapsed or refractory AML were enrolled, including 7 who had undergone prior hematopoietic cell transplantation, 7 with early relapse (<12 months from initial diagnosis), 1 with primary refractory AML, and 5 who had relapsed and were refractory to at least 1 prior salvage therapy (including 3 with early relapses). Patients were treated at dose levels 1 (n=6), 2 (n=5), or 3 (n=6), with no DLTs observed at any dose level (Table 1). Toxicities are consistent with intensive AML regimen and are presented in Table 2. Weekly EKG monitoring did not reveal QTc prolongation or other dysrhythmias. There were 14 episodes of febrile neutropenia and nine infections, including two episodes of streptococcal bacteremia and one case of Citrobacter freundii sepsis.

Response to single-agent panobinostat was assessed by centrally reviewed flow cytometric examination of peripheral blood samples on day 1, prior to the first dose of panobinostat, and on day 8, prior to the administration of chemotherapy. Among the 13 patients with values at days 1 and 8, none demonstrated a decrease in blast percentage (Table 1). Evaluation of response after one cycle among the 17 patients treated in all dose levels demonstrated morphologic complete remission in eight (47%) patients, six of whom had negative MRD; one partial response; and eight with no response (Table 1). Among six patients treated at dose level 3, complete remission was attained in five (83%), with four patients becoming MRD negative. Among patients with early relapse or refractory disease

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(N=11), 1 achieved a PR and 3 others had less than 20% disease in their marrow after 1 cycle, although the reduction was insufficient to deem them a PR. In contrast, all patients with a late, untreated relapse (N=8) achieved a CR or CRi (CR with incomplete hematologic recovery), including all 4 treated at dose level 3. Utilizing the revised International Working Group criteria,[9] there were 3 CR and 5 CRi.

Panobinostat pharmacokinetic studies performed on all 17 patients demonstrated no significant associations between pharmacokinetic parameters and age, weight, or body surface area. Estimated median (range) panobinostat plasma AUC (ng·hr/ml) at dose levels 1, 2, and 3 were 52.5 (23.2-93.1), 60.4 (45.1-103.4), and 103.5 (59.9-175.1), respectively (Table 3 and Figure 1a), while corresponding median (range) Cmax (ng/ml) were 8.4 (5.3-13.3), 11.8 (9.7-18.1), and 20.7 (11.6-30.8). Thus, systemic exposure to panobinostat was proportional to the dose given. Overall, the estimated body surface area normalized panobinostat clearance in the present study is between 1.4 and 2.5 times higher than those estimated in previous adult studies.[10–13] But, given that our study gave higher body surface area normalized doses compared to the adult studies (9.3 to 25.6 mg/m^2 vs 7.9 to 10.5 mg/m^2), the Cmax values were similar while the AUC 0-infinity were slightly lower for the 10 and 15 mg/m^2 panobinostat dose groups; both exposure measures were higher in the 20 mg/m^2 group.

Only nine patients had sufficient (>2%) circulating blasts to perform histone acetylation studies. Blasts from two patients showed no increases in H3 acetylation, whereas blasts from seven patients demonstrated at least 1.5-fold increases in acetylation (Figure 1b), a level observed in adult AML patients treated with panobinostat.[14] Peak increases were observed as early as 6 hours after the first dose of panobinostat and, in six of nine cases, maintained at day 8, 72 hours after the previous dose. The number of cases analyzed at each dose level was too small to determine associations between dose level and acetylation. However, despite these levels of histone acetylation change, no single agent activity was observed in our study, suggesting that clinical activity of panobinostat requires combination (rather than single agent) therapy.

In summary, this phase I trial demonstrates, for the first time, that panobinostat can be safely given with intensive chemotherapy to pediatric patients with AML. No toxicities were attributable to panobinostat, systemic exposure was proportional to the dose given, and some patients demonstrated increases in blast histone acetylation. At 20 mg/m^2 dosing, all four patients with sufficient peripheral blasts showed at least 1.5-fold increases in acetylation and five of the six patients achieved complete remission, suggesting treatment with panobinostat may prime the leukemia cells to increase their sensitivity to subsequent chemotherapy. However, the late occurrence of relapse in 7/8 patients who achieved complete remission, combined with the small number of patients enrolled, make it difficult to attribute the good responses to exposure to panobinostat. Caution is also indicated by the failure of a randomized vorinostat combination trial to show benefit in adult frontline AML.[15] Although a dose expansion cohort was planned, the trial closed early because of poor accrual. Thus, while we can conclude that panobinostat is safe and may increase histone acetylation, further studies are needed to determine if panobinostat or other histone deacetylase inhibitors actually increase chemosensitivity.

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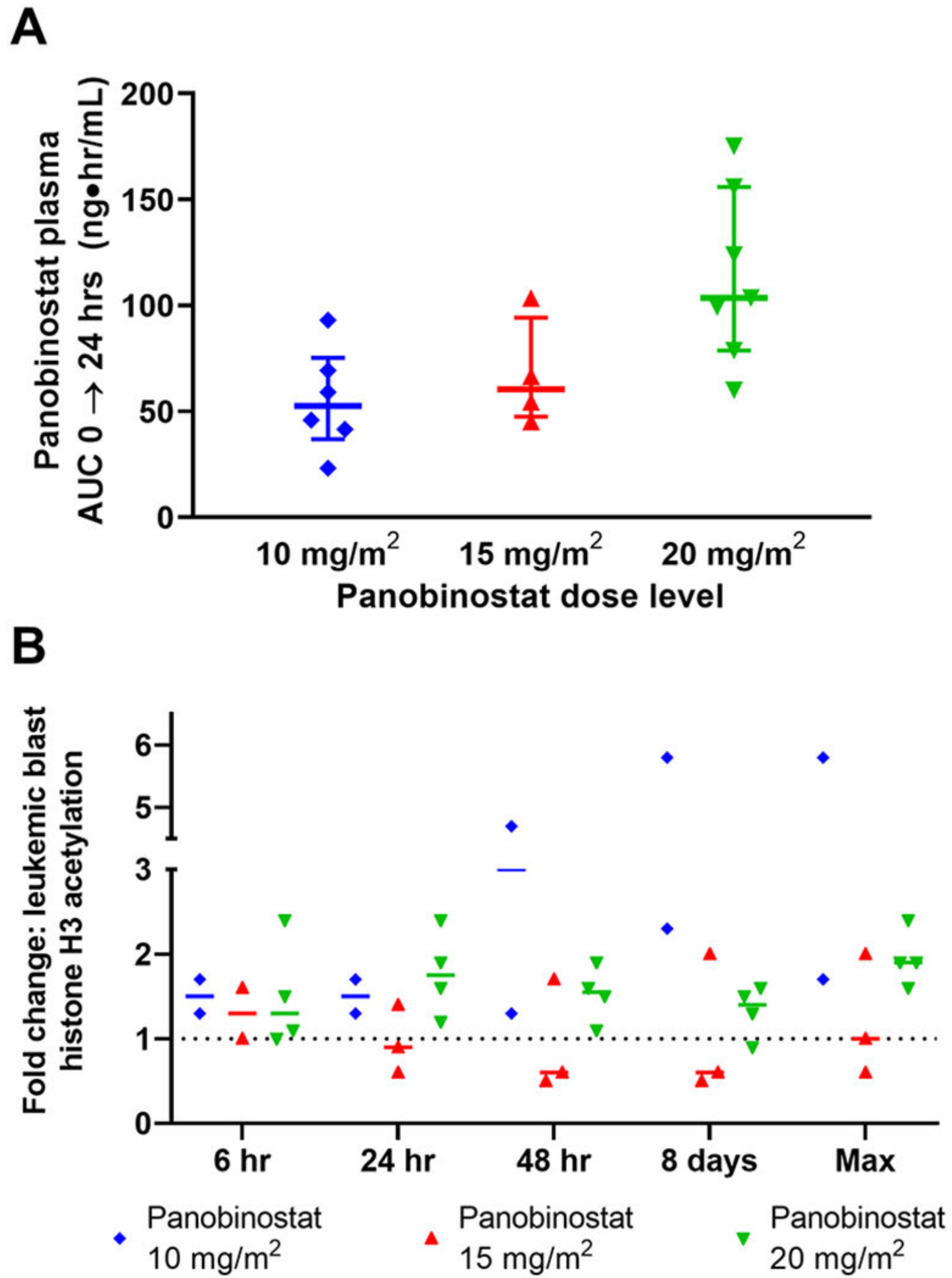

Figure 1:

Panobinostat systemic exposure and histone acetylation

A) Increasing panobinostat dose was associated with an increase in panobinostat systemic exposure. B) A 1.5-fold increase in leukemic blast histone acetylation was observed in 7 of 9 patients with available samples, including all 4 patients treated at 20 mg/m^2. One patient treated at 15 mg/m^2 did not have a 6-hour sample available.

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Table 1.

Patient Characteristics and Treatment Outcomes

ID	Dose (mg/m^2)	Age (years)	Sex	Genetics	Disease status	Prior HCT	Day 1 PB blast %	Day 8 PB blast %	Response
1	10	14	F	t(9;11)	Relapse, refractory	No	3.9	6.2	NR
2	10	14	M	der(12;17)(q10;q10), add(11)(p13), −17	Second relapse, refractory	Yes	0.2	2.8	NR
3	10	16	F	Normal	First relapse, late	No	0.1	0.4	CR, MRD <0.1%
4	10	6	F	Normal	First relapse, late	No	0.1	0.2	CR, MRD <0.1%
5	10	14	M	Normal	First relapse, early, refractory	No	49	67	NR
6	10	7	M	t(9;11)	Relapse, refractory	Yes	75	75	NR
7	15	11	F	Normal	Primary refractory	No	8	40	NR
8	15	16	M	NA	First relapse, early	No	NA	NA	NR
9	15	11	F	−7	Relapsed t-AML, early	Yes	44	61	NR
10	15	5	M	t(9;11)	Relapsed, refractory t-AML	No	55	52	PR, MRD 10%
11	15	6	F	*FLT3*-ITD	First relapse, late	Yes	NE	NE	CR, MRD NE #
12	20	13	F	*FLT3*-ITD	First relapse, early	No	NA	5	NR
13	20	15	M	Normal	First relapse, late	Yes	42	58	CR, MRD <0.1% #
14	20	17	M	add(22)(p12)	First relapse, late	Yes	3.9	7.8	CR, MRD <0.1% #
15	20	7	F	t(8;21)(q22;q22)	Second relapse	Yes	NA	0.13	CR, MRD 0.2%
16	20	21	M	Normal	First relapse, late	No	51	63	CR, MRD <0.1% #
17	20	18	M	del(7)(q22q34)	First relapse, late	No	82	81	CR, MRD <0.1% #

HCT, hematopoietic cell transplantation; PB, peripheral blood; blast %, blast percentage by flow cytometry; MRD, minimal residual disease; NR, no response; PR, partial response; CR, complete response; NE, not evaluable; NA, not available; early relapse: CR less than 12 months; late relapse: CR at least 12 months;

#CRi by revised International Working Group criteria.

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Table 2.

Episodes of Grade 3 and 4 toxicities

Toxicity	Common Terminology Criteria for Adverse Events Version 4.0 Grade					
	Panobinostat 10 mg/m^2 (6 patients)		Panobinostat 15 mg/m^2 (5 patients)		Panobinostat 20 mg/m^2 (6 patients)	
	3	4	3	4	3	4
Blood and lymphatic system disorders						
Anemia	17		11		14	
Gastrointestinal disorders						
Vomiting	1					
Mucositis oral	1					
Infections and infestations						
Febrile Neutropenia	7		3	1	3	
Lung infection	1		1		3	
Upper respiratory infection	1					
Bacteremia	1				1	
Sepsis		1				
Investigations						
Platelet count decreased	20	25	10	9	29	23
Neutrophil count decreased	2	4	5	5	11	10
White blood cell decreased	4	6	4	4	11	7
Lymphocyte count decreased	4	4	3	3	8	4
Aspartate aminotransferase increased	1				1	
Metabolism and nutrition disorders						
Anorexia			1		1	
Hypophosphatemia	1					
Hypomagnesemia			1			
Lipase increased						1

These numbers indicated individual episodes of toxicities such that each patient may experience more than one episode during a cycle of therapy.

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Table 3.

Estimated AUC and Cmax

Dose	10 mg/m^2; n=6			15 mg/m^2; n=4			20 mg/m^2; n=7		
	Min	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**
AUC 0-24hrs (ng·hr/mL)	26.9	46.4	80.1	34.0	51.9	100.4	51.1	90.4	155.4
AUC 0-infinity (ng·hr/mL)	23.2	52.5	93.1	45.1	60.4	103.4	59.9	103.5	175.1
Cmax(ng/mL)	5.3	8.4	13.3	9.7	11.8	18.1	11.6	20.7	30.8