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# A Phase 2 Study of Belinostat (PXD101) in Patients with Relapsed or Refractory Acute Myloid Leukemia or Patients Over 60 with Newly-Diagnosed Acute Myloid Leukemia: A California Cancer Consortium Study

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## Abstract

We performed a phase II study of belinostat in patients with acute myloid leukemia (AML). In this open label phase II study (NCT00357032), patients with relapsed/refractory AML, or newly diagnosed patients with AML over the age of 60 were eligible. Belinostat was administered intravenously (IV) at a dose of 1000 mg/m2 daily on days 1–5 of a 21-day cycle until progression or unacceptable toxicity. The primary endpoint was complete response (CR) rate, with secondary endpoints of overall response rate [CR+partial response (PR)], time to treatment failure (TTF), overall survival and safety. 12 eligible patients with AML were enrolled, of whom 6 had received at least one prior line of therapy. No CR or PR were seen. Four patients had stable disease for at least 5 cycles. Grade 3 non-hematological toxicities occurred in 4 patients. Belinostat as monotherapy has minimal single agent effect in AML on this dosing schedule.

### Keywords

histone deacetylase inhibitor; Leukemia; Phase II

## INTRODUCTION

Despite great efforts in treatment strategy including aggressive chemotherapy and transplant, there has not been a significant change in survival outcomes for older patients with acute myloid leukemia (AML). While the standard induction chemotherapy of anthracycline plus cytarabine can lead to a 50–75% complete remission rate in younger adults, the majority of AML patients eventually relapse and die of recurrent disease [1]. This is particularly true of the older patients with AML. Standard chemotherapy does not appear to be effective for the

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majority of patients over 60 who make up the majority of patients with AML [2], and the potentially curative modality of allogeneic transplant is generally not an option for this population, although reduced-intensity conditioning regimens are being investigated in this population. While much work has focused on identifying which older patients may benefit from “standard” chemotherapy, an alternative approach may be to identify novel targets and pathways which may control AML in the older patient population.

Preclinical and clinical evidence supports the use of histone deacetylase inhibitors (HDACi) in hematologic malignancies. HDACi as single agents have been shown to affect a host of cellular targets and processes that might lead to antitumor activity in various types of leukemia, including angiogenesis, apoptosis, the cell cycle, and tumor immunology [3,4]. The oral HDACi vorinostat demonstrated single agent activity in AML and myelodysplastic syndrome [5]. Furthermore, this class of agents may enhance response to the hypomethylating agents, a class of agents with known activity in MDS and AML [6].

Belinostat (PXD101) is a novel, low molecular weight inhibitor of HDAC activity, of the hydroxamic acid class, with activity against zinc based deacetylase enzymes of classes I, II, and IV. In vitro studies demonstrated histone H4 acetylation and growth inhibitory activity against a variety of solid tumor lines [7]. In phase I studies, the maximum tolerated dose (MTD) for a 5 day infusion schedule repeated every 21 days was 1000 mg/m$^2$/day, with a short intermediate half life [8,9]. The drug was reasonably well tolerated with the reported Grade 3 toxicities being atrial fibrillation in one patient and GI symptoms in two patients at the MTD. The fatigue often seen with drugs of this class were reported to resolve rapidly with withdrawal of drug. We report the results of a phase II study of belinostat in relapsed/refractory AML patients ≥18 years and newly diagnosed AML patients ≥60 years.

## PATIENTS/METHODS

### Patient Selection

Eligible patients were ≥18 years with AML, including relapsed or refractory AML after one to three prior induction regimens (not counting consolidation therapies while in CR, such as autologous transplant), or newly diagnosed AML if over age 60. Bone marrow studies were required for confirmation of diagnosis. Patients who have had prior stem cell transplant were eligible. A minimum of 4 weeks had to have elapsed since the completion of prior chemotherapy in order to be eligible. Hydroxyurea could be continued up to 24 hours prior to the initiation of therapy with belinostat, but must be discontinued at that point. Evidence of adequate pretreatment organ function was established by serum bilirubin ≤2.0 mg/dl, SGOT and SGPT ≤2.5 times the institutional upper limits of normal (ULN), and calculated creatinine clearance ≥60 ml/minute or serum creatinine <1.5 times ULN. There were no minimum hematological parameter requirements prior to enrollment, as patients with AML and MDS are understood to have low ANC and platelet counts when the disease is active. Patients were accrued from May 2006 until January 2007. Signed informed consent was obtained for all study participants and registered by the Data Coordinating Center at City of Hope National Cancer Center. Protocol and consent form were approved by the institutional review boards of the participating centers.

### Treatment Plan

Study patients received belinostat 1000 mg/m$^2$ daily administered as a 30-minute IV infusion on days 1 through 5 of each cycle, with cycle length defined as 21 days. Patients were to receive a minimum of one treatment cycle, with no pre-defined maximum number of cycles. Patients were allowed stay on the study as long as there was no unacceptable toxicity.

### Evaluation of response

Bone marrow aspiration and biopsies were performed as part of the on-study evaluation within two weeks prior to starting therapy. Patients were seen at a minimum of once weekly while on study, with peripheral blood counts and chemistry being monitored at least once weekly. Bone marrow studies were repeated at a minimum of every three cycles. Clinical responses were measured according to International Working Group criteria [10]. All patients who received any protocol treatment were considered in the determination of the response rate.

### Study Design

The primary endpoint was complete response rate. This study was designed to distinguish between a disappointing response rate of 5% and a response rate of 20% which would suggest that belinostat is active in AML. The two-stage Optimum design of Simon [11] was used, with a requirement of 1 response out of the initial 12 patients before continuing accrual to a final sample of 37 subjects. Belinostat was to be regarded as active in AML if at least 4 responses were observed among 37 subjects. With this design, the probability of erroneously declaring activity is <10% if the population response rate is 5%, and the probability of failing to declare activity when the actual response rate is 20% is <10% (90% power). The probability of early stopping under the discouraging rate of 5% is 54%. Time to treatment failure (TTF) was defined as time from initiation of protocol treatment to cessation of treatment for resistant disease, relapse, or death.

## RESULTS

### Demographics

A total of 12 eligible patients with AML were enrolled in the study from three centers (9 from City of Hope, 2 from UC Davis, and 1 from University of Pittsburgh). One additional patient was enrolled, but declared ineligible prior to receiving any treatment and excluded from the results. Demographic data are listed in Table 1. Median age was 78 (range 43–84), and 11 of the 12 patients were over 60 years of age. Six of the patients over age 60 had no prior treatment. Eight of the patients had adverse cytogenetic features and four had intermediate risk features. Two patients treated on this protocol after relapse had previously achieved CRs (durations ≤ 6 months), one of whom had received an allogeneic transplant with rapid progression of disease post transplant.

### Toxicity

Grade 3 non-hematological toxicities seen at any cycle on this regimen were observed in 4 patients (25%): QTc interval prolongation and low sodium (n=1), nausea (n=1), dehydration and febrile neutropenia (n=1), and stomatitis (n=1). There was one Grade 4 hematoma seen in a patient on treatment who developed a CNS hematoma after rolling off a bed while sleeping. Grade 2 toxicities included fatigue, nausea, vomiting, AST/ALT elevation, weakness, and abdominal discomfort (Table 2).

### Clinical Activity

There were 46 total cycles delivered to 12 patients. Median number of cycles was 2.5, range 1–10. There was no formal CR or PR seen among the first cohort of 12 patients, which closed the study. Neither of the patients who had obtained brief CRs previously received more than on cycle of treatment on this protocol. However, it is noteworthy that 4 patients remained stable for at least 4 cycles. Of these 4, 3 patients had abnormal cytogenetics, including t(x;20), DEL(12)(P11.2P13), and -7 abnormalities, at commencement of study treatment. The median overall survival was 9.1 months (95% CI: 0.5 to 13.5 months) and the median time to treatment failure was 1.6 months (95% CI: 0.4 to 4.4 months) for the 12 patients enrolled on this study.

## DISCUSSION

Belinostat is a novel hydroxamic acid derivative with histone and protein deacetylase activity. In this study, belinostat was given IV at the dose of 1000 mg/m$^2$/day for five consecutive days every 21 days in patients with AML. The drug was fairly well tolerated, but did not achieve the formal response rate required by the two-stage Simon optimum design to continue enrolling patients, although there were 4 patients who had stable disease for over five cycles, with two of the patients reaching 9 and 11 cycles.

A similar trial of belinostat at the same dose and schedule showed similar activity in myelodysplastic syndrome (MDS), with only one confirmed response, a hematologic improvement in neutrophils [12]. On the other hand, a structurally similar deacetylase inhibitor, vorinostat, showed more activity as a single agent against MDS and AML [5], and a deacetylase of a different structure, valproic acid, has also demonstrated meaningful response rates in this population [13,14]. In addition to other caveats inherent in comparing data across unrelated studies, one difference between the two belinostat studies and the other studies was the duration of treatment. While the phase II recommended dose of belinostat was established by a phase I study for the period of five days, the schedule was fixed at five days every three to four weeks. This interval may be too long for a drug with a short half - life in a rapidly growing disease like AML. Longer duration of exposure to drug has correlated with increased response with hypomethylating agents [15] and with deacetylase inhibitors, on continuous dosing with valproic acid [13,14] or on 14 day schedules with vorinostat [5,16]. Studies using more prolonged dosing schedules should be studied with belinostat. Preliminary data combining this agent with the hypomethylating agent azacitidine suggested promising activity [17]. Further studies of belinostat in myeloid malignancies may be most productive if they explore alternative schedules in combination with other agents.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Rowe JM. Evaluation of prognostic factors in AML. Preface Best Pract Res Clin Haematol. 2011; 24:485–488.
2. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood. 2010; 116:4422–4429. [PubMed: 20668231]
3. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. Nat Rev Drug Discov. 2002; 1:287–299. [PubMed: 12120280]
4. Kretzner L, Scuto A, Dino PM, et al. Combining histone deacetylase inhibitor vorinostat with aurora kinase inhibitors enhances lymphoma cell killing with repression of c-Myc, hTERT, and microRNA levels. Cancer Res. 2011; 71:3912–3920. [PubMed: 21502403]
5. Garcia-Manero G, Yang H, Bueso-Ramos C, et al. Phase 1 study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid [SAHA]) in patients with advanced leukemias and myelodysplastic syndromes. Blood. 2008; 111:1060–1066. [PubMed: 17962510]
6. Soriano AO, Yang H, Faderl S, et al. Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome. Blood. 2007; 110:2302–2308. [PubMed: 17596541]
7. Plumb JA, Finn PW, Williams RJ, et al. Pharmacodynamic response and inhibition of growth of human tumor xenografts by the novel histone deacetylase inhibitor PXD101. Mol Cancer Ther. 2003; 2:721–728. [PubMed: 12939461]
8. Steele NL, Plumb JA, Vidal L, et al. Pharmacokinetic and pharmacodynamic properties of an oral formulation of the histone deacetylase inhibitor Belinostat (PXD101). Cancer Chemother Pharmacol. 2011; 67:1273–1279. [PubMed: 20706839]
9. Gimsing P, Hansen M, Knudsen LM, et al. A phase I clinical trial of the histone deacetylase inhibitor belinostat in patients with advanced hematological neoplasia. Eur J Haematol. 2008; 81:170–176. [PubMed: 18510700]
10. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003; 21:4642–4649. [PubMed: 14673054]
11. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989; 10:1–10. [PubMed: 2702835]
12. Cashen A, Juckett M, Jumonville A, et al. Phase II study of the histone deacetylase inhibitor belinostat (PXD101) for the treatment of myelodysplastic syndrome (MDS). Ann Hematol. 2012; 91:33–38. [PubMed: 21538061]
13. Kuendgen A, Schmid M, Schlenk R, et al. The histone deacetylase (HDAC) inhibitor valproic acid as monotherapy or in combination with all-trans retinoic acid in patients with acute myeloid leukemia. Cancer. 2006; 106:112–119. [PubMed: 16323176]
14. Kuendgen A, Strupp C, Aivado M, et al. Treatment of myelodysplastic syndromes with valproic acid alone or in combination with all-trans retinoic acid. Blood. 2004; 104:1266–1269. [PubMed: 15155466]

15. Blum W, Klisovic RB, Hackanson B, et al. Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. J Clin Oncol. 2007; 25:3884–3891. [PubMed: 17679729]

16. Kirschbaum M, Gojo I, Goldberg SL, et al. Vorinostat in Combination with Decitabine for the Treatment of Relapsed or Newly Diagnosed Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS): A Phase I, Dose-Escalation Study. Blood (ASH Annual Meeting Abstracts). 2009; 114 (abstr 2089).

17. Odenike O, Godley LA, Madzo J, et al. A phase I and pharmacodynamic (PD) study of the histone deacetylase (HDAC) inhibitor belinostat (BEL) plus azacitidine (AZC) in advanced myeloid malignancies. J Clin Oncol. 2011; 29 (suppl; abstr 6521).

**Table 1**

Patient Characteristics

| Characteristic | Patients No. | % |
|---|---|---|
| Total patients | 12 | |
| Median age, years | 78 | |
| Range | 43–84 | |
| Age < 60 years | 1 | 8 |
| Male sex | 5 | 42 |
| Race\ethnicity | | |
| African American | 1 | 8 |
| Asian | 2 | 17 |
| Caucasian | 9 | 75 |
| Histology | | |
| Acute megakaryoblastic Leukemia | 3 | 25 |
| Acute myeloid Leukemia | 8 | 67 |
| Acute myelomonocytic leukemia | 1 | 8 |
| Karnofsky performance status score | | |
| 60 | 1 | 8 |
| 70 | 2 | 17 |
| 80 | 2 | 17 |
| 90 | 5 | 41 |
| 100 | 2 | 17 |

## Table 2

Treatment-related Toxicity

| | Treatment-Related Toxicities by Grade | | | |
|---|---|---|---|---|
| **Adverse Event** | **1** | **2** | **3** | **4** |
| *ALT, SGPT* | 3 (25%) | 1 (8%) | - | - |
| *AST, SGOT* | 1 (8%) | 2 (17%) | - | - |
| *Alkaline phosphatase* | 1 (8%) | - | - | - |
| *Anorexia* | 3 (25%) | - | - | - |
| *Bilirubin* | 1 (8%) | - | - | - |
| *Constipation* | 2 (17%) | - | - | - |
| *Cough* | 1 (8%) | - | - | - |
| *Creatinine* | 2 (17%) | - | - | - |
| *Dehydration* | - | - | 1 (8%) | - |
| *Dizziness* | 1 (8%) | - | - | - |
| *Dyspnea* | 1 (8%) | - | - | - |
| *Fatigue* | 4 (33%) | 2 (17%) | - | - |
| *Febrile neutropenia* | - | - | 1 (8%) | - |
| *Fever* | 1 (8%) | - | - | - |
| *Flu-like syndrome* | 1 (8%) | - | - | - |
| *Hematoma* | - | - | - | 1 (8%) |
| *Hypotension* | 1 (8%) | - | - | - |
| *Mucositis/stomatitis* | - | - | 1 (8%) | - |
| *Muscle weakness (not due to neuropathy)* | - | 1 (8%) | - | - |
| *Nausea* | 6 (50%) | 1 (8%) | 1 (8%) | - |
| *Pain - Abdomen NOS* | - | 1 (8%) | - | - |
| *Pain - Head/headache* | 2 (17%) | - | - | - |
| *Prolonged QTc interval* | - | - | 1 (8%) | - |
| *Sodium, serum-low* | - | - | 1 (8%) | - |
| *Supraventricula/nodal arrhythmia* | - | 1 (8%) | - | - |
| *Taste alteration* | 1 (8%) | - | - | - |
| *Vomiting* | 1 (8%) | 1 (8%) | - | - |