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Phase II study of the histone deacetylase inhibitor belinostat (PXD101) for the treatment of myelodysplastic syndrome (MDS)

Amanda Cashen,

Washington University School of Medicine, 660 S. Euclid Ave., Box 8007, St Louis, MO 63110, USA

Mark Juckett,

University of Wisconsin, 600 Highland Ave., Madison, WI 53792, USA

Alcee Jumonville,

Gundersen Clinic, Ltd., 1900 South Ave., EB2-001 La Crosse, WI, USA

Mark Litzow,

Mayo Clinic Rochester, 200 1st St. SW, Rochester, MI 55905, USA

P. J. Flynn,

Minnesota Oncology Hematology, 800 E 28th St, Suite 405, Minneapolis, MN 55407, USA

John Eckardt,

Center for Cancer Care and Research, 12855 North Forty Drive, Suite 200, St Louis, MO 63141, USA

Betsy LaPlant,

Mayo Clinic Cancer Center, 200 1st St. SW, Rochester, MI 55905, USA

Kristina Laumann,

Mayo Clinic Cancer Center, 200 1st St. SW, Rochester, MI 55905, USA

Charles Erlichman, and

Mayo Clinic Cancer Center, 200 1st St. SW, Rochester, MI 55905, USA

John DiPersio

Washington University School of Medicine, 660 S. Euclid Ave., Box 8007, St Louis, MO 63110, USA

Amanda Cashen: acashen@dom.wustl.edu

Abstract

The inhibition of histone deacetylase (HDAC) can induce differentiation, growth arrest, and apoptosis in cancer cells. This phase II multicenter study was undertaken to estimate the efficacy of belinostat, a potent inhibitor of both class I and class II HDAC enzymes, for the treatment of myelodysplastic syndrome (MDS). Adults with MDS and 2 prior therapies were treated with belinostat 1,000 mg/m² IV on days 1–5 of a 21-day cycle. The primary endpoint was a proportion of confirmed responses during the first 12 weeks of treatment. Responding patients could receive additional cycles until disease progression or unacceptable toxicity. Twenty-one patients were enrolled, and all were evaluable. Patients were a median 13.4 months from diagnosis, and 14 patients (67%) had less than 5% bone marrow blasts. Seventeen patients (81%) were transfusion dependent. Prior therapy included azacytidine ($n=7$) and chemotherapy ($n=8$). The patients were

treated with a median of four cycles (range, 1–8) of belinostat. There was one confirmed response—hematologic improvement in neutrophils—for an overall response rate of 5% (95% CI, 0.2–23). Median overall survival was 17.9 months. Grades 3–4 toxicities considered at least to be possibly related to belinostat were: neutropenia ($n=10$), thrombocytopenia ($n=9$), anemia ($n=5$), fatigue ($n=2$), febrile neutropenia ($n=1$), headache ($n=1$), and QTc prolongation ($n=1$). Because the study met the stopping rule in the first stage of enrollment, it was closed to further accrual.

Keywords

Belinostat; PXD101; Myelodysplastic syndrome; Histone deacetylase inhibitor

Introduction

Myelodysplastic syndrome (MDS) is a clonal disorder marked by dysplasia in one or more of the hematopoietic lineages, ineffective hematopoiesis, and consequent cytopenias. Currently, the most effective agents for treatment of MDS are the DNA methyltransferase inhibitors decitabine and azacitidine, which alter methylation patterns on DNA, leading to changes in gene expression and cellular differentiation. Histone deacetylase (HDAC) inhibitors also exert their activity via epigenetic changes in malignant cells, by promoting acetylation of histones and thereby, altering nucleosome and chromatin structure. Pre-clinical studies have shown the HDAC inhibitors induce differentiation in leukemic cell lines and in leukemia cells collected from acute myeloid leukemia (AML) patients [1]. Multiple HDAC inhibitors have been studied in MDS and AML, with activity observed in phase I and II studies [2–7].

Belinostat (PXD101) is a potent inhibitor of both classes I and II HDAC enzymes, and in vitro studies have demonstrated its ability to inhibit growth and promote apoptosis in cancer cell lines [8]. A phase I study in patients with advanced solid tumors demonstrated hyperacetylation of histone H4 that was sustained for 4–24 h after each dose of belinostat [9]. That study established a maximum tolerated dose of 1,000 mg/m² daily for 5 days of a 21-day cycle, with dose-limiting toxicities of fatigue, atrial fibrillation, diarrhea, nausea, and vomiting. No significant myelosuppression was observed. A similar toxicity profile was observed in a phase I study of belinostat in patients with advanced hematologic malignancies, with the exception that no cardiac events occurred. There was only one case of grades 3–4 hematologic toxicity over baseline. This multicenter phase II study was undertaken to estimate the efficacy and the toxicity of belinostat in patients with MDS.

Methods

Patient eligibility

Patients aged 18 years or older with histologically confirmed MDS (de novo or secondary) fitting any of the World Health Organization classifications (<20% bone marrow blasts) were eligible for this study. Patients with <5% bone marrow blasts also had to meet one of the following criteria: symptomatic anemia with a hemoglobin <10.0 g/dl or requiring red blood cell transfusions in the 3 months before study entry, thrombocytopenia with two or more platelet counts <50,000/μl or a significant hemorrhage requiring platelet transfusions, or neutropenia with two or more absolute neutrophil counts <1,000/μl. Additional inclusion criteria were: 2 prior therapies for MDS, ineligibility for allogeneic stem cell transplant, no prior therapy for MDS with a HDAC inhibitor, Eastern Cooperative Oncology Group performance status of 0–2, adequate renal and hepatic function, and life expectancy greater than 12 weeks. Patients were excluded if they had a marked baseline prolongation of QT/

QTc interval and/or significant cardiovascular disease. Cytogenetic risk was assigned based on the criteria of the International Prognostic Scoring System (IPSS) [10].

The study protocol was approved by the Human Research Protection Office at participating institutions. All patients provided written informed consent.

Study treatment

This was an open-label, single-arm, multicenter phase II study of belinostat administered as 1,000 mg/m² IV over 30 min on days 1–5 of a 21-day cycle. Growth factors were not routinely administered. Premedication with an antiemetic was recommended. A 25% dose reduction was allowed for patients who developed treatment-related toxicity, including worsening cytopenia. Patients continued to receive belinostat for eight cycles or until one of the following events occurred: disease progression, intercurrent illness preventing further treatment, unacceptable adverse event, or patient decision to withdraw from the study. Responding patients could continue the study treatment beyond eight cycles, until one of the above criteria applied.

Patients were evaluated by complete blood count performed weekly during cycle 1 and then at the beginning of each cycle. Bone marrow biopsy and aspiration were performed after every two cycles. Response criteria followed the definitions of the international working group [11]. Toxicities were graded per NCI CTC AE Version 3.0.

Statistical analysis

The primary endpoint was the proportion of evaluable patients achieving a confirmed response [complete response (CR), partial response (PR), or hematologic improvement (HI)] during the first 12 weeks of treatment. Secondary endpoints included time to progression, overall survival, duration of response, time to discontinuation of treatment, and toxicity. The study had 90% power to detect an effective treatment if the true proportion of patients who achieve a confirmed response rate is at least 25% versus the null hypothesis that the true confirmed response rate is at most 10%, using a two-stage Simon design with an α level of 0.10. Fifty patients were required, with 21 enrolled and assessed in the first stage. If two or fewer success were observed in stage I, accrual could be terminated.

Results

Patient characteristics and treatment

Twenty-one patients were accrued, and all were eligible and evaluable (Table 1). Patients were median 13.4 months (range, 0.3–210 months) from diagnosis, and at the time of study entry, two thirds had less than 5% bone marrow blasts (<5%, $n=14$; 5–9%, $n=6$; 10–19%, $n=1$). Thirteen patients (62%) had good risk cytogenetics, and seven (33%) had poor risk. IPSS risk score was low in six patients, intermediate-1 in eight patients, intermediate-2 in six patients, and high in one patient. Prior therapy included growth factors, azacitidine (33%), and chemotherapy (38%).

Patients were treated with median of four (range, 1–8) cycles of belinostat. Most of the 79 cycles administered were delivered on time, at full dose. Three patients had treatment delays for grade 3 hyperglycemia, recovery from surgery, and unavailability of study drug. Three patients had dose reductions for prolonged QT interval, weight loss, and unrelated medical issues. Thirteen patients (62%) completed 4 cycles of therapy. Patients ended treatment for disease progression ($n=5$), patient refusal ($n=3$), adverse event ($n=2$), or death ($n=1$).

Response to belinostat

There was one confirmed response to belinostat, hematologic improvement in neutrophils in a patient with RAEB-1 (8% bone marrow blasts, high-risk cytogenetics), for an overall response rate of 5% (95% CI, 0.2–22.9). The duration of the response was 2.1 months. Because the study met the stopping rule in the first stage of enrollment, it was closed to further accrual after 21 patients.

At a median follow-up of 12 months (range, 6.1–32.9), nine (43%) patients progressed, and 14 patients (67%) died. Median time to progression was 14.9 months (95% CI, 5.8–30), and median overall survival was 17.9 months (95% CI, 13.2–30; Fig. 1). Twelve-month time to progression was 66% (95% CI, 47–90), and 12-month overall survival was 71% (95% CI, 64–94).

Toxicity

Belinostat was generally well tolerated in this patient population, although hematologic adverse events were common. Grade 3 or 4 hematologic toxicity occurred in 19 (90%) and 15 (71%) patients, respectively, regardless of attribution. Grade 3 or 4 hematologic toxicities attributed to belinostat occurred in 13 (62%) and 11 (52%) patients, respectively, including neutropenia ($n=10$), thrombocytopenia ($n=9$), and anemia ($n=5$), although for many patients, the cytopenias were not changed from baseline (Table 2). In general, cytopenias persisted, but did not worsen, when patients received subsequent cycles. Grade 3 or 4 non-hematologic toxicities considered at least possibly related to belinostat occurred in five (24%) and one (5%) patients, respectively, and included fatigue ($n=2$), febrile neutropenia ($n=1$), headache ($n=1$), and QTc prolongation ($n=1$; Table 3). Two patients had grade 2 cytokine-release syndrome during belinostat infusion, which was managed with administration of steroids and reduction of the infusion rate.

Discussion

The aberrant acetylation of histones is a feature of malignant cells, and the inhibition of HDAC enzymes can change histone acetylation patterns in ways that lead to increased expression of genes involved in differentiation and apoptosis [12]. The use of HDAC inhibitors in MDS has been approached with enthusiasm, given the pre-clinical evidence that HDAC inhibitors promote differentiation in malignant myeloid cell lines [1] and the fact that hypomethylating agents, which also act via epigenetic mechanisms, have established efficacy in MDS [13, 14]. However, in phase I and II clinical trials, single agent activity of HDAC inhibitors in MDS and AML has been modest, with response rates ranging from 0% to 17% in trials that enrolled primarily patients with AML [2–6, 15]. In contrast, Kuendgen et al. reported a superior response rate in MDS patients treated with the HDAC inhibitor valproic acid, with or without all-trans retinoic acid [7]. In their trial, the subset of 23 patients with MDS and a normal blast count had an overall response rate of 52% (11 HI and 1 PR).

Belinostat, a member of the hydroxamate class of HDAC inhibitors, induces a concentration-dependent acetylation of histones H3 and H4 in tumor cell lines, associated with apoptosis or cytotoxicity, and it has an antitumor activity in *in vivo* xenograft models [8]. In a phase I clinical trial of belinostat in patients with advanced hematological malignancies, the maximum tolerated dose (MTD) was 1,000 mg/m² [16], the same MTD established in a phase I study in solid tumors [9]. The only grade 3 or 4 hematological toxicity observed in the phase I studies was a single case of grade 3 lymphopenia.

In the current study, belinostat had limited activity in patients with MDS, with one response observed in the study population. The patients in this study had received one or two lines of

prior therapy, and most were transfusion dependent, with two to three cytopenias. These high-risk disease features may have contributed to the low response rate. The treatment was generally well tolerated, and 13 of 21 patients completed at least four cycles of therapy, with rare dose delays or reductions. However, hematologic toxicities attributed to belinostat that occurred at a higher frequency than was reported in the phase I studies, with grades 3–4 neutropenia, anemia, and thrombocytopenia at least possibly secondary to belinostat occurring in 48%, 24%, and 43% of patients, respectively. Of note, all patients had at least one cytopenia at baseline, and the majority of patients with hematologic toxicity attributed to belinostat had no or one CTCAE grade shift in their cytopenia. Given that no patient in the phase I studies had acute leukemia or MDS, belinostat may cause myelosuppression primarily in patients with preexisting bone marrow dysfunction.

Histone deacetylase inhibitors may be more effective in the therapy of MDS and AML if they are given in combination with the hypomethylating agents azacytidine and decitabine, which can alter gene expression via changes in DNA methylation. For example, three studies that combined valproic acid with azacytidine [17, 18] or decitabine [19] for the treatment of AML or high-risk MDS reported CR + PR rates of 22–42%. Belinostat has been combined with azacytidine in a dose-finding study that enrolled patients with AML, intermediate to high-risk MDS, or advanced myeloproliferative disorders [20]. Seventy-eight percent of the 23 patients had primary refractory or relapsed disease. Belinostat was safely escalated to 1,000 mg/m² for 5 days every 4 weeks, in combination with standard dose azacytidine, and responses (CR, PR, and HI) were observed in seven patients (30%). Randomized trials should be pursued to determine the clinical benefit of adding belinostat and other HDAC inhibitors to hypomethylating agents for the treatment of MDS or AML.

Acknowledgments

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Fig. 1.
Overall survival (*solid line*) and time to progression (*broken line*) of study population

Table 1

Patient characteristics

	<i>n</i> (%)
Age, median (range)	67 (48–79)
Gender, male/female	17/4
Months from diagnosis, median (range)	13.4 (0.3–210)
MDS subtype	
RA	3 (14)
RARS	4 (19)
RCMD	2 (10)
RAEB-1	7 (33)
RAEB-2	2 (10)
Unclassified	3 (14)
Bone marrow cytogenetics	
Good risk	13 (62)
Intermediate risk	1 (5)
Poor risk	7 (33)
Number of cytopenias	
0–1	7 (33)
2–3	14 (67)
Transfusion dependent	17 (81)
Previous treatment	
ESA	11 (52)
G-CSF	7 (33)
Prednisone	2 (10)
Azacitidine	7 (33)
Chemotherapy	8 (38)

RA refractory anemia, *RARS* RA with ringed sideroblasts, *RCMD* refractory cytopenias with multilineage dysplasia, *RAEB* RA with excess blasts, *ESA* erythropoiesis-stimulating agent, *G-CSF* granulocyte colony-stimulating factor

Maximum severity of hematologic adverse events considered at least possibly related to belinostat

Table 2

Toxicity	Gr. 1	Gr. 2	Gr. 3-4	Shift in toxicity grade from baseline			
				0	+1	+2	+3
Neutropenia	0	4 (19)	10 (48)	4	6	3	1
Anemia	0	5 (24)	5 (24)	6	4	0	0
Thrombocytopenia	4 (19)	0	11 (52)	5	8	0	2

The number of events (% of patients) is given by toxicity grade (CTCAE version 3) and by shift in grade from baseline

Table 3

Maximum severity of non-hematologic adverse events considered at least possibly related to belinostat, number of events by toxicity grade (CTCAE version 3)

Toxicity	Gr. 2	Gr. 3-4
Fatigue	4	2
QTc Prolongation	1	1
Febrile neutropenia	0	1
Headache	0	1
Constipation	3	0
Diarrhea	2	0
Cytokine-release syndrome	2	0
Dyspnea	2	0
Pneumonia	1	0
Confusion	1	0
Hypoalbuminemia	1	0
Myalgia	1	0
Hiccups	1	0
Dyspepsia	1	0