A Phase I Study of Panobinostat in Combination With Gemcitabine in the Treatment of Solid Tumors

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Abstract: Purpose: To evaluate the safety and tolerability of the combination of orally administered panobinostat with gemcitabine in patients with advanced solid tumors. Patients and methods: Patients received oral panobinostat administered 2 or 3 times weekly (continuous or intermittent dosing in combination with intravenous gemcitabine administered on days 1, 8, and 15 every 28 days or on days 1 and 8 every 21 days). Toxicity assessments were ongoing, and disease assessments were repeated every 2 treatment cycles. Results: A total of 63 cycles of study treatment were administered to 17 patients over 5 different dose levels. Dose-limiting toxicities occurred at all dose levels. In all instances, dose-limiting toxicities were due to grade 4 myelosuppression or myelosuppression warranting dose modifications during the first treatment cycle. Nonhematologic toxicities were mild to moderate in intensity and consisted of anorexia, constipation, diarrhea, fatigue, nausea, vomiting, and rash. One patient with ovarian cancer had an unconfirmed partial response, and 5 patients had stable disease lasting more than 4 cycles. Conclusion: Dosing of the combination regimen of panobinostat and gemcitabine is limited by myelosuppression. The recommended doses for further study are intermittent oral panobinostat administered at a dose of 10 mg 3 times weekly for 2 weeks in combination with gemcitabine 800 mg/m^2 administered intravenously on days 1 and 8 every 21 days.

Introduction

Epigenetic modifications play an important role in tumorigenesis. Histone deacetylase (HDAC) inhibitors are a new class of anticancer agents that inhibit cell growth, trigger apoptosis, and inhibit angiogenesis but whose mechanism of action has not been fully elucidated.[1-4] Vorinostat (Zolinza, Merck Sharp & Dohme Corp) and romidepsin (Istodax, Celgene) are 2 HDAC inhibitors that are approved for the treatment of cutaneous T-cell lymphoma. Several additional compounds are also in development, including the pan-

deacetylase inhibitor panobinostat (LBH589, Novartis).[5,6] Panobinostat has demonstrated potent antitumor activity in a variety of preclinical models, including pancreatic cancer, and it has also demonstrated clinical antitumor activity in patients with cutaneous T-cell lymphoma, Hodgkin lymphoma, hematologic malignancies, multiple myeloma, and solid tumors.[5,7-10]

Both oral and intravenous formulations of panobinostat are being developed. The phase I study of intravenous panobinostat was conducted in patients with refractory hematologic malignancies.[9] The dose-limiting toxicity (DLT) was an asymptomatic reversible QTcF prolongation that was observed with higher repeated doses. Intermittent intravenous (weekly) and oral (twice or thrice weekly) panobinostat dosing schedules have demonstrated a much lower incidence of QTcF prolongation, a class effect of the HDAC inhibitors.[11-13] Other toxicities that have been observed in early clinical trials include anorexia, nausea, fatigue, diarrhea, and transient thrombocytopenia. The recommended oral panobinostat dose for subsequent studies was 30 mg every Monday, Wednesday, and Friday weekly. At this dose, histone acetylation of peripheral blood lymphocytes was observed for 72 hours or more postdose in 50% of patients. Two complete responses and 4 partial responses were observed among a subset of 10 patients with cutaneous T-cell lymphoma who were enrolled in the trial.[13,14]

The antitumor activity of the HDAC inhibitors in patients with solid tumors has been somewhat disappointing to date. In an attempt to increase the antitumor activity in the solid tumor setting, the drugs have been combined preclinically with a variety of chemotherapeutic agents. Numerous preclinical studies have demonstrated enhanced antitumor activity of gemcitabine (Gemzar, Lilly) when combined with an HDAC inhibitor.[15-21] Gemcitabine is an antimetabolite that has demonstrated activity in the treatment of pancreatic cancer, non–small cell lung cancer, breast cancer, ovarian cancer, bladder cancer, and lymphoma. This phase I protocol evaluated the safety and tolerability of the combination of orally administered panobinostat with gemcitabine in patients with advanced solid tumors.

Patients and Methods

Patient Selection

Patients were eligible if they had a histologically documented metastatic or locally advanced, incurable, and measurable malignancy for which gemcitabine was clinically appropriate. Patients were ages 18 years or older, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were allowed to have received a maximum of 3 prior regimens in a metastatic setting, which could have included other targeted agents, immunotherapy, and chemotherapy. Any chemotherapy, investigational drug therapy, or major surgery was to be completed at least 4 weeks prior to starting the study drug. Patients with the following baseline laboratory values were eligible: absolute neutrophil count (ANC) of 1,500/μL or greater, hemoglobin of 9 g/dL or greater, platelets of 100,000/μL or greater, bilirubin of 1.5 mg/dL or less, aspartate aminotransferase and alanine aminotransferase at or less than 2.5 × the upper limit normal (ULN) or at or less than 5.0 × ULN in patients with liver metastases, creatinine of 2.0 mg/dL or less or 24-hour creatinine clearance of 50 mL/min or greater, albumin of 3 g/dL or greater, and potassium, phosphorus, calcium, and magnesium levels at or exceeding the lower limit normal (LLN).

Patients were excluded from the trial for any of the following reasons: prior administration of HDAC, deacetylase, heat shock protein 90 inhibitors, or valproic acid for the treatment of cancer or the need to receive valproic acid during treatment or within 5 days prior to the start of panobinostat; impaired cardiac function; uncontrolled hypertension or cardiac arrhythmias; active central nervous system (CNS)/meningeal metastases; or known HIV infection. Also excluded were patients with diarrhea greater than grade 1 or any other gastrointestinal disease resulting in the impaired absorption of orally administered panobinostat, uncontrolled coagulopathy, or abnormal thyroid function at screening (defined as thyroid-stimulating hormone or free T4). Patients with hypothyroidism that was diagnosed prior to study entry and was stable on thyroid replacement were eligible. Pregnant or lactating women were ineligible, as were patients of childbearing potential not utilizing adequate contraception. This study was approved by a central Institutional Review Board, and written informed consents were obtained from all patients prior to enrollment.

Treatment Plan

Patients originally received oral panobinostat administered 1 time weekly continuously. Gemcitabine was administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days. Due to DLTs encountered in patients enrolled at the initial dose level, the protocol was amended to allow continuous or intermittent panobinostat administration 3 times weekly in combination with gemcitabine administered weekly × 3 weeks every 28 days or weekly × 2 weeks every 21 days. Toxicity assessments were ongoing, and disease assessments were repeated every 2 treatment cycles. Patients were allowed to receive study treatment until disease progression or until toxicities warranted drug discontinuation.

Table 1. Dose Escalation Schema

Dose Level	Panobinostat Dose	Gemcitabine Dose	Duration of Cycle	Number of Patients Enrolled	Dose-Limiting Toxicities
1	30 mg twice weekly continuously	1,000 mg/m^2 days 1, 8, 15	28 days	3	Grade 4 thrombocytopenia in cycle 1 (2 patients)
-1	20 mg twice weekly continuously	800 mg/m^2 days 1, 8, 15	28 days	3	Inability to administer full doses in cycle 1 due to myelosuppression (2 patients)
Protocol Amendment					
1 (Amd 1)	10 mg 3 times weekly continuously	1,000 mg/m^2 days 1, 8, 15	28 days	3	Inability to administer full doses in cycle 1 due to myelosuppression (2 patients)
-1 (Amd 1)	10 mg 3 times weekly × 2 weeks	1,000 mg/m^2 days 1, 8	21 days	2	Inability to administer full doses in cycle 1 due to myelosuppression (2 patients)
-2 (Amd 1)	10 mg 3 times weekly × 2 weeks	800 mg/m^2 days 1, 8	21 days	6	Inability to administer full doses in cycle 1 due to myelosuppression (1 patient)

Amd=amendment.

This was a single-center, dose escalation trial. Table 1 shows all dose levels assessed and the number of patients that were enrolled at each dose level. Three patients were enrolled at each dose level; if 1 or no patients out of the 3 experienced a DLT, the dose level was expanded to 6 patients. If 2 or more of 6 patients or 2 or more of 3 patients experienced DLT at any dose level, dose escalation was stopped. Dose escalation began at dose level 1. Because of DLTs encountered with the combination regimen, the dose was de-escalated after the first dose level, and the protocol was subsequently amended with further regimen modifications. The highest dose level that generated a DLT in 0 out of 3 or 1 out of 6 patients would be the maximum tolerated dose (MTD) or the dose recommended for subsequent studies. DLTs were assessed in the first treatment cycle and were used to determine subsequent dose escalation or reduction. A DLT was defined as the following: (1) ANC less than 500/μL, platelets less than 50,000/μL for more than 5 days, or grade 4 neutropenia with fever; (2) grade 3 or 4 treatment-related nonhematologic toxicity with the exception of alopecia, nausea, and vomiting; (3) grade 3 or higher nausea and/or vomiting despite the use of optimal antiemetic therapy; (4) grade 3 or higher diarrhea despite the use of supportive therapy; (5) an inability to administer all doses in cycle 1 at full dose (100%) or an inability to start cycle 2 of treatment as scheduled due to treatment-related toxicities; or (6) any treatment delay of greater than 2 weeks for toxicity. The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 were used to grade all adverse events. Patients were monitored for treatment-related toxicities throughout all cycles of treatment.

Drug Dosing and Administration

Panobinostat was provided by Novartis and was supplied as 5-mg or 20-mg hard gelatin capsules. Patients took their oral dose of panobinostat in the morning with an 8-oz (240-mL) glass of water after a fast lasting at least 2 hours. They were instructed to continue fasting for 2 hours after each dose.

Gemcitabine doses were calculated based on the actual body surface area for each patient. The appropriate amount of drug was added to normal saline and administered over a 30-minute period. Gemcitabine was obtained from commercial supplies.

Dose Modification/Reduction Guidelines

Toxicity assessments were based on clinical assessment and laboratory assessment of additional hematologic and nonhematologic toxicities taken on the day of therapy. For administration of panobinostat, patients were also monitored regularly for adequate cardiac function before receiving their dose of panobinostat. This included an assessment of serum potassium, magnesium, phosphorus, and calcium levels (total corrected for albumin, or ionized calcium) at or greater than the LLN, and mandatory electrocardiograms (ECGs) performed at screening and then again during at least the first cycle of treatment.

Panobinostat doses were held until resolution or reduced by 1 dose level for any of the following: grade 4 neutropenia, grade 3 or 4 febrile neutropenia, grade 3 or 4 thrombocytopenia, serum creatinine at or exceeding 2 × the ULN, serum bilirubin at or exceeding 2 × the ULN, grade 3 transaminase levels, and grade 2 or higher

diarrhea or vomiting. If the dosage was delayed longer than 2 weeks from the scheduled dose, then the patient was removed from the study. If doses of panobinostat were missed due to reasons aside from dose modifications, the patient was to take the missed dose the following day.

Day 1 treatment of a new cycle of gemcitabine could be administered only when the ANC was at 1,500/μL or higher, the platelets were at 100,000/μL or higher, and all nonhematologic toxicities were resolved to grade 2 or lower. Patients requiring a delay of 14 days or more for the administration of the next treatment cycle were removed from the study. Gemcitabine doses within a treatment cycle were based on the ANC, and platelet counts were obtained on the day of treatment. Patients with an ANC of 1,000/μL or higher and platelets of 75,000/μL or higher received 100% of the dose; if the ANC was between 500 and 1,000/μL or the platelets were between 50,000 and 75,000/μL, then the dose was reduced to 75%. The drug was held if the ANC was less than 500/μL or the platelets were less than 50,000/μL. Gemcitabine was also omitted in patients experiencing grade 3 or higher nonhematologic toxicities. Patients who experienced febrile neutropenia or grade 4 thrombocytopenia had the gemcitabine dose permanently reduced by 1 dose level.

Cardiac Monitoring Requirements

All patients had a baseline ECG performed to determine eligibility. Subsequently, patients were intensively monitored during cycles 1 and 2. On treatment days when ECGs were required, the patient was dosed with panobinostat in the clinic. The patient's QTc interval had to be at or within 450 msec before the patient could be dosed. Dose reductions and management guidelines for QTc prolongation were outlined in the protocol.

Disease Assessment

Disease evaluations were done within 4 weeks of starting study treatment. Evaluations were repeated every 2 cycles or when clinically necessary. Response and progression were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[22]

Results

Seventeen patients received a total of 63 cycles of treatment over the 5 dose levels outlined in Table 1. The patient demographics are described in Table 2. Five patients received 5 or more cycles of therapy (5, 6, 6, 8, and 10 cycles). Table 1 describes the dose levels explored and the DLTs encountered at each dose level. Panobinostat was initially dosed twice weekly, based on the monotherapy trials that were ongoing at the time of study initiation. The first dose level in the protocol was panobinostat 30 mg orally twice weekly continuously in combination with gemcitabine 1,000 mg/m^2 intravenously on days 1, 8, and 15 every 28 days. Three patients were enrolled at this initial dose level, with 2 of the 3 patients experiencing dose-limiting grade 4 thrombocytopenia on cycle 1, day 15 (platelets of 5,000/μL and 16,000/μL). As a result, subsequent patients were enrolled at dose level -1: panobinostat 20 mg orally twice weekly continuously in combination with gemcitabine 800 mg/m^2 intravenously on days 1, 8, and 15 every 28 days. Two of the 3 patients enrolled at this dose level experienced myelosuppression resulting in panobinostat doses being held (grade 3 thrombocytopenia and grade 4 neutropenia) and the cycle 1, day 15 gemcitabine doses being held (grade 3 thrombocytopenia) or reduced (grade 3 neutropenia). These dose modifications during cycle 1 of treatment were defined as DLTs per the protocol.

Table 2. Patient Demographics (N=17)

Median Age (range)	63 years (35–72 years)
Sex	11 Women/6 Men
ECOG Performance Status	
0	14 (82%)
1	3 (18%)
Prior Treatment	
Chemotherapy	15 (88%)
Radiation Therapy	7 (41%)
Surgery	13 (76%)
Tumor Type	
Breast	5 (29%)
Ovarian	3 (18%)
Pancreatic	3 (18%)
NSCLC	2 (12%)
Other*	4 (24%)

*Other tumor types: bladder cancer, thymoma, cholangiocarcinoma, and carcinoma of unknown primary (1 patient each).

ECOG=Eastern Cooperative Oncology Group; NSCLC=non-small cell lung cancer.

As a result of the toxicities encountered at the initial dose levels, the protocol was amended in an attempt to improve the tolerability of the regimen. Following the amendment, all newly enrolled patients received panobinostat in lower doses 3 times weekly in combination with gemcitabine. Three patients were enrolled at the first dose level following the amendment: panobinostat 10 mg orally 3 times weekly continuously plus gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 every 28 days. Two of the 3 patients enrolled required doses to be held or modified during cycle 1 of treatment due to myelosuppression

and were thus considered to have DLTs. Two patients were enrolled on dose level -1, which consisted of intermittent panobinostat dosing (10 mg 3 times weekly for 1 week only) in combination with gemcitabine 1,000 mg/m^2 on days 1 and 8 every 21 days. Again, both patients experienced myelosuppression during cycle 1, which warranted dose reductions or modifications and was defined as a DLT. As a result, the dose was again de-escalated to dose level -2 following a protocol amendment (panobinostat 10 mg 3 times weekly for 1 week only) in combination with gemcitabine 800 mg/m^2 on days 1 and 8 every 21 days. A total of 6 patients were enrolled at the final dose level, with only 1 patient experiencing a DLT defined as myelosuppression warranting doses to be held or reduced during cycle 1 of treatment. As a result, this dose level is the dose recommended for subsequent study.

Table 3 describes the grade 1–4 toxicities that were reported during the trial. Hematologic toxicities were reported most often and defined the DLTs of the protocol. During study treatment, most patients (14, 82%) received darbepoetin. No patients received platelet transfusions, while only 2 patients (12%) received packed red blood cell transfusions. The nonhematologic toxicities were predominantly mild to moderate in intensity and consisted primarily of anorexia, constipation, diarrhea, fatigue, nausea, vomiting, and rash. Grade 3 diarrhea, dyspnea, hypophosphatemia, nausea, and vomiting were reported in 1 patient each. No QTc changes of grade 2 or higher were observed in any of the ECGs obtained from patients treated with panobinostat and gemcitabine. Of the 17 patients enrolled, none were removed from the study due to treatment-related toxicities.

Table 3. Grade 1–4 Toxicities (N=17)

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	1 (6%)	12 (71%)	2 (12%)	0 (0%)
Neutropenia	2 (12%)	2 (12%)	4 (24%)	6 (35%)
Thrombocytopenia	2 (12%)	2 (12%)	9 (53%)	3 (18%)
Diarrhea	4 (24%)	0 (0%)	1 (6%)	0 (0%)
Dyspnea	6 (35%)	0 (0%)	1 (6%)	0 (0%)
Hypophosphatemia	0 (0%)	0 (0%)	1 (6%)	0 (0%)
Nausea	7 (41%)	3 (18%)	1 (6%)	0 (0%)
Vomiting	7 (41%)	1 (6%)	1 (6%)	0 (0%)

Antitumor Activity

Sixteen patients were evaluable for response. One unconfirmed partial response was reported in a patient with ovarian cancer. Eight patients had stable disease as the best response to treatment. The median duration of stable disease was 6 cycles (range, 3–10 cycles). Five patients had stable disease lasting more than 4 cycles: 1 patient with pancreatic cancer (lasting 6 cycles), 1 patient with non–small cell lung cancer (lasting 6 cycles), and 3 patients with breast cancer (lasting 5, 8, and 10 cycles). Seven patients had progressive disease as their best response to treatment, and 1 patient was unevaluable for response due to patient request.

Discussion

The initial dose level for this phase I dose escalation trial was oral panobinostat 30 mg administered twice weekly continuously in combination with gemcitabine 1,000 mg/m^2 intravenously on days 1, 8, and 15 every 28 days. Dose-limiting grade 4 thrombocytopenia was encountered on day 15 of cycle 1 in 2 out of 3 patients enrolled at this dose level. As a result, the dose was de-escalated to dose level -1, which was also intolerable due to myelosuppression, warranting dose modifications during cycle 1. In an attempt to improve the tolerability of the regimen, the protocol was amended to change the panobinostat dose to a lower dose administered 3 times weekly in combination with standard-dose gemcitabine (1,000 mg/m^2 days 1, 8, and 15 every 28 days). Myelosuppression warranting cycle 1 dose reductions was again encountered, so the treatment regimen was then modified to administer panobinostat 3 times weekly on an intermittent schedule (2 weeks out of 3) in combination with gemcitabine on days 1 and 8 of a 21-day dosing regimen. Despite the modified panobinostat dosing, patients were still unable to tolerate full-dose gemcitabine on the 3-week dosing schedule. However, the final dose level explored (panobinostat 10 mg 3 times weekly × 2 weeks in combination with gemcitabine 800 mg/m^2 on days 1 and 8 every 21 days) was well tolerated in 5 of the 6 patients enrolled. Although multiple dose de-escalations were required in this trial due to myelosuppression, the incidence of grade 4 neutropenia and thrombocytopenia were relatively low (35% and 18%, respectively). Three patients developed grade 4 thrombocytopenia during

this trial; 1 of these events were encountered at the first dose level. According to the definitions outlined in the protocol, an inability to administer all doses in cycle 1 at full dose was considered a DLT. Panobinostat doses were held for grade 4 neutropenia or grade 3 or higher thrombocytopenia. Gemcitabine doses were reduced for grade 3 neutropenia or platelet counts of 50–75,000/μL and were held for grade 4 neutropenia or platelet counts were less than 50,000/μL during a treatment cycle. As a result, the DLTs in this protocol were predominantly defined by treatment regimen modifications based on hematologic values rather than severe hematologic or nonhematologic toxicities.

The antitumor activity of gemcitabine is enhanced when combined with HDAC inhibitors in preclinical models. The data from this trial suggest that this is true in the clinical setting as well. Despite the use of attenuated doses of panobinostat and gemcitabine in the combination regimen, 1 partial response was reported in a patient with ovarian cancer, and prolonged stable disease (>4 cycles) was reported in patients with breast cancer (3 patients), pancreatic cancer (1 patient), and non–small cell lung cancer (1 patient).

The initial phase I trial of intravenous panobinostat utilized an intensive 7-consecutive day dose schedule and was dose-limited by grade 2 and 3 QTcF prolongation.[9] Subsequent trials utilizing weekly intravenous dosing or oral doses administered on days 1, 3, and 5 weekly demonstrated a much lower incidence and severity of QTcF prolongation.[11] Further evaluation of QTcF prolongation in patients receiving up to 40 mg per dose of oral panobinostat 3 times weekly showed an infrequent incidence of QTcF prolongation of grade 2 or greater.[23] Patients in this trial had serial ECGs performed at several time points throughout the study. No patients experienced grade 2 (increase in baseline QTc value >60 msec) or grade 3 (QTc >500 msec) QTcF prolongation.

Dosing of the combination regimen of panobinostat and gemcitabine is limited by myelosuppression. The recommended doses for further study are intermittent oral panobinostat administered at a dose of 10 mg 3 times weekly for 1 week in combination with gemcitabine 800 mg/m^2 administered intravenously on days 1 and 8 every 21 days. Phase II trials of the combination should be considered in patients with tumor types that are appropriate for gemcitabine-based therapy, such as pancreatic, breast, lung, and ovarian cancer.

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