Phase II Study of Panobinostat and Bortezomib in Patients with Pancreatic Cancer Progressing on Gemcitabine-based Therapy

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Abstract. Background: This single-arm, phase II study was designed to determine the efficacy and safety of panobinostat and bortezomib in patients with advanced pancreatic cancer. Patients and Methods: Patients had to have a histological diagnosis of pancreatic cancer and progression on a standard gemcitabine-based therapy. Treatment cycles consisted of 21 days, with bortezomib given twice weekly at 1.3 mg/m² and panobinostat three times weekly at 20 mg during the first two weeks, followed by a 9-day rest period. Results: Seven patients (3 female, 4 male) were treated with at least one cycle, but the study was suspended after the enrollment of these patients because of a complete lack of treatment responses and early treatment-related toxicity. Median progression-free survival was 2.1 months (95% Confidence interval: 1.7-2.3 months). The most common grade 3 or 4 adverse events were thrombocytopenia (57%) and diarrhea (29%). Conclusion: Treatment of advanced pancreatic cancer with bortezomib in combination with panobinostat is not supported by our clinical study.

Pancreatic cancer accounts for fewer than 3% of all cancer cases, but it is the third leading cause of cancer-related death in the United States. At the time of diagnosis, approximately 80% of patients have locally advanced or metastatic disease and are ineligible for surgery, and the 5-year survival rate for these patients is only 6% and <2%, respectively (1). In patients with advanced disease, gemcitabine alone or in combination with other agents has demonstrated only a minimal improvement in survival in a first-line setting (2). Thus, there is an urgent need to develop new systemic agents to improve the survival of patients with advanced pancreatic cancer.

Bortezomib, a small-molecule proteasome inhibitor, has activity in multiple myeloma and a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (3-5). A recent clinical trial, however, has shown that bortezomib in combination with gemcitabine was disappointing as a treatment for advanced solid tumors (6). Preclinical studies have shown that proteasome inhibition and histone deacetylase (HDAC) inhibition can act synergistically against chronic myelogenous leukemia, lymphoma, non-small cell lung cancer, and pancreatic cancer cell lines (7-10). When pancreatic cancer cells are exposed to bortezomib, they form aggregates of ubiquitin-conjugated proteins, called aggresomes, in both in vitro and in vivo models, and inhibition of aggresome formation with an HDAC inhibitor can strongly potentiate the efficacy of bortezomib (11).

DACs are enzymes that regulate DNA structure and organization through deacetylation and play a critical role in chromatin modification and gene expression. DAC activity is associated with DNA modifications that lead to increased growth and proliferation of cancer cells (12-16). Studies indicate that HDACs can also regulate the function of nonhistone proteins by promoting ubiquitin-dependent proteasomal degradation (17). Recently, the HDAC inhibitor vorinostat was approved by the FDA for the treatment of refractory cutaneous manifestations of cutaneous T-cell lymphoma (18). Another promising drug in this class is panobinostat (LBH589), a deacetylase inhibitor belonging to a structurally novel cinamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor that has shown antitumor activity in pre-clinical models and in phase I and II studies of advanced solid tumors and hematological malignancies (19-21).

Taken together, these data provide an excellent rationale for combining bortezomib and panobinostat in pancreatic cancer. We designed a nonrandomized, phase II study to evaluate the combination of bortezomib and panobinostat in patients with advanced pancreatic cancer.
Patients and Methods

Patient selection. All patients were recruited from the University of Minnesota Masonic Cancer Center between March 2010 and November 2010. Patients were included in this trial if they were ≥18 years of age, had a histological diagnosis of pancreatic cancer (except neuroendocrine tumors), had tumor progression after receiving gemcitabine therapy (single agent or combination) and had one or more metastatic tumors measurable on computed tomographic (CT) scan per RECIST criteria. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, adequate organ function and bone marrow reserve [defined as absolute neutrophil count ≥1.5×10⁹/l; platelet count ≥100×10⁹/l; hemoglobin ≥9 g/dl; bilirubin ≤1.5 times the institutional upper limit of normal (ULN); aspartate aminotransferase/serum glutamic oxaloacetic transaminase and alanine aminotransferase/serum glutamate pyruvate transaminase ≤2.5×ULN or ≤5.0×ULN if the transaminase elevation was due to disease involvement; serum creatinine ≤1.5×ULN or calculated creatinine clearance ≥50 ml/min using the Cockroft and Gault formula; serum sodium, potassium, phosphate, magnesium ≥LLN; and baseline uri- nalysis; serum creatinine ≤1.5×10⁹/l; hemoglobin ≥9 g/dl; bilirubin ≤1.5 times the institutional upper limit of normal (ULN); aspartate aminotransferase/serum glutamic oxaloacetic transaminase and alanine aminotransferase/serum glutamate pyruvate transaminase ≤2.5×ULN or ≤5.0×ULN if the transaminase elevation was due to disease involvement; serum creatinine ≤1.5×ULN or calculated creatinine clearance ≥50 ml/min using the Cockroft and Gault formula; serum sodium, potassium, phosphate, magnesium ≥LLN; and baseline multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO) demonstrating left ventricular ejection fraction ≥50% and without evidence of significant cardiovascular disease].

Patients were required to provide signed informed consent and use an appropriate contraceptive method. The study protocol was approved by the Institutional Review Board prior to study initiation and was performed in compliance with the principles of good clinical practice (GCP) as outlined by the Helsinki Declaration and federal and institutional guidelines. The study was registered with ClinicalTrials.gov (NCT01056601).

Treatment schedule. Treatment was administered on a 21-day schedule. Panobinostat was administered orally as a single daily dose of 20 mg on days 1, 3, 5, 8, 10, and 12 followed by a 9-day rest period. Bortezomib was given at a dose of 1.3 mg/m² by intravenous push, on days 1, 3, 5, 8, and 10, and 12. Dose modification guidelines were provided in the study protocol. Tumors were measured with CT or magnetic resonance imaging (MRI) scans every two cycles. All scans were centrally reviewed by an independent reviewer. Drug toxicity grades were reported using Common Toxicity Criteria version 2.0 (22) and were coded by using preferred terms of the modified Medical Dictionary for Regulatory Activities (MedDRA) version 9.0 (23).

Statistical considerations. The study was designed to accrue 60 patients with a 81% power to detect a 50% increase in median PFS from 2 months to 3 months. Continuous variables were summarized by using descriptive statistics, and categorical variables were summarized by using frequencies and percents. Responses were assessed per RECIST 1.0 (24) and overall response rates were estimated along with their exact binomial two-sided 95% confidence intervals (CIs). The Kaplan-Meier method was used to assess time-to-event variables of PFS.

Results

Patient characteristics. Between March 2010 and November 2010, 12 patients were enrolled in this study and 7 received treatment at the University of Minnesota (Table I). The trial was terminated before reaching the intended sample size of 60 patients because no clinical efficacy was observed and patients experienced significant toxicities. All seven patients treated in this study had stage IV disease, with six diagnosed with pancreatic adenocarcinoma and one diagnosed with ampullary carcinoma of the pancreas.

Drug administration. A total of 12 cycles of therapy were completed, with a median of 2 cycles per patient (range: 1-2). Five (67%) patients had one or more dose adjustments, including two (27%) dose omissions and three dose reductions (43%). One patient (14%) withdrew from the study after the first cycle of therapy due to transportation inconvenience; he later died from progressive disease.

Antitumor activity. No patient continued beyond two cycles of therapy. All seven patients experienced disease progression and died from their disease. The median PFS was 0.86 months (95% CI=0.36-1.05 months) (Figure 1). The median overall survival was 4.01 months (95% CI=1.64-5.95 months) (Figure 2).

Drug safety. Grade 3 or 4 hematologic and non-hematologic toxicities were common (Table II). Thrombocytopenia of all grades was 4/7. Two patients had dosing withheld during cycle 1, and all who continued onto cycle 2 either had a dose reduction with the start of the next cycle or had the drug...
withheld during that cycle. One patient experienced asymptomatic prolongation of corrected QT (QTC) interval. One patient with prior history of pulmonary embolus who had been treated with inferior vena cava filter and fondaparinux sodium developed subcortical white matter frontal lobe and right posterior occipital infarcts during cycle 2; this patient became blind but later recovered vision; this event was attributed to tumor embolic infarcts and was unlikely related to the study drug.

Discussion

This study is the first to combine a proteasome inhibitor with an HDAC inhibitor for pancreatic cancer therapy. A majority of patients (4/7) experienced thrombocytopenia, and given the overlapping toxicities of panobinostat and bortezomib, this finding was not unexpected. However, the overall incidence of grade 4 non-hematological adverse events was high and came close to triggering early study termination. We decided to stop the study after the first seven patients due to a lack of clinical benefit. A PFS of only 0.86 months was less than the one observed in historic data, in patients treated with best supportive care only (25).

There was one thromboembolic event in which a patient had sudden vision change after one cycle of treatment. An MRI scan of the brain revealed an ischemic area in the occipital area. Our patient’s experience was complicated by concurrent diagnosis of vein thrombosis and history of pulmonary emboli. Olsen et al. previously reported a patient with cutaneous T-cell lymphoma receiving vorinostat who experienced an ischemic stroke (26). In contrast, Kim et al. reported a neuroprotective effect of HDAC inhibitors in rat stroke models (27). The evidence so far is conflicting regarding the relationship between HDAC inhibitors and stroke. Bortezomib has not been reported to be associated with stroke when it is mostly used in combination with steroids to treat multiple myeloma. It is therefore unknown whether combining bortezomib and panobinostat potentiates the stroke risk.

The previously reported overall incidence of panobinostat-induced QT prolongation varies from as high as 33.3% with intensive dose regimens of daily intravenous panobinostat for 7 days to as low as 6.3% in patients treated with oral panobinostat three times weekly (28-29). One patient in our study experienced QTC prolongation, likely in association with proactive recognition and correction of hypokalemia and hypomagnesemia. During treatment, the patient’s cardiac function remained stable.

Finding a druggable target in advanced pancreatic cancer is exceedingly difficult, in part due to the complexity of cellular signaling networks, genetic heterogeneity, the tumor environment and the poorly predictive preclinical model systems. Despite plausible preclinical evidence, the use of
bortezomib in combination with panobinostat in advanced pancreatic cancer is not supported by our clinical study. This study by no means precludes future efforts to explore the role of HDAC inhibition in mediating the effects of proteasome inhibition for other indications. The stellar 62% response rate reported by San-Miguel et al. of refractory multiple myeloma to oral panobinostat and bortezomib demonstrates the potential for strong synergy of this drug combination (21). However, for solid tumor malignancies, we need to develop a better understanding of tumorigenesis and interactions between the tumor and its environment, and hopefully identify potential biomarkers predictive of patients most likely to benefit from such treatment.

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References


