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ORIGINAL ARTICLE

A dose-finding and pharmacodynamic study of bortezomib in combination with weekly paclitaxel in patients with advanced solid tumors

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Abstract
Purpose A phase I study to determine the maximum tolerated dose (MTD) of bortezomib (B) when combined with weekly paclitaxel in patients with advanced solid tumors.
Patients and methods Eligible patients received escalating doses of intravenous (IV) bortezomib (0.6–2 mg/m^2) on days 2 and 9 and IV paclitaxel at 100 mg/m^2 on days 1 and 8 of a 21-day cycle. Dose escalation was based on two end-points: not exceeding 80% 20S-proteasome inhibition (20-S PI) and the development of dose-limiting toxicity defined as grade 3 or greater non-hematologic or grade 4 hematologic toxicities.
Results Forty-five patients with advanced solid tumors and a median of 3 prior chemotherapy regimens (range 0–9), received 318 doses (median 5, range 1–34) of bortezomib and paclitaxel. Dose-related inhibition of 20-S PI was observed with a maximum inhibition of 70–80% at the MTD of 1.8 mg/m^2 of bortezomib. At the MTD ($N = 9$) the following toxicities were observed: grade 4 neutropenia without fever ($n = 2$) and cerebrovascular ischemia ($n = 1$); grade 3 neutropenia ($n = 3$), diarrhea ($n = 2$), nausea ($n = 1$), and fatigue ($n = 1$); grade 2 fatigue ($n = 5$), diarrhea ($n = 4$), and dyspnea ($n = 2$). There was one partial response in a patient with an eccrine porocarcinoma. Stabilization of disease was observed in 7 (16%) patients, 3 of whom had advanced pancreatic cancer.
Conclusion Sequential paclitaxel and bortezomib in previously treated patients with advanced solid tumors resulted in acceptable toxicity and no evidence of interaction. The recommended phase II dose of bortezomib in combination with weekly paclitaxel was 1.8 mg/m^2.

Keywords Bortezomib · Phase I · Solid tumors · Paclitaxel

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Introduction

The ubiquitin–proteasome pathway plays an essential role in cellular functions including transcription, cell cycle regulation, stress response, cellular differentiation, and DNA repair, all of which are involved in the oncogenic process [1, 2]. The dipeptide boronic acid bortezomib is a selective, reversible inhibitor of the ATP-dependent 26S proteasome. This proteasome is a degradative enzyme complex involved in the catabolic pathways of many regulatory proteins including nuclear factor kappa-B (NF-kB), p53, p21, and p27 [3, 4]. The basis of the anti-tumor activity of bortezomib presumably results from an impeded degradation of regulatory proteins [5]. Bortezomib can repress NF-kB signal transduction [6] and interfere with the sequential degradation of cyclins and other cell-cycle regulators such as p27, leading to cell-cycle arrest [6]. Proteasome inhibitors can also stabilize the pro-apoptotic proteins p53 and Bax, while reducing levels of anti-apoptotic proteins such as Bcl-2 [7].

Bortezomib has been evaluated for the treatment of multiple myeloma and a randomized phase III study led to FDA-approval for patients who had received at least one prior therapy [8–10]. Bortezomib is also approved for the treatment of patients with mantle cell lymphoma [11].

Preclinical data demonstrated that bortezomib displayed in vitro and in vivo activity against numerous solid tumors. These results prompted phase I/II trials which showed that bortezomib was well tolerated when administered once or twice weekly (dose range = 0.13–2.0 mg/m^2) using different schedules [12–21]. The major adverse events in these studies included sensory neuropathy, syncope, hypotension, diarrhea, and fatigue.

There is substantial pre-clinical data that demonstrates anti-tumor activity for bortezomib in combination with chemotherapy with potential synergistic effects [13–15]. Treatment with chemotherapeutic agents including the tubulin-stabilizing agent paclitaxel results in activation of NF-kB and phosphorylation of Bcl-2, which can subsequently confer resistance to apoptosis [14, 16–18]. Through its ability to inhibit NF-kB and reduce Bcl-2 [7], bortezomib can potentially overcome this resistance and act synergistically with conventional chemotherapy. Based on this rationale, several other trials of bortezomib in combination with taxanes or the combination of paclitaxel and carboplatin have been reported [19, 20]. Preclinical evidence suggests that giving taxane before bortezomib works better than other schedules in decreasing cell-survival and inducing apoptosis [21].

Two studies have been reported using a combination of taxane and bortezomib in advanced solid tumors and metastatic breast cancer. Bortezomib was given twice weekly in both these studies (on days 1, 4, 8, and 11) along with either docetaxel 75 mg/m^2 on day 1 or paclitaxel days 8 and 11 [19, 28]. This treatment schedule of bortezomib resulted in significant neuropathy when combined with paclitaxel and grade 3/4 neutropenia when combined with docetaxel.

We report here the results of a single institution, open-label, phase I study of bortezomib in combination with paclitaxel in metastatic solid tumors. Our primary objective was to establish the MTD of bortezomib that resulted in a maximal 70–80% proteasome inhibition when administered with weekly paclitaxel [22]. The secondary objectives were to determine the effects of bortezomib alone and in combination with paclitaxel on the level of p27 and Bax proteins in peripheral blood mononuclear cells (PBMC) and on serum inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and C-reactive protein.

Patients and methods

Eligibility

Eligibility criteria included histologically confirmed metastatic or locally advanced solid tumors and the following: age > 18 years; ECOG performance status $\leq$ 2; adequate organ function as defined by leukocytes > 3,000/μl; absolute neutrophil count > 1,500/μl; platelets > 100,000/μl; total bilirubin within normal limits; AST/ALT < 2.5 × upper limit institutional normal (ULIN); creatinine < ULIN; and left ventricular ejection fraction > lower limit of institutional normal. Prior paclitaxel was permitted. Patients with known central nervous system metastases, recent thrombotic events, orthostatic hypotension (clinically euvolemic) uncontrolled intercurrent illness, and known immune deficiency were excluded from the study. Patients who received chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who had not recovered from adverse events due to previous chemotherapy were also excluded.

Study design and dose escalation

This study was conducted at The Ohio State University James Cancer Hospital following approval of the Institutional Review Board. Bortezomib was provided by the National Cancer Institute (NCI) under the Cooperative Research and Development Agreement (CRADA). A standard 3 + 3 cohort study design was used for dose escalation. During cycle 1, bortezomib was administered intravenously (IV) on days 2 and 9 and paclitaxel was administered IV only on day 8 of a 21 day cycle. During all subsequent cycles, paclitaxel was administered on days 1 and 8. This design permitted an assessment of 20S proteasome inhibition (PI) following bortezomib alone (Day 2) and following the combination (Day 9) during cycle 1.

Bortezomib was administered as a bolus IV infusion over 3–5 s and weekly paclitaxel was administered over 1 h. All patients received 10–20 mg oral dexamethasone administered 12 and 6 h before paclitaxel, 25–50 mg of diphenhydramine and 300 mg of cimetidine (or 20 mg of famotidine or 50 mg of ranitidine) for 30–60 min prior to the infusion. Patients were allowed to receive full supportive care as clinically indicated including transfusion of blood and blood products, anti-emetics, and steroids for hypersensitivity reactions. Concurrent bisphosphonate therapy for skeletal metastases was permitted.

The primary objective was to determine the MTD of once weekly bortezomib that resulted in no more than 80% 20S-PI (post administration time point) when administered with weekly paclitaxel at 100 mg/m^2. Table 1 describes the dose levels of bortezomib. The two primary endpoints for stopping dose escalation were greater than 80% 20S-PI and/or observing DLT (defined on the first cycle as either grade 3 or greater non-hematologic toxicity or grade 4 hematologic toxicity (with the exception of asymptomatic absolute neutrophil count (ANC) of less than 500/μl for less than 7 days) during the first treatment cycle. Failure to

Table 1 Dose levels of bortezomib and paclitaxel

Dose level	# Patients	Dose	
		Bortezomib (mg/m^2)	Paclitaxel (mg/m^2)
1a	4	0.8	100
−1	6	0.6	80
1b	6	0.6	100
2	6	0.8	100
3	3	1.2	100
4	8	1.6	100
5	9	1.8	100
6	3	2.0	100

complete one cycle for reasons other than disease progression was also considered a DLT. Three patients were enrolled on each dose level and if no DLT was observed and no more than 80% 20S-PI was observed, the bortezomib dose was escalated to the next dose level. If a DLT or greater than 80% 20S-PI was observed, then 3 more patients were enrolled in that dose level. If less than 2 out of 6 patients had a DLT and/or greater than 80% 20S-PI, bortezomib was then escalated to the next dose level.

Patients continued to receive therapy until disease progression or development of unacceptable adverse events. Paclitaxel was reduced to dose level-1 in patients who developed DLT. If DLT occurred at dose level-1 of paclitaxel, treatment was delayed until toxicity reverted to grade 1 or less and then bortezomib was reduced by one dose level. Treatment could be delayed up to a maximum of 2 weeks. If treatment-related toxicity failed to resolve in 2 weeks, the patient was removed from the trial.

For grade 2 or higher neuropathy, treatment was held until the toxicity reverted to grade 1 or less. The dose of paclitaxel was reduced first and if grade 2 or higher neuropathy occurred again and reverted to grade 1 or less, the dose of bortezomib was reduced by one dose level. If grade 2 or higher neuropathy persisted for more than 2 weeks, the patient was removed from the study. A maximum of two dose reductions was allowed for each patient (1-paclitaxel and 1-bortezomib).

Study assessments

Baseline evaluations of ECOG performance status and physical examination, including baseline neurological exam, were performed within 1 week prior to the start of the protocol. All radiological imaging of sites of metastases were obtained within 4 weeks of initiation of the study. Routine laboratory evaluations were performed weekly. Patients were assessed for toxicities every week using CTCAE v3.0. A complete neurological exam was performed before each cycle. Tumor imaging was repeated every 9 weeks or after 3 cycles. In patients with measurable disease, assessment of response was conducted by RECIST criteria [23]. Tumor markers were followed in patients with elevated levels at baseline.

Correlative studies

Whole blood samples for 20S-PI assessment were drawn prior to bortezomib infusion, then at 1 and 4–6 h after each infusion on Week 1 (Day 2) and Week 2 (Day 9). This permitted an assessment of 20S-PI following bortezomib alone (Day 2) and when combined with paclitaxel (Day 9). Venous whole blood (7 ml) was collected in a heparinized tube, placed on ice, and transferred to two polypropylene vials as soon as possible. Blood samples were kept frozen at −70°C until the time of analysis. 20S-PI was assessed by a spectrofluorometric kinetic enzyme assay conducted at Millennium Pharmaceuticals (Cambridge, MA) using the validated *ex vivo* protease assay based on the chymotryptic:tryptic ratio method described by Lightcap et al. [24]. The extent of inhibition at each post-dose time point was reported as a percentage of the baseline value.

In addition, peripheral blood was collected during pretreatment evaluation, 4–6 h after treatment with bortezomib alone in week 1 and after the combination in week 4 for evaluation of protein expression of p27 and Bax in PBMCs. Plasma to investigate inflammatory cytokines such as TNF-α, IL-1β, IL-6, and C-reactive protein was first isolated from whole blood by centrifugation and frozen for later analysis. The remaining PBMC were isolated via density-gradient centrifugation using Ficoll-Paque Plus (Amersham). Immunoblot analyses were performed in duplicate [25]. Antibodies to p27 and Bax were obtained from Santa Cruz Biotechnology. Bands were quantified on a ChemiDoc system with Quantity One software (BioRad Laboratories, Hercules, CA). Plasma samples were analyzed for the cytokines using commercially available ELISA kits. All samples were assayed in duplicate per manufacturer's recommendations (R&D Systems, Inc.).

Statistical analysis

Statistical analysis is primarily descriptive and not inferential. The primary aim of the study was to identify the MTD of bortezomib/paclitaxel combination given weekly. All patients who received at least one dose of the treatment were included in the summary statistics and safety analysis. A sigmoidal maximum effect pharmacodynamic model was fit to describe the dose–response relationship between bortezomib and inhibition of 20S-PI. The maximum effect (Emax), dose at which 50% of the maximum is produced (ED_{50}), and steepness factor (γ) were estimated. Paired *t* tests were used to evaluate the difference in protein

expression pre- and post-treatment. Analysis of variance was used to determine if there were any differences in expression (post-treatment relative to pre-treatment) according to dose levels.

Results

Patient characteristics

Forty-five patients were entered into the study and assessed for toxicity (Table 2). Forty-five patients received a total of 318 doses of bortezomib (median 5, range 1–34). The median ECOG performance status was 1 (range 0–2). More than one-third of patients received greater than 3 prior chemotherapeutic regimens (median 3, range 0–9). Ten patients (22%) had received prior paclitaxel therapy.

Dose escalation and dose limiting toxicities

The study was originally designed to administer bortezomib at the dose of 0.8 mg/m^2 twice weekly along with paclitaxel at 100 mg/m^2 weekly. After 2 of 4 patients experienced DLT at these doses, the protocol was amended to reduce the frequency of bortezomib to once a week starting at a dose of 0.6 mg/m^2 on days 2 and 9 and paclitaxel at 80 mg/m^2 on days 1 and 8 weekly for 2 weeks, repeated every 21 days (modified schedule). The MTD using the modified schedule was 1.8 mg/m^2 of bortezomib and 100 mg/m^2 of paclitaxel. Table 3 describes the toxicities during the first treatment cycle at each dose level and the DLTs for each dose level.

The most frequent grade 2 toxicities among all dose levels and treatment cycles included fatigue (51%), anemia (38%), leucopenia (31%), neutropenia (22%), anorexia (22%), diarrhea (20%), nausea (20%), and sensory neuropathy (11%). Grade 3 or 4 toxicities included leucopenia (31%), neutropenia (27%), fatigue (16%), diarrhea (11%), nausea (4%), sensory neuropathy (4%), thrombosis (4%), and cerebrovascular accident (2.2%). No febrile neutropenia was reported.

The toxicities resulting in dose reduction of paclitaxel after cycle 1 included grade 2 sensory neuropathy ($n = 4$), grade 3 fatigue ($n = 2$), and grade 3 diarrhea ($n = 1$). Two patients had dose level reductions of bortezomib for grade 3 sensory neuropathy ($n = 1$) and fatigue ($n = 1$). There was no clear association between dose of bortezomib and frequency of development of neuropathy or fatigue. All the patients requiring dose reductions for fatigue had a baseline performance status of 1 or above. One of the patients with grade 2 neuropathy had prior paclitaxel. No clear association was found between number of prior therapies and development of these dose limiting toxicities. Nine patients received only 1 cycle of therapy and were removed from study either due to toxicity ($n = 6$) or disease progression ($n = 3$).

Efficacy

Among the 45 patients, one (2%) partial response (PR) and seven (16%) had stable disease (SD) with a median duration of 3 months (range 2.2–11.9 months). The PR was in a patient with an eccrine porocarcinoma, a very rare tumor of the sweat glands, who had not received prior systemic chemotherapy. He presented with a large ulcerating mass in his right ear with cervical and mediastinal nodes and a lung mass. After two cycles, he had complete regression of the mass on his right auricle and after three cycles had a 41% reduction of the lymph nodes and lung mass by RECIST criteria. He came off study for progressive neuropathy after 9 cycles. Ten patients with advanced pancreatic cancer were treated and three had SD for durations of 2.5, 9.0, and 11.9 months. One pancreatic cancer patient, who had failed three prior chemotherapy regimens with metastatic disease in lung and liver, received 18 treatment cycles and came

Table 2 Patient characteristics

All patients ($n = 45$)	
Age, median (range)	57 (36–79)
Sex, *n* (%)	
Male	20 (44)
Female	25 (56)
ECOG performance status, *n* (%)	
0	18 (40)
1	22 (49)
2	5 (11)
Tumor type, *n* (%)	
Breast	6 (13)
Gastrointestinal	22 (49)
Lung	7 (16)
Neuroendocrine	4 (9)
Thyroid	2 (4)
Others	4 (9)
Metastatic sites, *n* (%)	
Liver	27 (60)
Lung	25 (57)
Soft tissue/bone	33 (73)
Number of metastatic sites, *n* (%)	
0–3	35 (78)
>3	10 (22)
Number of prior therapies, *n* (%)	
0–3	28 (62)
>3	17 (38)
Prior paclitaxel therapy	10 (22)

Table 3 Toxicities and DLTs for each dose level reported cycle 1

	Dose level	1a	−1	1b	2	3	4	5	6
	Bortezomib dose (mg/m^2)	0.8	0.6	0.6	0.8	1.2	1.6	1.8	2
	Paclitaxel dose (mg/m^2)	100	80	100	100	100	100	100	100
	N	4	6	6	6	3	8	9	3
Adverse event	Grade	Number of patients experiencing event in cycle 1 (Percent)							
Hemoglobin	Gr 1/2	1 (25)	1 (17)	3 (50)	4 (67)	2 (67)	3 (38)	4 (44)	3 (100)
	Gr 3/4	0	0	0	0	0	0	0	0
Leukopenia	Gr 1/2	0	0	1 (17)	5 (83)	3 (100)	2 (25)	3 (33)	1 (33)
	Gr 3/4	0	0	1 (17)	0	0	0	1 (11)	2 (67)
Neutropenia	Gr 1/2	0	0	1 (17)	0	0	0	0	2 (67)
	Gr 3/4	0	0	0	0	0	0	0	1 (33)
Platelets	Gr 1/2	1 (25)	0	0	0	0	0	0	2 (67)
	Gr 3/4	0	0	0	0	0	0	0	1 (33)
Anorexia	Gr 1/2	2 (50)	1 (17)	1 (17)	0	0	2 (25)	1 (11)	1 (33)
	Gr 3/4	0	0	0	1 (17)	0	0	0	0
Diarrhea	Gr 1/2	2 (50)	0	0	0	0	1 (13)	4 (44)	2 (67)
	Gr 3/4	1 (25)	0	0	0	0	0	0	1 (33)
Nausea	Gr 1/2	1 (25)	1 (17)	2 (33)	1 (17)	1 (33)	1 (13)	5 (56)	3 (100)
	Gr 3/4	0	0	0	0	0	0	0	0
Vomiting	Gr 1/2	2 (50)	0	2 (33)	1 (17)	1 (33)	1 (13)	1 (11)	2 (67)
	Gr 3/4	0	0	0	0	0	0	0	0
Fatigue	Gr 1/2	3 (75)	2 (33)	2 (33)	1 (17)	0	1 (13)	3 (33)	2 (67)
	Gr 3/4	0	1 (17)	1 (17)	1 (17)	0	0	0	1 (33)
CVA	Gr 1/2	0	0	0	0	0	0	0	0
	Gr 3/4	0	0	0	0	0	0	1 (11)	0
Sensory neuropathy	Gr 1/2	3 (75)	1 (17)	0	1 (17)	0	1 (13)	2 (22)	0
	Gr 3/4	0	0	0	0	0	0	0	0
Thrombosis	Gr 1/2	0	0	0	0	0	0	0	0
	Gr 3/4	1 (25)	0	0	0	0	0	0	0
Orthostatic	Gr 1/2	0	0	0	0	0	0	0	0
Hypotenstion	Gr 3/4	0	0	0	0	0	1 (13)	0	0
DLT		Gr 3 DVT and Gr 3 diarrhea	Gr 4 fatigue	Gr 3 fatigue	Gr 3 fatigue/ anorexia	None	Gr 3 orthostatic hypotension	Gr 4 CVA	Gr 3 diarrhea/ fatigue

Table 4 Mean ± SD (*N*) percent 20S proteasome inhibition induced 1 h after bortezomib alone (Week 1, Day 2) or following paclitaxel + bortezomib (Week 2, Day 9) as a function of bortezomib dose in milligrams per meter squared

Dose (mg/m^2)	Week 1–Day 2	Week 2–Day 9
0.6	35.5 ± 10.7 (12)	40.4 ± 17.4 (10)
0.8	45.6 ± 10.7 (6)	51.6 ± 9.6 (6)
1.2	66.9 ± 2.9 (3)	60.9 (2)
1.6	69.8 ± 5.8 (8)	70.0 ± 4.9 (8)
1.8	72.1 ± 1.9 (9)	73.2 ± 2.7 (7)
2.0	77.8 ± 3.9 (3)	76.0 ± 5.3 (3)

off study because his physician deemed that he had achieved maximum benefit from therapy. Another patient with non-measurable disease who had failed two prior chemotherapy regimens experienced a drop in the CA19–9 (from 539 to 233 U/ml) after two cycles and received 11 treatment cycles. None of these patients had received prior paclitaxel.

Correlative studies

The mean (±SD) percentage of inhibition of proteasome activity during week 1 (bortezomib alone) and week 2 (paclitaxel + bortezomib) for each dose level of bortezomib is listed in Table 4. The degree of inhibition observed with paclitaxel + bortezomib was similar to that observed with bortezomib alone. As was observed in other studies, the maximum mean percentage inhibition of proteasome activity occurred at 1 h post dosing with a return toward baseline at 4–6 h. A complete return to baseline values was evident by the following week (data not shown). At the MTD, the mean percentage 20S-PI at 1 h post dosing ranged from 68.6 to 74.4% on Week 1 (Day 2) and 68.8 to 76.6% on Week 2 (Day 9). The percentages of proteasome inhibition, measured 1 h after the first dose of bortezomib, in the 41 patients enrolled post-amendment were fit to a sigmoidal maximum effect (Sigmoidal Emax) pharmacodynamic model (Fig. 1). The model demonstrates a relatively steep dose–response curve (i.e., γ approaching 2) up to about 1.2 mg/m^2, followed by a tendency to plateau for higher doses with a calculated ED50 of 0.72 mg/m^2 and an Emax of 85%. This sigmoidal relationship was seen in monotherapy studies of bortezomib and suggests that the combination with paclitaxel does not alter its effect on the proteasome inhibition.

Peripheral blood mononuclear cells obtained from patients before and 4–6 h after bortezomib treatment, with and without paclitaxel, were evaluated for p27 and Bax protein expression. There was no significant difference in Bax protein expression before and after treatment and no significant dose-dependent induction of Bax protein.

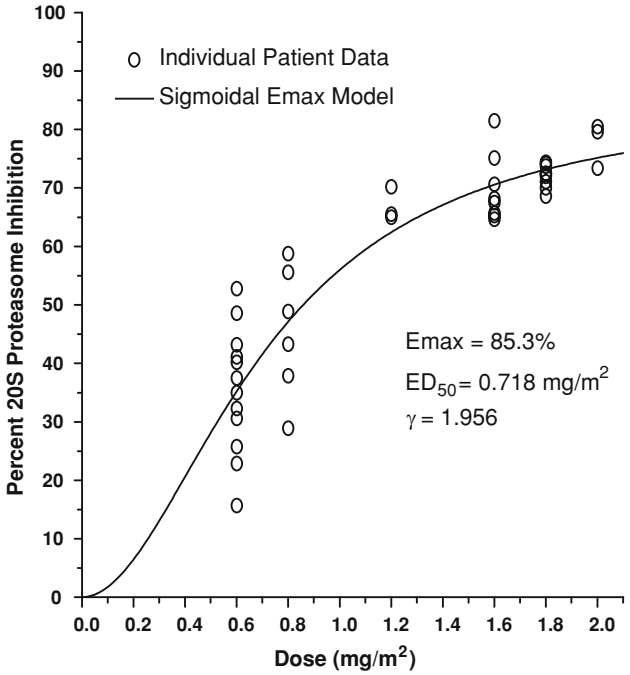

Fig. 1 Sigmoidal maximum effect (Sigmoidal Emax) inhibitor model fit to 20S proteasome inhibition as a function of bortezomib dose in mg/m^2 determined 1 h post dosing on Day 2

However, there was a moderate increase in p27 following treatment with bortezomib, both with and without paclitaxel ($P = 0.01$ and $P = 0.02$, respectively). Although a larger increase in p27 was observed with the combination treatment compared with bortezomib alone, this did not reach statistical significance ($P = 0.14$). Further, the increase in p27 did not appear to be dose-dependent. No correlation between escalating doses of bortezomib and the serum level of cytokines (TNF, IL-1, IL-6, and CRP) was observed, nor was there any correlation with toxicity observed (data not shown).

Discussion

The MTD of bortezomib given weekly on days 2 and 9 with paclitaxel at 100 mg/m^2 on days 1 and 8 on a 21-day cycle was 1.8 mg/m^2. This dose is slightly higher than that recommended for single-agent therapy on a weekly schedule [26, 27]. At this MTD, the combination of bortezomib and paclitaxel was well tolerated, with neuropathy and diarrhea being similar to those trials of single-agent bortezomib in pretreated solid tumor patients [12, 27]. In contrast, in recent phase I trials combining taxanes with twice weekly bortezomib at MTD, the incidence of neuropathy and diarrhea was higher than the current trial [19, 28]. Other trials that used weekly dosing of bortezomib combined with chemotherapy reported lower rates of sensory

neuropathy suggesting that weekly bortezomib may be better tolerated [29, 30].

One patient with metastatic eccrine porocarcinoma achieved a PR and had a durable response. Eccrine porocarcinoma is a rare malignant sweat gland tumor that is inherently resistant to chemotherapy [31–33]. In case reports, paclitaxel in combination with alpha-interferon had clinical activity, however, the patients were unable to tolerate multiple cycles [34].

Among the 7 patients with stable disease, 3 had pancreatic cancer and were heavily pretreated. The apparent activity of bortezomib in pancreatic cancer could be related to increased NF-kB activity in this malignancy [35]. NF-kB inhibitors such as cyclooxygenase inhibitors, Ik-B mutant proteins, curcumin, and proteasome inhibitors are currently under pre-clinical or early clinical investigation [35]. Taxanes in combination with other chemotherapies have shown activity in pancreatic cancer but there is no data using single-agent paclitaxel. Weekly paclitaxel as a radiosensitizer with concurrent radiation has been studied in locally advanced, unresectable pancreatic cancer and shown promising results [36]. Our study demonstrates that proteasome inhibition in combination with paclitaxel resulted in stable disease for a limited number of patients with metastatic pancreatic cancer.

The degree of 20S-PI observed in response to treatment with bortezomib and paclitaxel was similar to that observed with bortezomib alone suggesting no pharmacodynamic interaction. No correlation was observed between the dose of bortezomib and plasma levels of pro-inflammatory cytokines (IL-6, TNF, IL-1, and CRP). We hypothesized that bortezomib with and without paclitaxel will increase the cyclin-dependent kinase inhibitor p27 and the proapoptotic protein Bax. However, there was no significant difference in Bax proteins before and after treatment as well as no dose-dependency. Levels of p27 protein were increased with treatment, although a clear dose–response relationship was not seen. We were unable to obtain sequential biopsies of metastatic sites in this trial.

In conclusion, these results demonstrate the combination of paclitaxel (100 mg/m^2) and bortezomib (1.8 mg/m^2) given sequentially on a weekly basis in these heavily pretreated patients results in the desired proteasome inhibition, a manageable toxicity profile, and thus, is the recommended dose for phase II studies. Ongoing clinical trials are establishing if bortezomib needs to be given sequentially or concurrently. Given the preliminary activity of our combination in pancreatic cancer, this cytotoxic backbone could be used for combinations with other targeted therapies such as vorinostat.

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