A Parallel Dose-Escalation Study of Weekly and Twice-Weekly Bortezomib in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced Solid Tumors

Jens Voortman,[1] Egbert F. Smit,[2] Richard Honeywell,[1] Bart C. Kuenen,[1] Godefridus J. Peters,[1] Helgi van de Velde,[3] and Giuseppe Giaccone[1]

Abstract

Purpose: To establish maximum tolerated dose (MTD) and tolerability of two schedules of bortezomib in combination with cisplatin and gemcitabine as first-line treatment of patients with advanced solid tumors.

Experimental Design: Patients were assigned to increasing doses of bortezomib days 1 and 8 (weekly schedule) or days 1, 4, 8, and 11 (twice-weekly schedule), in addition to gemcitabine 1,000 mg/m^2 days 1 and 8 and cisplatin 70 mg/m^2 day 1, every 21 days. Maximum of six cycles. Plasma pharmacokinetics of cisplatin and gemcitabine were determined at MTD.

Results: Thirty-four patients were enrolled of whom 27 had non–small cell lung cancer (NSCLC). Diarrhea, neutropenia, and thrombocytopenia were dose-limiting toxicities leading to an MTD of bortezomib 1.0 mg/m^2 in the weekly schedule. Febrile neutropenia and thrombocytopenia with bleeding were dose-limiting toxicities in the twice-weekly schedule, leading to an MTD of bortezomib 1.0 mg/m^2 as well. Most common $\geq$grade 3 treatment-related toxicities were thrombocytopenia and neutropenia. No grade $\geq$3 treatment-related sensory neuropathy was reported. Of 34 evaluable patients, 13 achieved partial responses, 17 stable disease, and 4 progressive disease. Response and survival of NSCLC patients treated with twice weekly or weekly bortezomib were similar. However, increased dose intensity of bortezomib led to increased gastrointestinal toxicity as well as myelosuppression. Pharmacokinetic profiles of cisplatin and gemcitabine were not significantly different in patients receiving either schedule.

Conclusions: Weekly bortezomib 1.0 mg/m^2 plus gemcitabine 1,000 mg/m^2 and cisplatin 70 mg/m^2 is the recommended phase 2 schedule, constituting a safe combination, with activity in NSCLC.

The ubiquitin-proteasome pathway plays a pivotal role in the degradation of most intracellular proteins in eukaryotic cells, including those regulating apoptosis, cell cycle progression, transcription factor activation, and angiogenesis (1–3). Bortezomib (VELCADE; Millennium Pharmaceuticals, Inc; Johnson & Johnson Pharmaceutical Research and Development, LLC), a dipeptide proteasome inhibitor, is a novel antineoplastic agent presently approved for the treatment of patients with relapsed and refractory multiple myeloma and relapsed mantle-cell lymphoma (4). Inhibition of the chymotryptic-like proteolytic activity of the proteasome by bortezomib suppresses tumor survival through multiple mechanisms, including induction of G_2-M phase cell cycle arrest, cleavage of bcl-2, up-regulation and/or accumulation of BH3-only proteins, activation of caspases, and inhibition of nuclear factor-κB activation (5–9). In preclinical and clinical studies, it has shown a unique and promising cytotoxicity profile in a variety of solid tumors as well (10, 11).

When the recommended schedule for multiple myeloma patients, twice-weekly administration of bortezomib 1.3 mg/m^2, was administered as second-line treatment to non–small cell lung cancer (NSCLC) patients, 8% achieved a partial response (12, 13).

Gemcitabine in combination with cisplatin is a widely used chemotherapeutic regimen for the treatment of advanced NSCLC, urothelial cell cancer, and other solid tumors (14, 15). Preclinical and clinical studies indicate synergistic or additive activity when bortezomib is combined with gemcitabine and/or platinum agents (16–20). Inhibition of nuclear factor-κB activation, a factor thought to play a role in resistance to chemotherapy, and accumulation of proteins, misfolded or damaged by the effects of chemotherapy, might play important contributory roles (21, 22). A sequence-specific interaction of bortezomib and several chemotherapeutics has been shown in some preclinical studies, suggesting

Authors' Affiliations: Departments of [1]Medical Oncology and [2]Pulmonology, VU University Medical Center, Amsterdam, the Netherlands; and [3]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium

Received 1/11/07; revised 3/15/07; accepted 3/29/07.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: This study was presented in part at the American Society of Clinical Oncology 2005 (abstract no. 2103) and the European Cancer Conference 2005 (abstract no. 1468).

Requests for reprints: Giuseppe Giaccone, Department of Medical Oncology, VU University Medical Center, De Boelelaan 1117, 1081HV Amsterdam, the Netherlands. Phone: 31-20-444-321; Fax: 31-20-444-079; E-mail: g.giaccone@vumc.nl.

doi:10.1158/1078-0432.CCR-07-0061

administration of chemotherapy before bortezomib increases apoptosis induction in cell lines, compared with administrating chemotherapy after bortezomib administration (17, 23).

The present phase 1B study was designed to establish safety and maximum tolerated dose (MTD) of bortezomib in combination with cisplatin and gemcitabine in patients with advanced solid tumors, especially NSCLC, to determine a recommended phase 2 dose. Considering potentially overlapping toxicities between bortezomib and chemotherapy, and as an attempt to develop a more patient-friendly schedule, a weekly schedule of bortezomib was evaluated next to a twice-weekly schedule.

Patients and Methods

Patients. Chemonaive adult patients with inoperable, locally advanced, or metastatic cancer, for whom gemcitabine and cisplatin therapy was an acceptable therapeutic option, were eligible for this study. Tumors were cytologically or histologically confirmed. Other eligibility criteria included: Karnofsky performance status ≥70; life expectancy >3 months; measurable or evaluable disease. An adequate method of birth control had to be used, and women of childbearing potential had to have a negative urine pregnancy test. Patients were excluded if they had received prior treatment with chemotherapy or bortezomib; had received treatment with monoclonal antibodies, other biological therapies, or investigational agents ≤4 weeks before enrollment; underwent major surgery ≤4 weeks before enrollment; underwent prior extensive radiation therapy (>25% of bone marrow reserve); underwent radiation therapy within 4 weeks before enrollment (except for limited radiation of bone metastases with 1-2 fractions); had inadequate bone marrow and/or organ function, defined as creatinine clearance <60 mL/min (calculated according to Cockcroft-Gault formula), total bilirubin ≥2 times the upper limits of normal, aspartate transaminase ≥3 times the upper limits of normal, alanine transaminase ≥3 times the upper limits of normal, hemoglobin ≤9.0 g/dL, platelet count <100× 10^9/L, absolute neutrophils count <1.5 × 10^9/L; had grade ≥2 peripheral neuropathy or grade ≥3 hearing loss as defined by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; had symptomatic central nervous system metastases (corticosteroid use was allowed to suppress symptoms); were hypersensitive for boron or mannitol; had serious uncontrolled medical disease, active infection, significant cardiovascular disorder, or any psychiatric illness or other disorders that could potentially impair compliance. This study was reviewed and approved by the institutional review board of the study center. Informed consent was obtained from all patients before undergoing any study-related procedures.

Study design. This was a phase 1B, open-label, dose-escalation study conducted in one study center. Two different schedules of bortezomib were evaluated in combination with gemcitabine and cisplatin. Patients were alternately assigned to either schedule. In the twice-weekly schedule, bortezomib was administered on days 1, 4, 8, and 11, followed by gemcitabine on days 1 and 8, and cisplatin on day 1. In the weekly schedule, bortezomib was administered on days 1 and 8, followed by gemcitabine on days 1 and 8 and cisplatin on day 1 (see Fig. 1). Planned bortezomib dose levels were 1.0, 1.3, and 1.6 mg/m^2 for the weekly schedule and 0.7, 1.0, and 1.3 mg/m^2 for the twice-weekly schedule. Doses of cisplatin and gemcitabine were chosen at 70 and 1,000 mg/m^2, respectively. If well tolerated at maximum planned bortezomib dose, cisplatin dose was to be increased to 80 and 100 mg/m^2.

At least three patients were enrolled per dose level. MTD determination was based on occurrence of dose-limiting toxicity (DLT) in cycle 1. DLT was defined as any drug-related nonhematologic toxicity grade 3 or 4 (excluding nausea and vomiting or diarrhea responding to symptomatic management), grade 4 neutropenia lasting >5 days, grade 3 or 4 febrile neutropenia, grade 4 thrombocytopenia of any duration, and toxicity causing a delay in the start of the next cycle of >2 weeks. When a DLT was encountered, the cohort was expanded to six patients. Dose escalation was continued until a DLT was observed in two of two to six patients.

Initially, doses of gemcitabine and cisplatin were reduced by 25% in case of grade 4 neutropenia and/or grade 3 thrombocytopenia or occurrence of any nonhematologic DLT in the previous cycle. In a protocol amendment, the threshold for thrombocytopenia was lowered to grade 4. In case of a DLT in the previous cycle, bortezomib dose was reduced to the next lower dose level. If the patient was receiving 0.7 mg/m^2, bortezomib was discontinued. Day 8 gemcitabine was reduced by 50% in case of neutrophils of 0.75 × 10^9/L to 1.5 × 10^9/L and/or platelets of 50 × 10^9/L to 100 × 10^9/L. Drug-specific dose modifications were made in case of neuropathy (cisplatin, bortezomib), nephrotoxicity (cisplatin), or ototoxicity (cisplatin).

Patients could receive a maximum of six cycles until disease progression, occurrence of an unacceptable adverse event, death, or meeting of any criterion for withdrawal from treatment. When deemed beneficiary, patients were allowed to continue with bortezomib monotherapy for a maximum of 1 year.

Drug administration. Bortezomib was provided as a sterile lyophilized powder for reconstitution in vials containing 3.5 mg bortezomib and 35 mg mannitol. Cisplatin and gemcitabine were provided using available commercial supplies. Bortezomib was administered as an i.v. 3- to 5-s bolus injection, gemcitabine as an i.v. infusion over 30 min,

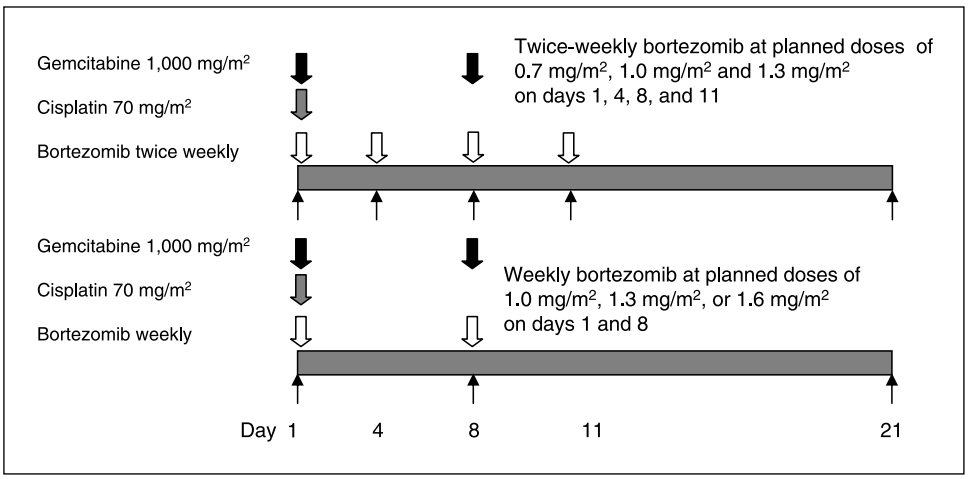

Fig. 1. Treatment schemas.

and cisplatin as an i.v. infusion over 3 h. Cisplatin prehydration and posthydration consisted of a 1 and 4 L 0.9% NaCl infusion over 2 and 21 h, respectively, with 2 g $MgSO_4$ and 20 mmol KCl added per liter. The antiemetic regimen consisted of dexamethasone 8 mg twice-daily day 1, and ondansetron 8 mg twice-daily days 1 through 4, 8, and, in the twice-weekly schedule, day 11 as well. When deemed beneficiary, aprepitant was added days 1 (125 mg) and days 2 and 3 (80 mg). For the remainder of the cycle, metoclopramide was provided on an as-needed basis.

Patient evaluation. Patients were evaluated at scheduled visits during screening, treatment, and follow-up. At screening, a complete medical history, including Karnofsky performance status; Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity questionnaire version 4.0; chest X-ray; audiometry; electrocardiogram; and laboratory samples for hematology, coagulation tests, clinical chemistry, serum tumor markers (when applicable), and urinalysis (including pregnancy test) were obtained. A physical examination was done. Target and nontarget lesions were identified and measured by spiral-computed tomography scan and/or magnetic resonance imaging. Follow-up assessments were conducted weekly (days 1, 8, and 15) or twice-weekly (days 1, 4, 8, 11, and 15), depending on the treatment schedule, until the end of treatment. One additional visit was planned 6 weeks after ending treatment (6-week follow-up). Safety evaluations included symptom-directed physical examination, Karnofsky performance status, laboratory analyses, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity questionnaire (at screening, start of every cycle, end of treatment, and at 6-week follow-up), and audiometry (at screening and at least every three cycles). Upon occurrence of severe left ventricular dysfunction in one patient, left ventricular ejection fraction (LVEF) measurement by multiple-gated acquisition scan was conducted in subsequently enrolled patients at screening and end of treatment. All adverse events were documented. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Patients were evaluated for response using the Response Evaluation Criteria in Solid Tumors guidelines at screening, every two cycles, at end of treatment, and at 6-weeks follow-up (24). An objective response was to be confirmed after at least 6 weeks. Patients were observed for disease and survival assessment until death.

Blood sampling and pharmacokinetic analysis. At the MTD, blood plasma samples were drawn from 12 patients (six patients in each group) for determination of total platinum, gemcitabine, dFdC (2′,2′-difluoro-2′-deoxycytidine, gemcitabine), its metabolite dFdU (2′,2′-difluoro-2′-deoxyuridine), and endogenous deoxycytidine (CdR) at the following time points: cycle 1, day 1, before infusion of gemcitabine, at the end of gemcitabine infusion, just before starting the cisplatin infusion, and at 30, 60, 120, and 180 min after cisplatin infusion and 24 h after gemcitabine infusion; day 8, before infusion of gemcitabine, at the end of gemcitabine infusion, and at 30 min after gemcitabine infusion. Processing of samples and determination of compounds were as described previously (25–27). Briefly, 150 μL of plasma was extracted and stored at -20°C until analysis. Separation and quantification of gemcitabine and dFdU from the plasma was achieved with an isocratic reversed-phase high-performance liquid chromatography system using a μBondapak C18 column. Peak areas were quantified using the data acquisition program Chromeleon (version 3.02; Chromeleon Chromatography Data Systems, Gynkotek HPLC). For CdR measurement, plasma extracts were prepared by protein precipitation and an ethyl acetate/water back extraction. Quantitation was done by multireaction monitoring tandem mass spectrometry, using $^{15}N_3$ CdR as an isotopic internal standard. For total plasma, platinum samples were diluted 10 times with 0.38 mol/L NaCl/0.5 mol/L HCl, and 0.2% Triton + 0.2% antifoam before measurement by flameless atomic absorption spectrophotometry (spectra AA-300 Zeeman AAS Varian).

Statistical analysis. Descriptive statistics were used for baseline characteristics, safety assessment, and pharmacokinetic data. The response rate was calculated for all response-evaluable patients along with the 95% confidence interval (95% CI). Median duration of response, stable disease, progression-free survival, and overall survival was calculated using the Kaplan-Meier method, along with their 95% CI.

Table 1. Patient characteristics

	All patients	NSCLC patients
No. patients	34	27
Median age, y (range)	55 (35-71)	53 (35-67)
Gender, male/female	21/13	15/12
Karnofsky performance status 70%/≥80%	6/28	4/23
Locally advanced	7	5
Metastatic	27	22
Central nervous system	10	10
Bone	12	10
Liver	9	7
Lung	15	13
Primary tumor		
Lung (NSCLC)	27	
Urothelium	4	
Breast*	1	
Pancreas	1	
Liver	1	
Histology (NSCLC patients)		
Squamous cell carcinoma		6
Adenocarcinoma		12
Mixed adenosquamous cell carcinoma		2
Undifferentiated non–small cell carcinoma		7

*Later diagnosis, at study entry, diagnosed as adenocarcinoma of unknown primary.

Results

Patients and treatment. A total of 34 chemonaive patients were enrolled between August 2004 and June 2005. All patients were included in the safety and efficacy analyses and received at least one dose of study drug. Table 1 shows patient baseline characteristics. Most patients (n = 27) had NSCLC. Twenty-six of 27 NSCLC patients (96%) were current or former smokers and four patients (15%) had received prior treatment with erlotinib.

Twenty-seven patients (79%) had metastatic disease, 10 of whom with involvement of the central nervous system (37%). At study entry, one patient was diagnosed with adenocarcinoma of unknown primary, which was later diagnosed as breast carcinoma. Thirty-four patients received a total of 142 cycles. In total, 15 patients received twice-weekly bortezomib in combination with chemotherapy, at a dose of 0.7 mg/m^2 (3 patients) and 1.0 mg/m^2 (12 patients). Nineteen patients received weekly bortezomib in combination with chemotherapy, at a dose of 1.0 mg/m^2 (12 patients) and 1.3 mg/m^2 (7 patients). Five patients experienced drug-related DLT during cycle 1 of treatment. Two of those five patients were treated with twice-weekly bortezomib 1.0 mg/m^2. The first patient had NSCLC; Karnofsky performance status 70% on study entry; with liver, bone, and central nervous system metastases; who experienced grade 4 neutropenic sepsis and grade 4 symptomatic thrombocytopenia

(gastrointestinal bleeding). The second patient had grade 4 asymptomatic thrombocytopenia. Therefore, the MTD of twice-weekly bortezomib in combination with gemcitabine and cisplatin was established at 1.0 mg/m^2. Three patients treated with weekly bortezomib 1.3 mg/m^2 developed grade 4 asymptomatic thrombocytopenia during cycle 1, which coincided with grade 4 neutropenia in two patients and grade 3 diarrhea in one patient. This led to an MTD of 1.0 mg/m^2 bortezomib in the weekly schedule as well.

Exposure to treatment is listed in Table 2. Median number of cycles was four in all dose groups. Median cumulative bortezomib dose was highest in patients treated with twice-weekly bortezomib 1.0 mg/m^2 and lowest in patients treated with weekly bortezomib 1.0 mg/m^2: 13.7 and 7.2 mg/m^2, respectively. Seventy-nine percent of patients had study drugs (cisplatin, gemcitabine, and/or bortezomib) reduced during treatment. Reasons for dose reduction were thrombocytopenia (38%), neutropenia (37%), neutropenia combined with thrombocytopenia (10%), asthenia (8%), ototoxicity (3%), and other (5%). Comparing patients receiving weekly and twice-weekly bortezomib 1.0 mg/m^2, the reasons for dose reduction were neutropenia, 60% versus 53%; thrombocytopenia, 6% versus 37%; and combined neutropenia and thrombocytopenia, 0% versus 5%. In the weekly schedule of bortezomib 1.3 mg/m^2, reasons for dose reduction were thrombocytopenia 29%, combined neutropenia and thrombocytopenia 29%, neutropenia 18%, and asthenia 24%. In 41% of patients, start of one or more treatment cycles was delayed due to toxicity. Delays were caused by neutropenia (75%) or nonhematologic toxicity (25%).

Common treatment-related adverse events occurring throughout the trial are shown in Table 3 and included asthenia (100%), nausea (91%), taste alteration (82%), anorexia (79%), constipation (79%), tinnitus (71%), and sensory neuropathy (62%). Weekly bortezomib 1.0 mg/m^2 was generally better tolerated than twice-weekly 1.0 mg/m^2 treatment. We observed a trend toward higher incidence of (severe) myelotoxicity as well as gastrointestinal toxicity and asthenia with increased dose-intensity of bortezomib. Due to grade 3 gastrointestinal toxicity, 1 (8%) and 3 (25%) patients treated with bortezomib 1.0 mg/m^2 weekly or twice weekly, respectively, were treated with aprepitant. For anemia treatment or prophylaxis, 17 (50%) of patients received (darb)epoetin. Three patients (9%) repeatedly experiencing neutropenia received pegfilgrastim injections.

Sixteen (47%) of patients developed a low-grade rash, which was typically acneiform. Fifteen (44%) patients experienced facial/periorbital edema. One patient, who was being treated with gemcitabine and bortezomib only, after discontinuation of cisplatin due to asthenia and gastrointestinal toxicity, experienced severe, grade 3 periorbital edema that recurred to a lesser degree on later treatment with gemcitabine only.

Results of additional assessments of neurotoxicity, ototoxicity, nephrotoxicity, and cardiotoxicity are listed in Table 4. Of 91% of patients, baseline and end-of-treatment neurotoxicity questionnaires were available for assessment. Surprisingly, we did not observe a significant difference of baseline versus end of treatment scores combining bortezomib and cisplatin-based chemotherapy. Nevertheless, mild, low-grade neuropathy, typically characterized by paresthesias in fingers and toes, was present in 62% of patients. Sensory neuropathy, as well as orthostasis/dizziness, which might represent autonomic dysfunction, was slightly more frequent in patients treated with twice-weekly bortezomib 1.0 mg/m^2 than in other treatment cohorts. No neuropathic pain was reported.

Six (18%) patients experienced subjective hearing loss, 24 (71%) experienced tinnitus during treatment, and in 2 (6%) patients cisplatin was discontinued due to progressive ototoxicity. Renal function, as calculated by the Cockcroft-Gault formula, was significantly reduced at end of treatment in all cohorts. In one patient, the cisplatin dose was reduced due to nephrotoxicity. One patient developed severe left ventricular dysfunction, which restored gradually after discontinuation of treatment. This deterioration of LVEF upon treatment was documented by NT-proBNP measurements in archived serum samples as well as by LVEF assessment by echocardiography and multiple-gated acquisition scan (28). Because bortezomib might have been the cause for the observed cardiac effect in this patient, subsequently enrolled patients underwent LVEF measurement by multiple-gated acquisition scan at baseline and end of treatment. In total, 18 patients were evaluated at screening. Three patients, without signs of cardiac failure, were not evaluated after completing treatment due to rapid disease progression (n = 2)

Table 2. Dose intensity per bortezomib dose group

Dose level	Median number of cycles (range)	Median time to treatment failure, d (range)	Cisplatin projected/actual dose, mg/m^2*	Gemcitabine projected/actual dose, mg/m^2/wk*	Bortezomib projected/actual dose, mg/m^2/wk*
Twice-weekly bortezomib 0.7 mg/m^2	4 (4-6)	126 (91-133)	23.3/17.3 (74%)	667/470 (70%)	0.93/0.88 (95%)
Twice-weekly bortezomib 1.0 mg/m^2	4 (1-6)	87.5 (28-136)	23.3/21.5 (92%)	667/547.2 (82%)	1.33/1.14 (86%)
Weekly bortezomib 1.0 mg/m^2	4 (2-6)	84 (36-126)	23.3/21.0 (90%)	667/570.9 (86%)	0.67/0.60 (90%)
Weekly bortezomib 1.3 mg/m^2	4 (2-6)	89.5 (55-148)	23.3/17.7 (76%)	667/531.5 (80%)	0.87/0.74 (85%)

*Actual administered doses per square meter of study drugs were divided by the actual number of weeks between first dose of study drugs and day 21 of the final cycle. Projected doses were calculated as the projected dose per cycle per square meter divided by 3 (weeks).

Table 3. Adverse events attributed to cisplatin, gemcitabine, and/or bortezomib (any cycle)

Schema	Twice-weekly bortezomib 0.7 mg/m^2 (n = 3)			Twice-weekly bortezomib 1.0 mg/m^2 (n = 12)			Weekly bortezomib 1.0 mg/m^2 (n = 12)			Weekly bortezomib 1.3 mg/m^2 (n = 7)		
Toxicity grade	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4
Constitutional												
Asthenia	67%	33%		33%	67%		67%	33%		71%	29%	
Flu-like syndrome	67%			50%			50%			29%		
Hot flush	33%			42%			8%			43%		
Hematologic												
Anemia	100%			92%	8%		92%	8%		72%	14%	14%
Neutropenia	33%	67%		8%	33%	25%	8%	50%	8%		43%	57%
Trombocytopenia		100%		42%	33%	25%	25%	50%	17%	29%	14%	57%
Digestive												
Nausea	100%			92%	8%		75%			100%		
Taste alteration	100%			83%			83%			71%		
Anorexia	100%			83%			75%			57%	14%	
Vomiting	100%			42%	33%		50%	8%		86%		
Constipation	67%			92%			83%			57%		
Diarrhea		33%		67%			42%			57%	14%	
Stomatitis	33%			25%			25%				14%	
Heart burn	33%			33%			25%			14%		
Dry mouth				25%						43%		
Nervous system												
Sensory neuropathy	67%			75%			50%			57%		
Tinnitus	67%			67%			67%			86%		
Headache	33%			33%	8%		33%			43%		
Orthostasis/dizziness	33%			50%			17%			29%		
Skin and appendages												
Alopecia	33%			50%			67%			57%		
Rash	33%			50%			58%			29%		
Injection site reaction				58%			25%			29%		
Dry skin	33%			25%			8%			14%		
Respiratory system												
Cough	33%			33%			67%			43%		
Dyspnea	33%			17%			33%	25%				
Infection	67%			33%			25%	8%		29%		
Epistaxis				33%			8%			43%		
Hiccoughs				8%			25%			14%		
Ocular/visual												
Conjunctivitis	67%			42%			17%			14%		
Blurred vision	33%			42%			8%			14%		
Fluid homeostasis												
Edema (except facial)	67%			42%			67%			57%		
Periorbital edema	33%			58%			25%			43%	14%	
Pain												
Pain abdomen	33%			33%			33%			29%		
Myalgia				33%			8%			29%		
Skeletal pain							25%			29%		
Nutritional/metabolic												
Weight loss	67%			58%			67%			57%		
Elevated ALT/AST	67%			58%			42%			29%	14%	

NOTE: Events reported by 15% or more of patients, considered possibly, probably, or certainly related to cisplatin, gemcitabine, and/or bortezomib by the treating physician and the investigator are presented. Several episodes in the same patient are counted as one adverse event and only the worst grade is mentioned.
Abbreviations: ALT, alaninine aminotransferase; AST, aspartate aminotransferase.

and death (n = 1). No significant decline in LVEF in patients receiving weekly or twice-weekly bortezomib 1.0 mg/m^2 was observed.

Two patients experienced grade 4 nonhematologic toxicity. One NSCLC patient, who was being treated with corticosteroids because of central nervous system metastases, had a gastric perforation from which she recovered without surgical intervention. Another patient, who had a partial response, presented with acute abdominal pain. Explorative laparotomy showed a large intra-abdominal collection of pus without signs of gastrointestinal perforation at that time.

One NSCLC patient died during treatment. A bronchial stent placed before start of chemotherapy had migrated, most probably due to tumor shrinkage. During an endoscopic replacement procedure, an acute fatal pulmonary hemorrhage occurred.

Tumor response. All enrolled patients were evaluable for response. As shown in Table 5, overall response rate was 38%

Table 4. Baseline and end of treatment assessment of neurotoxicity, ototoxicity, nephrotoxicity, and cardiotoxicity

Assessment	All cohorts	Weekly bortezomib 1.0 mg/m^2 (MTD)	Twice-weekly bortezomib 1.0 mg/m^2 (MTD)
Neurotoxicity questionnaire (score)			
Baseline	3.0 (n = 31)	2.2 (n = 11)	3.1 (n = 10)
EOT	3.5 (n = 31)	2.6 (n = 11)	3.9 (n = 10)
ΔEOT	+0.5 (P = 0.62)	+0.4 (P = 0.73)	+0.8 (P = 0.70)
Hearing loss (dB)			
Baseline	38.6 (n = 31)	47.1 (n = 10)	31.3 (n = 11)
EOT	46.0 (n = 31)	58.3 (n = 10)	35.7 (n = 11)
ΔEOT	+7.4 (P = 0.24)	+10.8 (P = 0.34)	+4.4 (P = 0.66)
Renal function (GFR, mL/min)			
Baseline	93.9 (n = 34)	91.9 (n = 12)	91.1 (n = 12)
EOT	83.9 (n = 34)	85.0 (n = 12)	80.8 (n = 12)
ΔEOT	-10.0 (P < 0.05)	-7.0 (P < 0.05)	-10.3 (P < 0.05)
Left ventricular function (%)			
Baseline	61.2 (n = 15)	60.9 (n = 7)	61.6 (n = 8)
EOT	58.7 (n = 15)	60.0 (n = 7)	57.6 (n = 8)
ΔEOT	-2.5 (P = 0.20)	-0.9 (P = 0.80)	-4.0 (P = 0.096)

NOTE: Data are Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity questionnaire, version 4.0, scores; average hearing loss at 4 and 8 kHz by audiometric measurement; glomerular filtration rate as calculated by the Cockcroft-Gault formula; and LVEF by multiple-gated acquisition scan. Only patients from whom baseline and end of treatment assessments were available were included. Reported values are averages. Three patients had no follow-up audiometric measurements due to disease progression. LVEF was routinely measured in all patients after incidence of a possible treatment-related grade 4 left ventricular dysfunction in a patient. P value expresses significance.
Abbreviations: EOT, end of treatment; ΔEOT, difference between baseline value and end of treatment value; GFR, glomerular filtration rate.

(95% CI, 21-55%). Response rate in NSCLC patients combining all dose groups and both treatment schedules was 33% (95% CI, 15-51%). In NSCLC patients, twice-weekly administration of bortezomib resulted in a response rate of 25% (95% CI, 0-50 %) compared with 40% (95% CI, 15-65 %) in patients who received weekly administration of bortezomib. Disease control rate (responses plus stable disease) in NSCLC patients was 89% with a median stable disease duration of 3.0 months (95% CI, 2.0-4.0 months) and median response duration of 5.6 months (95% CI, 4.1-7.1 months). Of four patients with urothelial cell cancer, three had a partial response. Only one patient, with pancreatic cancer, who experienced stable disease after six cycles of therapy, opted to continue on monotherapy bortezomib, which was discontinued after two cycles due to progressive disease. No other responding patients or patients with stable disease opted to continue with bortezomib monotherapy. In patients with progressive disease, we observed an average weight loss of 6% at end of treatment compared with 2% in patients with stable disease and a weight gain of 2% in patients responding to treatment.

As the study population constituted a heterogenous group of patients with various solid tumor types, we did a subgroup analysis for time to progression and survival in NSCLC patients (n = 27) only. In an intention-to-treat analysis, median follow-up was 19 months. One NSCLC patient was lost to follow-up at

Table 5. Treatment efficacy in all patients and in NSCLC patients

Investigator-assessed response	All patients (N = 34)	NSCLC all (N = 27)	NSCLC weekly bortezomib (N = 15)*	NSCLC twice-weekly bortezomib (N = 12)†
PR	NSCLC (9) Urothelial cell cancer (3) ACUP‡ (1)	9 (33%)	6 (40%)	3 (25%)
SD§	NSCLC (15) Urothelial cell cancer (1) Pancreatic cancer (1)	15 (56%)	8* (53%)	7 (58%)
PD	NSCLC (3) Hepatocellular cancer (1)	3 (11%)	1 (7%)	2 (17%)

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.
*Ten patients treated at 1.0 mg/m^2; five patients treated at 1.3 mg/m^2 bortezomib.
† One patient treated at 0.7 mg/m^2; 11 patients treated at 1.0 mg/m^2 bortezomib.
‡ Identified as breast carcinoma at a later stage.
§ Including a NSCLC with a partial response that could not be confirmed because of death due to fatal bleeding during broncoscopic procedure.

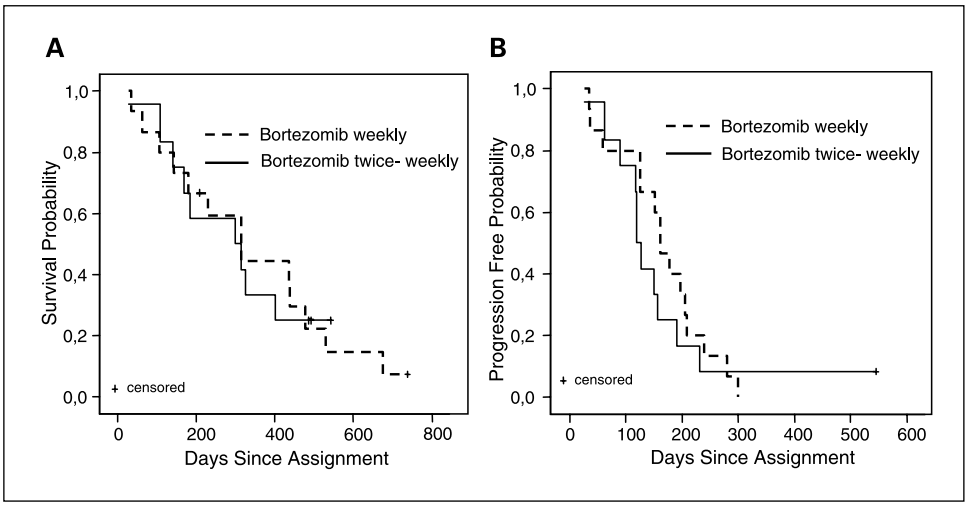

Fig. 2. Kaplan-Meier survival (*A*) and time to progression (*B*) curves in NSCLC patients, by treatment schedule (intent-to-treat population, $n = 27$).

7 months due to emigration. As shown in Fig. 2, median overall survival and time to progression were 315 days (95% CI, 206-424 days; six patients censored; 10.4 months) and 152 days (95% CI, 101-203 days; one patient censored; 5.0 months), respectively. The 1-year survival probability for NSCLC patients was 41%. In patients treated with bortezomib twice-weekly ($n = 12$) median survival and time to progression were 299 days (95% CI, 90-508 days; four patients censored; 9.8 months) and 120 days (95% CI, 110-130 days; one patient censored; 3.9 months), respectively. In patients treated weekly with bortezomib ($n = 15$), median survival and time to progression were 315 days (95% CI, 168-462 days; two patients censored; 10.4 months) and 162 days (95% CI, 129-194 days; 5.4 months), respectively.

Pharmacokinetic analysis. Table 6 and Fig. 3 show the plasma pharmacokinetic variables for cisplatin (platinum) and gemcitabine (dFdC and the inactive metabolite of gemcitabine, dFdU). Addition of bortezomib did not seem to alter these variables compared with historical controls generated in our laboratory (25, 29). No significant difference was found in variables comparing patients treated with weekly or twice-weekly bortezomib.

In addition to measurements of the deoxycytidine analogue gemcitabine, the plasma level of endogenous deoxycytidine

Table 6. Pharmacokinetic variables for cisplatin (platinum) and gemcitabine (dFdC and dFdU)

Compound	All patients mean ± SD ($n = 12$)	Twice-weekly bortezomib 1.0 mg/m^2, mean ± SD ($n = 6$)	Weekly bortezomib 1.0 mg/m^2, mean ± SD ($n = 6$)	P*
Platinum (plasma)				
C_{max}, μmol/L	11.0 ± 2.2	10.7 ± 1.4	11.3 ± 3.0	0.63
AUC, min mmol/L	50.0 ± 12.8	47.0 ± 8.8	52.9 ± 16.3	0.45
dFdC (plasma)				
C_{max} day 1, μmol/L	48.7 ± 14.9 †	47.6 ± 15.1	50.0 ± 16.4 ‡	0.81
C_{max} day 8, μmol/L	50.5 ± 24.7	44.6 ± 17.9	56.3 ± 30.6	0.44
AUC day 1 (0-60 min) min•μmol/L§	1,441 ± 376 †	1,398 ± 357	1,491 ± 434 ‡	0.71
AUC day 8 (0-60 min) min•μmol/L§	1,516 ± 666 †	1,369 ± 515	1,662 ± 812‖	0.45
dFdU (plasma)				
C_{max} day 1, μmol/L	98.6 ± 13.8	100.1 ± 11.1	97.2 ± 17.1	0.74
C_{max} day 8, μmol/L	102.1 ± 23.2	106.6 ± 23.2	97.7 ± 24.5	0.53
AUC day 1 (0-60 min) min•μmol/L¶	3,850 ± 641	3,938 ± 564	3,763 ± 754	0.66
AUC day 8 (0-60 min) min•μmol/L¶	4,163 ± 1,109	4,189 ± 1,205	4,137 ± 1,120	0.94

Abbreviation: AUC, area under the concentration curve.
*Twice-weekly compared with weekly bortezomib.
† $n = 11$.
‡ $n = 5$.
§Partial area under the concentration curve (0-60 min) was used to compare the pharmacokinetic profiles of dFdC and dFdU on days 1 and 8.
‖ $n = 6$.
¶Partial area under the concentration curve (0-60 min) was used to compare the pharmacokinetic profiles of dFdC and dFdU on days 1 and 8.

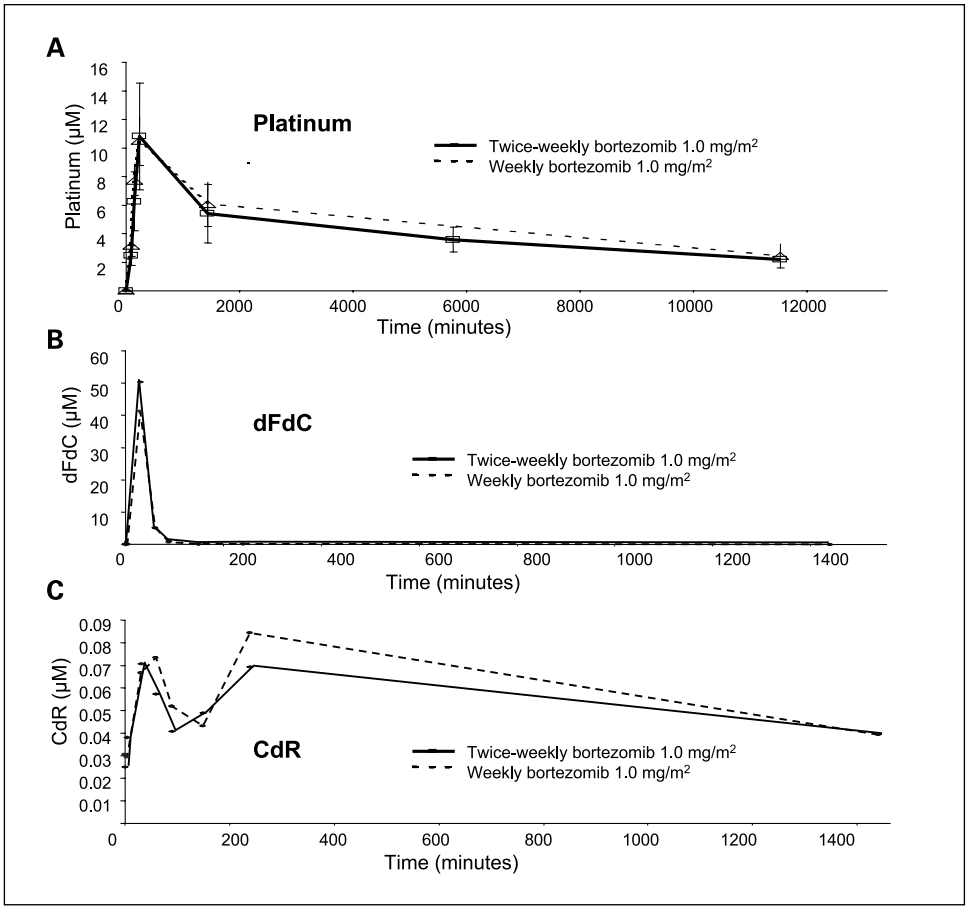

Fig. 3. Mean plasma concentration time curves for (*A*) cisplatin (*platinum*), (*B*) gemcitabine (*dFdC*), and (*C*) endogenous deoxycytidine (*CdR*), by treatment schedule.

(CdR) was also determined. We observed an unexpected, transient drop in the level of plasma CdR in the current combination of bortezomib, gemcitabine, and cisplatin.

Discussion

Bortezomib is a novel and promising antineoplastic agent, presently approved for the treatment of second-line multiple myeloma and mantle cell lymphoma patients. Many studies are being conducted in solid tumor patients and as a single agent bortezomib has shown modest activity in NSCLC patients (12). As inhibition of proteasome activity might sensitize for chemotherapy-induced cytotoxicity, combinations of bortezomib and chemotherapy are being investigated (30).

In this study, we combined bortezomib and cisplatin-gemcitabine chemotherapy as a first-line treatment for patients with advanced solid tumors, preferentially including NSCLC patients. We evaluated the tolerability of two schedules of bortezomib, a standard twice-weekly schedule and an alternative weekly schedule. Overall, treatment was well tolerated in both schedules with an equal MTD of bortezomib of 1.0 mg/m^2.

The toxicity profile of gemcitabine and cisplatin combined with bortezomib seems comparable with gemcitabine and cisplatin chemotherapy without bortezomib. Hematologic toxicity was prominent, and nonhematologic toxicity was relatively mild. However, increased dose intensity of bortezomib led to higher grade hematologic as well as nonhematologic toxicity, notably gastrointestinal toxicity and asthenia. In general, incidences of neutropenia and especially thrombocytopenia, in patients treated with cisplatin, gemcitabine, and bortezomib seem to be higher compared with reported incidences in larger groups of patients treated with a three-week regimen of gemcitabine (1,200-1,250 mg/m^2) and cisplatin (75-80 mg/m^2) alone (31, 32). However, the cause and kinetics of bortezomib-induced thrombocytopenia differ from conventional chemotherapy-induced thrombocytopenia. Bortezomib-induced thrombocytopenia is due to a reversible effect on megakaryocytic function rather than a direct cytotoxic effect on megakaryocytes. Consequently, bortezomib-induced thrombocytopenia is characterized by rapid recovery during the washout period and is associated with a low incidence of bleeding, which was also our experience in the combination with cisplatin and gemcitabine (33).

Surprisingly, combining cisplatin and bortezomib, we did not observe treatment-emergent neuropathy, although the majority of patients experienced low-grade neuropathy. Refractory multiple myeloma patients treated with twice-weekly bortezomib 1.0 mg/m^2 were reported to have a 21% incidence of treatment-emergent neuropathy (34). This might be due to the fact that patients in our study were not pretreated with neurotoxic drugs, patients with ≥grade 2 neuropathy were excluded, and, in multiple myeloma patients, paraproteinemic-associated neuropathy might contribute to the relatively high incidence of observed neuropathy (35).

Neutropenia was the primary cause of treatment delay. Three patients (9%) experienced repeatedly prolonged neutropenia, causing unacceptable treatment delay. Growth factor support with granulocyte colony-stimulating factor injections was effective in preventing persisting neutropenia in these patients and could therefore be considered in patients experiencing prolonged neutropenia following the first treatment cycle. We do not recommend standard use of granulocyte colony-stimulating factor injections with this combination treatment as these patients formed a small subgroup of the total study population.

Plasma pharmacokinetic variables of cisplatin and gemcitabine were not affected by the addition of bortezomib. As the effectiveness of deoxycytidine (CdR) analogues, such as gemcitabine, can be linked to the direct competition with active forms of endogenous CdR, we also determined the plasma level of endogenous deoxycytidine in patient samples (26). Endogenous deoxycytidine plasma levels showed an unexpected, transient drop. This was not observed in other patients treated with cisplatin-gemcitabine in our hospital (data not shown). The significance of this finding, notably if there might be an effect of bortezomib coadministration on intracellular gemcitabine metabolism, is unclear and is currently being investigated.

A recently published phase 1 study reported that the inhibition of 20S proteasome activity in peripheral blood mononuclear cells by bortezomib was unaffected by gemcitabine coadministration (36). As for pharmacodynamic activity of bortezomib in combination with gemcitabine and cisplatin, a pilot experiment, measuring proteasome activity in a few remaining peripheral blood mononuclear cell samples, showed a decrease in proteasome activity upon treatment (37). Furthermore, we observed throughout the study population a typical bortezomib-associated cyclical thrombocytopenia pattern while on treatment.

The achieved overall response rate in NSCLC patients in our study is 33%. Notably, as much as 10 (37%) of our 27 NSCLC patients presented with brain metastases, 4 patients (15%) using corticosteroids at study entry and 2 additional patients (7%), early progressive on treatment, started shortly after study entry with corticosteroids. The response rate seems to be similar to those observed in advanced NSCLC patients treated with only cisplatin and gemcitabine, generally at higher doses of up to 80 mg/m^2 and up to 1,250 mg/m^2, respectively (14, 31, 32, 38–40). Although this study was not powered to show a difference between the two schedules, response rates were similar in the weekly regimen compared with the twice-weekly regimen and overall survival as well as progression-free survival curves seemingly superimposable.

Recently, final results were presented from a phase 2 study in which efficacy of bortezomib twice-weekly 1.0 mg/m^2, carboplatin AUC 5, and gemcitabine 1,000 mg/m^2, was assessed in 114 chemonaive stage advanced NSCLC patients (20). At a median follow-up of 13 months, progression-free survival and overall survival were 5 and 11 months, respectively. The 11-month median survival achieved was regarded as unprecedented by the authors. In that trial, chemotherapy was administered before bortezomib based on preclinical results indicating that this sequence might favor efficacy (17, 23). In our trial, we administered chemotherapy after bortezomib, achieving comparable progression-free survival and median overall survival duration in advanced NSCLC patients. Furthermore, a weekly schedule of bortezomib in combination with carboplatin and gemcitabine was not investigated by Davies et al. (20), nor were pharmacokinetic variables for gemcitabine or carboplatin was determined. Interestingly, a weekly administration of bortezomib is currently being studied as a more convenient alternative in multiple myeloma and non–Hodgkin's lymphoma as well (41, 42).

In conclusion, bortezomib can be safely combined with cisplatin-gemcitabine chemotherapy and constitutes an active regimen in advanced stage NSCLC patients. Although this is a nonrandomized, phase 1 study does not allow comparison between the two schedules, the weekly schedule of bortezomib seems to be favorable over a twice-weekly schedule, based on lower toxicity and no indication of inferior activity compared with the twice-weekly schedule.

Acknowledgments

We thank Adrie C. Laan for his valuable contribution to the pharmacokinetic studies, Chantal Dinkgreve for assisting in data management, and Atie van Wijk for her help at the Department of Pulmonology, all at VU University Medical Center, Amsterdam, the Netherlands; and Deborah Brouwer at Janssen-Cilag, Tilburg, the Netherlands, for her contribution to this study.

References

1. King RW, Deshaies RJ, Peters JM, Kirschner MW. How proteolysis drives the cell cycle. Science 1996; 274:1652–9.
2. Palombella VJ, Rando OJ, Goldberg AL, Maniatis T. The ubiquitin-proteasome pathway is required for processing the NF-κB1 precursor protein and the activation of NF-κB. Cell 1994;78:773–85.
3. Read MA, Neish AS, Luscinskas FW, Palombella VJ, Maniatis T, Collins T. The proteasome pathway is required for cytokine-induced endothelial-leukocyte adhesion molecule expression. Immunity 1995;2:493–506.
4. Twombly R. First proteasome inhibitor approved for multiple myeloma. J Natl Cancer Inst 2003;95:845.
5. Adams J. The proteasome: a suitable antineoplastic target. Nat Rev Cancer 2004;4:349–60.
6. Beg AA, Baltimore D. An essential role for NF-κB in preventing TNF-α-induced cell death. Science 1996; 274:782–4.
7. Ling YH, Liebes L, Ng B, et al. PS-341, a novel proteasome inhibitor, induces Bcl-2 phosphorylation and cleavage in association with G_2-M phase arrest and apoptosis. Mol Cancer Ther 2002;1:841–9.
8. Fernandez Y, Verhaegen M, Miller TP, et al. Differential regulation of noxa in normal melanocytes and melanoma cells by proteasome inhibition: therapeutic implications. Cancer Res 2005;65:6294–304.
9. Perez-Galan P, Roue G, Villamor N, Montserrat E, Campo E, Colomer D. The proteasome inhibitor bortezomib induces apoptosis in mantle-cell lymphoma through generation of ROS and Noxa activation independent of p53 status. Blood 2006;107:257–64.
10. Ludwig H, Khayat D, Giaccone G, Facon T. Proteasome inhibition and its clinical prospects in the treatment of hematologic and solid malignancies. Cancer 2005;104:1794–807.
11. Adams J, Palombella VJ, Sausville EA, et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 1999;59:2615–22.
12. Fanucchi MP, Fossella FV, Belt R, et al. Randomized phase II study of bortezomib alone and bortezomib in combination with docetaxel in previously treated advanced non-small-cell lung cancer. J Clin Oncol 2006;24:5025–33.
13. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–98.
14. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2000;18:122–30.
15. Lehmann J, Retz M, Steiner G, et al. [Gemcitabine/cisplatin vs. MVAC. 5 year survival outcome of the phase III study of chemotherapy of advanced urothelial carcinoma in Germany]. Urologe A 2003;42: 1074–86.
16. Aghajanian C, Dizon DS, Sabbatini P, Raizer JJ, Dupont J, Spriggs DR. Phase I trial of bortezomib and carboplatin in recurrent ovarian or primary peritoneal cancer. J Clin Oncol 2005;23:5943–9.
17. Mortenson MM, Schlieman MG, Virudachalam S,

Bold RJ. Effects of the proteasome inhibitor bortezomib alone and in combination with chemotherapy in the A549 non-small-cell lung cancer cell line. Cancer Chemother Pharmacol 2004;54:343–53.

18. Kamat AM, Karashima T, Davis DW, et al. The proteasome inhibitor bortezomib synergizes with gemcitabine to block the growth of human 253JB-V bladder tumors *in vivo*. Mol Cancer Ther 2004;3:279–90.

19. Teicher BA, Ara G, Herbst R, Palombella VJ, Adams J. The proteasome inhibitor PS-341 in cancer therapy. Clin Cancer Res 1999;5:2638–45.

20. Davies AM, McCoy J, Lara PN, et al. Bortezomib + gemcitabine (Gem)/carboplatin (Carbo) results in encouraging survival in advanced non-small cell lung cancer (NSCLC): Results of a phase II Southwest Oncology Group (SWOG) trial [abstract 7017]. Int J Clin Oncol 2006;24:18S.

21. Imai J, Yashiroda H, Maruya M, Yahara I, Tanaka K. Proteasomes and molecular chaperones: cellular machinery responsible for folding and destruction of unfolded proteins. Cell Cycle 2003;2:585–90.

22. Fahy BN, Schlieman MG, Mortenson MM, Virudachalam S, Bold RJ. Targeting BCL-2 overexpression in various human malignancies through NF-κB inhibition by the proteasome inhibitor bortezomib. Cancer Chemother Pharmacol 2005;56:46–54.

23. Mack PC, Davies AM, Lara PN, Gumerlock PH, Gandara DR. Integration of the proteasome inhibitor PS-341 (Velcade) into the therapeutic approach to lung cancer. Lung Cancer 2003;41 Suppl 1:S89–96.

24. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

25. van Moorsel CJ, Kroep JR, Pinedo HM, et al. Pharmacokinetic schedule finding study of the combination of gemcitabine and cisplatin in patients with solid tumors. Ann Oncol 1999;10:441–8.

26. Honeywell R, van Groeningen CJ, Laan AC, et al. Analysis of deoxycytidine accumulation in gemcitabine treated patients. Nucleosides Nucleotides Nucleic Acids 2006;25:1225–32.

27. Honeywell R, Laan AC, van Groeningen CJ, et al. The determination of gemcitabine and 2′-deoxycytidine in human plasma and tissue by APCI tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2007;847:142–52.

28. Voortman J, Giaccone G. Severe reversible cardiac failure after bortezomib treatment combined with chemotherapy in a non-small cell lung cancer patient: a case report. BMC Cancer 2006;6:129.

29. Kroep JR, Smit EF, Giaccone G, et al. Pharmacology of the paclitaxel-cisplatin, gemcitabine-cisplatin, and paclitaxel-gemcitabine combinations in patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol 2006;58:509–16.

30. Scagliotti G. Proteasome inhibitors in lung cancer. Crit Rev Oncol Hematol 2006;58:177–89.

31. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002;20:4285–91.

32. Zatloukal P, Petruzelka L, Zemanova M, et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer 2003;41:321–31.

33. Lonial S, Waller EK, Richardson PG, et al. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. Blood 2005;106:3777–84.

34. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 2006;24:3113–20.

35. Ropper AH, Gorson KC. Neuropathies associated with paraproteinemia. N Engl J Med 1998;338:1601–7.

36. Ryan DP, Appleman LJ, Lynch T, et al. Phase I clinical trial of bortezomib in combination with gemcitabine in patients with advanced solid tumors. Cancer 2006;107:2482–9.

37. Lightcap ES, McCormack TA, Pien CS, Chau V, Adams J, Elliott PJ. Proteasome inhibition measurements: clinical application. Clin Chem 2000;46:673–83.

38. Mazzanti P, Massacesi C, Rocchi MB, et al. Randomized, multicenter, phase II study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer 2003;41:81–9.

39. Gebbia V, Galetta D, Caruso M, et al. Gemcitabine and cisplatin versus vinorelbine and cisplatin versus ifosfamide+gemcitabine followed by vinorelbine and cisplatin versus vinorelbine and cisplatin followed by ifosfamide and gemcitabine in stage IIIB-IV non small cell lung carcinoma: a prospective randomized phase III trial of the Gruppo Oncologico Italia Meridionale. Lung Cancer 2003;39:179–89.

40. Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 1999;17:12–8.

41. Greco FA, Spigel DR, Barton JH, et al. Weekly bortezomib in the treatment of patients (pts) with previously treated multiple myeloma: a phase II trial of the Minnie Pearl Cancer Research Network [abstract 7547]. J Clin Oncol 2006;24:18S.

42. Suvannasankha A, Smith GG, Juliar BE, Abonour R. Weekly bortezomib/methylprednisolone is effective and well tolerated in relapsed multiple myeloma. Clin Lymphoma Myeloma 2006;7:131–4.

Clinical Cancer Research

A Parallel Dose-Escalation Study of Weekly and Twice-Weekly Bortezomib in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced Solid Tumors

Jens Voortman, Egbert F. Smit, Richard Honeywell, et al.

Clin Cancer Res 2007;13:3642-3651.