British Journal of Cancer (2008) 98, 1500 – 1507

www.bjcancer.com

Clinical Studies

Bortezomib/docetaxel combination therapy in patients with anthracycline-pretreated advanced/metastatic breast cancer: a phase I/II dose-escalation study

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The aim of this study was to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of bortezomib plus docetaxel in patients with anthracycline-pretreated advanced/metastatic breast cancer. Forty-eight patients received up to eight 21-day cycles of docetaxel (60–100 mg m^{-2} on day 1) plus bortezomib (1.0–1.5 mg m^{-2} on days 1, 4, 8, and 11). Pharmacodynamic and pharmacokinetic analyses were performed in a subset of patients. Five patients experienced DLTs: grade 3 bone pain ($n = 1$) and febrile neutropenia ($n = 4$). The MTD was bortezomib 1.5 mg m^{-2} plus docetaxel 75 mg m^{-2}. All 48 patients were assessable for safety and efficacy. The most common adverse events were diarrhoea, nausea, alopecia, asthenia, and vomiting. The most common grade 3/4 toxicities were neutropenia (44%), and febrile neutropenia and diarrhoea (each 19%). Overall patient response rate was 29%. Median time to progression was 5.4 months. In patients with confirmed response, median time to response was 1.3 months and median duration of response was 3.2 months. At the MTD, response rate was 38%. Pharmacokinetic characteristics of bortezomib/docetaxel were comparable with single-agent data. Addition of docetaxel appeared not to affect bortezomib inhibition of 20S proteasome activity. Mean alpha-1 acid glycoprotein concentrations increased from baseline at nearly all time points across different bortezomib dose levels. Bortezomib plus docetaxel is an active combination for anthracycline-pretreated advanced/metastatic breast cancer. The safety profile is manageable and consistent with the side effects of the individual agents.
British Journal of Cancer (2008) **98,** 1500 – 1507. doi:10.1038/sj.bjc.6604347 www.bjcancer.com
Published online 29 April 2008

Keywords: anthracycline-pretreated; breast cancer; bortezomib; docetaxel; metastatic; proteasome inhibitor

Anthracyclines and taxanes are widely used in treating patients with metastatic breast cancer. In anthracycline-pretreated advanced/metastatic breast cancer, docetaxel administered once every 3 weeks is more active than the same schedule of paclitaxel (Jones *et al*, 2005). The efficacy of docetaxel as a single agent (Nabholtz *et al*, 1999; Sjostrom *et al*, 1999; Jones *et al*, 2005) or in combination with cytotoxic agents (O'Shaughnessy *et al*, 2002; Chan *et al*, 2005) has been established in phase III trials in this setting. The standard dose of single-agent docetaxel is 75–100 mg m^{-2} every 21 days. In combination, the dose is reduced, typically to 75 mg m^{-2} (Aventis Pharmaceuticals Inc, 2005). Dose reduction potentially reduces efficacy; therefore, careful identification of dosing regimens that provide acceptable safety profiles without compromising efficacy is essential.

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Phase I study of bortezomib in combination with docetaxel in anthracycline-pretreated advanced breast cancer was presented at the 2003 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31–June 3, 2003 (abstract 63).
Received 31 January 2008; accepted 5 March 2008; published online 29 April 2008

Combining agents with unique modes of action may improve outcomes and overcome chemoresistance without significantly increasing toxicity. Docetaxel acts by disrupting the microtubular network essential for cellular functions (Bissery *et al*, 1995; Eisenhauer and Vermorken, 1998). Bortezomib, which is approved for treating multiple myeloma and mantle cell lymphoma patients who have received at least one prior therapy (Kane *et al*, 2006), acts by inhibiting the 26S proteasome, the degradative enzyme complex involved in the catabolism of numerous intracellular regulatory proteins, including NF-κB (nuclear factor-κB)-inhibitor IκBα, p53, p21, and p27 (Adams, 2002; Cusack, 2003; Lenz, 2003; Boccadoro *et al*, 2005). Malignancies with high concentrations of activated NF-κB, such as breast cancer, are logical targets for agents that interrupt this pathway (Orlowski and Dees, 2003). Mutations in the tumour suppressor gene p53 occur in 20–40% of sporadic breast cancers (Osin and Lakhani, 1999) and are associated with a poor prognosis (Pharoah *et al*, 1999; Overgaard *et al*, 2000) and poor response to treatment with certain chemotherapeutic and hormonal agents (Berns *et al*, 2000; Kandioler-Eckersberger *et al*, 2000). The cyclin-dependent kinase inhibitors p21 and p27 also play important roles in breast cancer (Osin and Lakhani, 1999), supporting the investigation of bortezomib in breast malignancies.

Bortezomib has demonstrated cytotoxic activity in breast, lung, pancreatic, prostate, and head and neck tumour models *in vivo*

(Adams *et al*, 1999; Teicher *et al*, 1999; Shah *et al*, 2001; Sunwoo *et al*, 2001; Nawrocki *et al*, 2002; Williams *et al*, 2003; Ikezoe *et al*, 2004). Preliminary *in vitro* and *in vivo* studies in a range of solid tumours demonstrated an additive antitumour effect of bortezomib with standard cytotoxic agents, including docetaxel (Gumerlock *et al*, 2002, 2004; Mack *et al*, 2003; Nawrocki *et al*, 2004; Farneth *et al*, 2005). Bortezomib $1\,mg\,kg^{-1}$ combined with docetaxel $5\,mg\,kg^{-1}$ was active in pancreatic xenograft models (Nawrocki *et al*, 2004). Interestingly, sequential administration led to greater tumour growth inhibition than with either agent alone (Gumerlock *et al*, 2004). Preclinical studies in prostate and lung cancer models indicated that the sequence docetaxel → bortezomib was more effective than bortezomib → docetaxel (Gumerlock *et al*, 2002; Farneth *et al*, 2005). A possible explanation is that bortezomib promotes cell cycle arrest before the M phase, consequently interfering with docetaxel-induced apoptosis (Nawrocki *et al*, 2004). Additionally, *in vitro* studies have shown that docetaxel is extensively plasma protein-bound, especially to alpha-1 acid glycoprotein (AAG), albumin, and lipoproteins (Aventis Pharmaceuticals Inc, 2005). As AAG is an acute-phase protein that may be elevated by IL (interleukin)-6, which is inhibited by bortezomib (Hideshima *et al*, 2001), bortezomib may decrease AAG concentrations and improve docetaxel efficacy.

In clinical studies in patients with solid tumours, bortezomib/docetaxel combination therapy demonstrated encouraging activity, and the side effects were predictable and manageable (Meluch *et al*, 2005; Fanucchi *et al*, 2006; Lara *et al*, 2006; Dreicer *et al*, 2007). There is no evidence of a drug interaction between bortezomib and docetaxel (Messersmith *et al*, 2006).

Based on the known single-agent antitumour activity of bortezomib and docetaxel, and their additive efficacy in preclinical models, complementary mechanisms of action (Nawrocki *et al*, 2004), different toxicity profiles, and feasibility in clinical studies in various solid tumours, we conducted the current study to explore the potential of bortezomib/docetaxel combination therapy in patients with advanced/metastatic breast cancer. Our primary aim was to identify the most appropriate regimen for further evaluation.

PATIENTS AND METHODS

Study objectives

The primary objective was to establish the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of bortezomib/docetaxel combination therapy in patients with advanced and/or metastatic breast cancer that had previously been treated with anthracyclines. Secondary objectives were to assess tumour response rate (complete response (CR), partial response (PR), or stable disease (SD)), time to response, duration of response, and time to disease progression (TTP); evaluate disposition profiles of docetaxel and bortezomib administered in combination using pharmacokinetic analyses; evaluate pharmacodynamic properties of bortezomib in combination with docetaxel using 20S proteasome inhibition assay (Lightcap *et al*, 2000); and investigate the possible influence of bortezomib/docetaxel combination treatment on serum concentrations of AAG.

Eligibility

All study participants provided written, informed consent. Patients who had advanced/metastatic breast cancer, had received at least one anthracycline-containing regimen, were aged $\geqslant 18$ years, and had a Karnofsky Performance Status $\geqslant 80\%$ (ECOG 0–1) were considered eligible. Prior treatment with endocrine or biologic agents was permitted. Patients were excluded if they had previously received docetaxel or paclitaxel as adjuvant treatment within the previous year or for metastatic disease at any time; radiotherapy to $>35\%$ of bone marrow (e.g., pelvic radiation), major surgery, or chemotherapy within 4 weeks of enrollment; nitrosoureas within 6 weeks or antibody therapy within 8 weeks of enrollment; or high-dose chemotherapy and peripheral blood stem cell transplantation at any time. Patients were excluded if they had grade $\geqslant 1$ peripheral neuropathy; abnormal laboratory values within 2 weeks of enrollment; history of severe hypersensitivity reaction to docetaxel; not recovered from all toxic effects (except alopecia) of previous chemotherapy, radiotherapy, or antibody therapy. The following were prohibited during the study treatment: any investigational agent other than bortezomib, haematopoietic growth factors during the first cycle (except for haematologic DLT, or continued erythropoietin for pre-existing anaemia), immunotherapeutic agents, steroids (except dexamethasone), chemotherapeutic agents other than docetaxel, radiotherapy, or surgery for cancer.

Study design

This prospective, phase I/II, open-label dose-escalation study was conducted at six centers in Europe (Belgium, Spain, UK) in accordance with the International Conference on Harmonisation for Good Clinical Practice. The protocol and informed consent were approved by the Institutional Review Board at each clinical site before study initiation.

Each 3-week treatment cycle consisted of docetaxel (Taxotere®; Sanofi-Aventis, Paris, France) infusion on day 1 and bortezomib (Velcade®; Millennium Pharmaceuticals Inc., Cambridge, MA, USA and Johnson & Johnson Pharmaceuticals, Rariman, NY, USA, Research and Development, L.L.C) injections on days 1, 4, 8, and 11. Bortezomib was administered 1 h after docetaxel. Treatment comprised eight cycles. Docetaxel was administered at doses of 60, 75, or $100\,mg\,m^{-2}$ with standard oral dexamethasone premedication (six 8-mg doses administered the night before, morning of, immediately before, evening after, and morning and evening of day 2 after each docetaxel infusion). Bortezomib doses were 1.0, 1.3, or $1.5\,mg\,m^{-2}$, based on tolerability and efficacy in heavily pretreated patients with solid tumours. All patients received appropriate supportive therapy. Patients achieving a tumour response at the end of the treatment could receive further treatment at the investigator's discretion. Patients with progressive disease discontinued treatment.

Patients were evaluated for toxicities before each scheduled study drug dose. Adverse events (AEs) were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). The following AEs during the first cycle were considered DLTs: platelet count $\leqslant 25\times10^{9}\,l^{-1}$; febrile neutropenia (absolute neutrophil count [ANC] $<1\times10^{9}\,l^{-1}$ with temperature $\geqslant 38.5^{\circ}C$); ANC $<0.5\times10^{9}\,l^{-1}$ for days 1–7, or $<0.2\times10^{9}\,l^{-1}$ without fever for $\geqslant 7$ days starting on or after day 8; any other grade 4 haematologic toxicity; grade 2 peripheral neuropathy; any grade 3 or 4 non-haematologic toxicity (except inadequately treated nausea, vomiting, and diarrhoea). In patients experiencing grade 4 haematologic or grade 3/4 non-haematologic toxicity, the start of the next cycle was delayed for up to 2 weeks or bortezomib therapy was interrupted for up to 2 weeks until toxicity returned to baseline or better. Treatment was re-initiated at a reduced dose (25% dose reduction of the drug considered by the investigator to have caused the toxicity). A maximum of two dose reductions for each drug was recommended. If toxicity did not resolve, the patient was excluded from further study.

Doses of both agents were reduced if patients experienced grade 2 neuropathic pain or peripheral neuropathy. In patients with either toxicity at grade 3 intensity or both toxicities at grade 2, bortezomib treatment was interrupted until resolution to grade $\leqslant 1$, when dose was reduced, and at resolution, treatment was continued using weekly bortezomib (days 1 and 8 only). In

patients experiencing grade 4 neuropathic pain or peripheral neuropathy, or both toxicities with grade 3 intensity, bortezomib and docetaxel were discontinued.

Doses were escalated in a stepwise fashion if fewer two out of three patients in a dose cohort experienced a DLT. The MTD was defined as the dose below that causing DLTs in at least two out of three patients. Up to 10 additional patients were to be enrolled at the MTD.

Study assessments

Karnofsky Performance Status assessments, physical examinations, and laboratory sampling were undertaken during screening, during the first cycle, at the end-of-therapy visit (10 days after the last dose of study drug), and at the end-of-study visit (3 weeks after the end-of-therapy visit).

Lesions were assessed by CT/MRI every 6 weeks using the Response Evaluation Criteria in Solid Tumours (Therasse *et al*, 2000). Response was confirmed 6 weeks later in patients with CR/PR. Efficacy was also assessed based on the expression of tumour marker CA15.3, Karnofsky Performance Status, and C-reactive protein, IL-6, and AAG concentrations. Blood samples were collected at screening, on day 1 of cycles 3, 5, and 7 (and all odd-numbered cycles thereafter in responding patients receiving further treatment), and at the end-of-study visit.

In patients participating in pharmacokinetic analysis, blood samples were taken on day 1, cycle 1, to determine the plasma concentration time profile of docetaxel and bortezomib. Samples were collected immediately before docetaxel infusion and bortezomib injection and at prespecified intervals on day 1. Samples were also taken for bortezomib pharmacokinetic analysis on day 11 of cycle 1. Whole-blood samples were taken for pharmacodynamic analysis using 20S proteasome inhibition assay (Lightcap *et al*, 2000) immediately before and 1 h after bortezomib dosing on days 1 and 11 of cycles 1 and 2, and on days 2 and 12 of cycle 1, in a subset of patients participating in pharmacokinetic analysis. Samples for determination of AAG concentrations were collected at screening and before docetaxel administration on day 1 of cycles 1, 2, 4, and 6.

Statistical analysis

Statistical analyses were primarily descriptive; the aim of the study was to establish the MTD of bortezomib/docetaxel combination therapy. Planned enrollment was up to 70 patients.

Safety and efficacy were evaluated in all patients who received any amount of either study drug. Patients who underwent dose reduction were analysed in the dose group in which they were initially treated. The MTD-evaluable population included all patients in the dose-escalation phase with sufficient safety assessments during cycle 1 to determine whether a DLT occurred. Patients were excluded from the MTD-evaluable population if they had discontinued during cycle 1 for reasons other than DLTs or had received alternate antineoplastic therapies during that period.

RESULTS

Patient characteristics and disposition

Forty-eight patients were enrolled (47 females and 1 male); all received at least one dose of docetaxel or bortezomib. Patient characteristics are summarised in Table 1 (sites of metastases at study entry: bone ($n=23$), liver ($n=12$), lung ($n=4$), skin and soft tissues ($n=8$), nodes ($n=6$), and others ($n=8$)). The median duration of treatment was 95 days (range: 11–179) or 4 cycles (range: 1–9); 12 patients (25%) completed all 8 cycles of planned therapy.

Table 1 Patient demographics and baseline characteristics ($N=48$)

	Bortezomib/docetaxel dose ($mg\,m^{-2}\,dose^{-1}$)								
	1.0/60 ($n=3$)	1.0/75 ($n=3$)	1.0/100 ($n=11$)	1.0 subtotal ($n=17$)	1.3/75 ($n=11$)	1.3/100 ($n=4$)	1.3 subtotal ($n=15$)	1.5/75 ($n=16$)	Total ($N=48$)
Mean age (years)	52	62	50	53	55	53	54	59	55
Karnofsky performance score									
80 (%)	0	1 (33)	3 (27)	4 (24)	4 (36)	1 (25)	5 (33)	6 (38)	15 (31)
90–100 (%)	3 (100)	2 (67)	8 (73)	13 (76)	7 (64)	3 (75)	10 (67)	10 (63)	33 (69)
Regional lymph node metastases at diagnosis[a] (TNM stage N1, N2, N3)	3 (100)	1 (33)	5 (45)	9 (53)	6 (55)	3 (75)	9 (60)	13 (81)	31 (65)
Distant metastases at diagnosis[a] (TNM stage M1)	1 (33)	2 (67)	1 (9)	4 (24)	0	0	0	3 (19)	7 (15)
Median number of prior chemotherapy regimens[b], *n* (range)	2 (2–3)	3 (2–4)	3 (1–6)	3 (1–6)	3 (1–6)	3.5 (2–7)	3 (1–7)	4 (1–6)	3 (1–7)

TNM = tumour-node metastasis. [a]Per protocol, all patients had metastatic disease at the time of enrollment for the study. [b]Including neoadjuvant/adjuvant chemotherapy.

Table 2 Patients treated and DLTs observed by bortezomib and docetaxel dose level

Bortezomib (mg m^{-2})	Docetaxel (mg m^{-2})	Treated *n*	MTD evaluable[a] *n*	DLT
1.0	60	3	3	—
1.0	75	3	3	—
1.0	100	11	7[b]	Febrile neutropenia ($n=1$)
1.3	75	11	10[c]	Grade 3 bone pain ($n=1$)
1.5	75	16	6[d]	Febrile neutropenia ($n=1$)
1.3	100	4	4	Febrile neutropenia ($n=2$)
Total		48	33	

MTD = maximum tolerated dose; DLT = dose-limiting toxicity. [a]The MTD-evaluable population included all patients in the dose-escalation phase with sufficient safety assessments during cycle 1 to determine whether a DLT occurred. [b]Three patients did not complete cycle 1 of treatment, and one patient was excluded due to pre-existing peripheral neuropathy. [c]One patient had study drug held in cycle 1 and was not used in the determination of MTD. [d]Ten additional patients enrolled following determination of dose level as MTD.

Table 3 Percentage of patients experiencing the most common AEs (all grades; ⩾25% of all patients) and grade 3 or 4 AEs (⩾5% of all patients)

	Bortezomib/docetaxel doses (mg m^{-2} dose^{-1})						
	1.0/60 $n=3$	**1.0/75 $n=3$**	**1.0/100 $n=11$**	**1.3/75 $n=11$**	**1.3/100 $n=4$**	**1.5/75 $n=16$**	**Total $n=48$**
AE (all grades)							
Diarrhoea	100	67	73	82	100	75	79
Nausea	100	67	64	73	50	56	65
Alopecia	33	67	55	64	75	50	56
Asthenia	33	67	55	82	50	44	56
Vomiting	67	33	36	82	25	50	52
Neutropenia	100	67	45	55	25	38	48
Myalgia	67	100	45	45	50	31	46
Anorexia	33	33	27	73	75	31	44
Peripheral neuropathy	0	67	36	64	50	31	42
Dysgeusia	33	67	45	64	50	13	40
Paresthesia	0	67	36	64	50	25	40
Fatigue	67	33	36	27	50	31	35
Arthralgia	67	67	27	45	25	19	33
Conjunctivitis	0	67	55	18	50	13	29
Headache	67	33	36	27	25	19	29
Constipation	33	0	27	45	25	19	27
Pyrexia	0	33	27	27	25	31	27
Mucosal inflammation	0	33	36	27	25	19	25
Neuralgia	0	33	36	36	25	13	25
AE (grade 3/4)							
Neutropenia	100	33	45	55	25	31	44
Febrile neutropenia	0	0	18	18	50	19	19
Diarrhoea	33	0	18	27	25	13	19
Peripheral neuropathy	0	0	9	9	0	19	10
Leukopenia	0	33	27	0	0	6	10
Asthenia	0	33	0	18	0	6	8
Fatigue	0	0	0	0	25	13	6
Neuralgia	0	0	0	0	25	13	6

AEs = adverse events.

Identification of MTD

Table 2 summarises patients treated and DLTs observed at each dose level. No DLTs occurred at the first two dose levels (1.0/60 and 1.0/75 mg m^{-2}). At the 1.3/75 mg m^{-2} dose level, one patient developed grade 3 bone pain, which is considered a DLT and possibly related to an induced flare of pain associated with bone metastases. One patient each at the 1.0/100 and 1.5/75 mg m^{-2} dose levels, and two at the 1.3/100 mg m^{-2} dose level developed febrile neutropenia. Consequently, the MTD was defined as bortezomib 1.5 mg m^{-2} plus docetaxel 75 mg m^{-2}.

Safety

All 48 patients experienced at least 1 AE, most commonly diarrhoea, nausea, alopecia, asthenia, and vomiting (Table 3). Grade 3/4 AEs occurred in 37 patients (77%) and were considered drug-related in 34 (71%) patients. The most common grade 3/4 AEs were neutropenia, febrile neutropenia, and diarrhoea (Table 3).

Eighteen (50%) out of the 36 patients who withdrew prematurely had unacceptable AEs listed as the primary reason for treatment discontinuation: 4 at the bortezomib 1.0 mg m^{-2} dose level, 6 at the 1.3 mg m^{-2} dose level, and 8 at the 1.5 mg m^{-2} dose level. Events leading to discontinuation included peripheral neuropathy (nine patients), neuralgia (four patients), paraesthesia and diarrhoea (two patients each), and neutropenia (one patient). Twelve patients (33%) withdrew because of progressive disease. Dose reductions were most common in the second and third cycles of treatment (19 and 15% patients, respectively). Two patients died on study, one due to cardiac tamponade 3 days after the last dose of study drug and the other from disease progression 22 days after the last dose of study drug.

Table 4 Summary of efficacy

	Bortezomib/docetaxel dose (mg m^{-2} dose^{-1})								
	1.0/60 ($n=3$)	**1.0/75 ($n=3$)**	**1.0/100 ($n=11$)**	**1.0 subtotal ($n=17$)**	**1.3/75 ($n=11$)**	**1.3/100 ($n=4$)**	**1.3 subtotal ($n=15$)**	**1.5/75 ($n=16$)**	**Total ($N=48$)**
Best response[a]									
CR/PR	0	2 (67)	1 (9)	3 (18)	3 (27)	2 (50)	5 (33)	6 (38)	14 (29)
SD	2 (67)	1 (33)	9 (82)	12 (71)	7 (64)	2 (50)	9 (60)	6 (38)	27 (56)
CR, PR, or SD	2 (67)	3 (100)	10 (91)	15 (88)	10 (91)	4 (100)	14 (93)	12 (75)	41 (85)
Time to response (days)									
N	0	2	1	3	3	2	5	6	14
Median (range)	NE	79.5 (77–82)	34.0 (34–34)	77.0 (34–82)	37.0 (34–77)	139.5 (90–189)	77.0 (34–189)	38.5 (31–80)	39.0 (31–189)
Duration of response (days)									
Median (range)	NE	95.5 (34–157)	130.0	130.0 (34–157)	121.0 (108–141)	29.5 (3–56)	108.0 (3–141)	84.5 (14–153)	96.5 (3–157)
Duration of SD (days)									
N	2	1	9	12	7	2	9	6	27
Median (range)	133.5 (77–190)	183.0	118.0 (35–190)	122.0 (35–190)	111.0 (41–195)	63.0 (53–73)	108.0 (41–195)	63.5 (28–80)	100.0 (28–195)
Time to progression (days)									
N/Censored[b]	3/2	3/1	11/5	17/8	11/6	4/2	15/8	16/8	48/24
Median	NE	182	183	182	175	146	175	98	164

CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease. [a]Confirmed or unconfirmed. [b]Patients who had not progressed were censored on the end-of-study visit date or, if unavailable, date of last dose.

Efficacy

Overall, 29% (14 out of 48) patients achieved a confirmed PR and 56% (27 out of 48) achieved SD. There were no CRs. At MTD (1.5/75 mg m^{-2}), 38% (6 out of 16) patients achieved a PR, with an overall clinical benefit (PR + SD) rate of 75% (12 out of 16 patients; Table 4).

Among 14 patients achieving confirmed PR, median time to response was 39 days (1.3 months) and median duration of response was 96.5 days (3.2 months). Among 27 patients achieving SD, median duration of disease stabilisation was 100.0 days (3.3 months). Median TTP for all patients was 164 days (5.4 months). Data are shown by bortezomib dose level in Table 4.

Pharmacokinetics

Bortezomib plasma profiles exhibited an initial rapid distribution phase followed by a slower elimination phase, demonstrating apparent multi-exponential decay characteristics, similar to those reported previously. Bortezomib was eliminated from plasma with similar terminal half-lives across dose levels, with mean values of 15–18 h following the first dose in patients with measurable plasma concentrations at 24 h post-dose (Table 5). Pharmacokinetic characteristics of bortezomib/docetaxel were comparable with single-agent data (Millennium Pharmaceuticals Inc.; Rosing *et al*, 2000).

Pharmacodynamics

In total, 33 patients provided whole-blood samples for measurement of 20S proteasome inhibition at baseline. Inhibition of proteasome activity was greatest at 1 h post-dose (46.14–88.80%). Immediately prior to the dose on day 11, percent inhibition was 10.93–51.18%. Percent inhibition was greater in cycle 2 than cycle 1 for all dose groups. Coadministration of docetaxel with bortezomib did not appear to affect 20S proteasome inhibition by bortezomib. The degree of inhibition observed is similar to that observed in studies of bortezomib monotherapy (Aghajanian *et al*, 2002; Orlowski *et al*, 2002; Blaney *et al*, 2004; Papandreou *et al*, 2004; Hamilton *et al*, 2005).

Limited blood samples were collected for IL-6 and CRP analysis. Therefore, no analyses of these data were conducted. Mean AAG concentrations increased from baseline for nearly all time points across all three bortezomib dose levels (Figure 1).

DISCUSSION

In this phase I/II study in patients with pretreated advanced/metastatic breast cancer, the MTD was bortezomib 1.5 mg m^{-2} on days 1, 4, 8, and 11, plus docetaxel 75 mg m^{-2} on day 1 of a 21-day cycle. The DLTs were bone pain and febrile neutropenia. The bortezomib dose was slightly higher than the approved 1.3 mg m^{-2} on the same schedule, but similar to that identified in phase I studies evaluating single-agent bortezomib administered on the same schedule (Aghajanian *et al*, 2002; Dy *et al*, 2005). Slightly higher doses were tolerated when bortezomib was administered weekly (Papandreou *et al*, 2004) or on days 1 and 4 every 14 days (Hamilton *et al*, 2005). In other combination dose-escalation studies in advanced non-small-cell lung cancer and other refractory solid tumours (Lara *et al*, 2006), MTDs were bortezomib 1.0 mg m^{-2} plus docetaxel 75 mg m^{-2} on the same schedule, and bortezomib 0.8 mg m^{-2} twice weekly for 2 weeks plus docetaxel 25 mg m^{-2} on days 1 and 8 of a 21-day cycle (Messersmith *et al*, 2006). The docetaxel dose in our study is consistent with that used in combination with chemotherapeutic agents in anthracycline-pretreated breast cancer (O'Shaughnessy *et al*, 2002; Chan *et al*, 2005).

Table 5 Pharmacokinetic parameters of bortezomib and docetaxel by dose level

		All values shown as mean (%CV)							
	Day	**C_0 (ng ml^{-1})**	**AUC_{0-t} (h ng ml^{-1})**	**$AUC_{0-\infty}$ (h ng ml^{-1})**	**$T_{\frac{1}{2},z}$ (h)**	**$T_{\frac{1}{2},z}$ 24-h (h)**	**CL (l h^{-1})**	**V_{ss} (l)**	**V_z (l)**
Bortezomib dose (mg m^{-2})									
1.0 ($n=5$)	1	208 (34)	43.0 (38)	54.6 (31)	9.15 (64)	15.1 ($n=2$)	33.7 (30)	222 (75)	408 (63)
1.3 ($n=3$)	1	137 (54)	35.5 (31)	49.0 (28)	14.2 (47)	18.1 ($n=2$)	51.0 (38)	596 (45)	924 (26)
1.5 ($n=8$)	1	268 (71)	69.0 (43)	85.3 (51)	6.9 (99)	17.8 ($n=2$)	36.9 (57)	209 (68)	282 (77)
1.0 ($n=5$)	11	552 (148)	112 (32)	133 (24)	12.2 (32)	14.3 ($n=4$)	13.5 (25)	151 (49)	237 (46)
1.3 ($n=3$)	11	237 (59)	90.5 (27)	111 (18)	12.2 (73)	17.1 ($n=2$)	21.0 (11)	237 (96)	374 (78)
1.5 ($n=6$)	11	153 (41)	103 (25)	161 (31)	23.6 (36)	23.6	16.0 (23)	391 (47)	538 (42)
Docetaxel dose (mg m^{-2})									
		C_{max} (ng ml^{-1})	**AUC_{0-t} (h ng ml^{-1})**	**$AUC_{0-\infty}$ (h ng ml^{-1})**	**$T_{\frac{1}{2},z}$ (h)**	**$T_{\frac{1}{2},z}$ 24-h (h)**	**CL (l h^{-1})**	**V_{ss} (l)**	**V_z (l)**
75 ($n=7$)	1	1620 (38)	1704 (50)	1847 (54)	10.4 (86)	17.6 ($n=3$)	85.2 (47)	180 (72)	920 (33)
100 ($n=6$)	1	2522 (51)	2547 (36)	2731 (34)	15.0 (42)	17.4 ($n=5$)	69.6 (31)	372 (85)	1514 (55)

C_0 = back-extrapolated time 0 plasma drug concentration (bortezomib alone); C_{max} = observed maximum plasma drug concentration (docetaxel alone); AUC_{0-t} = area under plasma concentration time curve from time 0 to last time point with measurable drug concentration; $AUC_{0-\infty}$ = area under plasma concentration time curve extrapolated to infinity; $T_{\frac{1}{2},z}$ = apparent plasma half-life; $T_{\frac{1}{2},z}$ (24-h) = apparent plasma half-life in patients with measurable plasma concentrations at 24 h post-dose; CL = total body clearance; CV = coefficient of variance; V_{ss} = volume of distribution at steady state; V_z = apparent volume of distribution in terminal elimination phase.

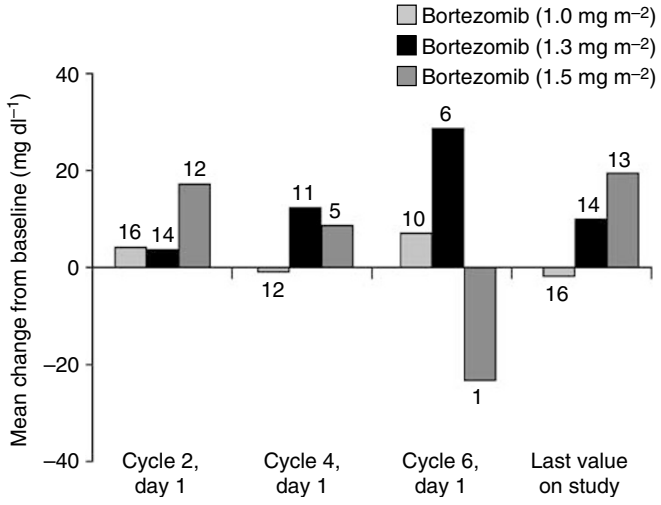

Figure 1 Mean change from baseline in alpha-1 acid glycoprotein concentrations by bortezomib dose level during the study. The number of patients available for each analysis are shown above or below each column; notably, the significant decrease from baseline seen at cycle 6, day 1, in the bortezomib 1.5 mg m^{-2} group arises from evaluation of data from only one patient.

The safety profile of the combination was consistent with that observed in phase II studies in other solid tumours evaluating bortezomib alone (Shah *et al*, 2004; Maki *et al*, 2005) or in combination with docetaxel (Meluch *et al*, 2005; Fanucchi *et al*, 2006; Dreicer *et al*, 2007). The most common grade 3/4 toxicities were neutropenia, febrile neutropenia, diarrhoea, and peripheral neuropathy. Dose modifications were implemented to try and prevent evolution of neurotoxicity and worsening of existing symptoms. Nevertheless, in these heavily pretreated patients, 15 patients discontinued treatment due to neurological complaints, a known side effect of bortezomib and, to a lesser extent, docetaxel. The high incidence of neutropenia was expected given the typically high incidence of neutropenia and febrile neutropenia with single-agent docetaxel (Nabholtz *et al*, 1999; O'Shaughnessy *et al*, 2002) and the partially overlapping side-effect profiles of the two agents. Supportive therapies and strategies for side-effect management can prevent worsening of these symptoms, thereby avoiding treatment delays or discontinuations (Colson *et al*, 2004). Notably, bortezomib-associated neutropenia has been shown to be transient and reversible (Lonial *et al*, 2005); consistent with this, only one patient discontinued the study drug due to neutropenia.

Bortezomib/docetaxel combination treatment demonstrated antitumour activity. The response rate was 29% and median TTP was 5.4 months. These data are similar to those reported for docetaxel (75 mg m^{-2}) in combination with either gemcitabine or capecitabine, which have been compared in a phase III trial (Chan *et al*, 2005). Recent studies have shown response rates of 62.5% with docetaxel plus cisplatin (Lin *et al*, 2007) and 50% with docetaxel plus epirubicin (Hainsworth *et al*, 2006). The 38% response rate at the MTD compares favourably with docetaxel and paclitaxel administered as single agents in anthracycline-pretreated metastatic breast cancer: in a recent study comparing docetaxel and paclitaxel, response rates were 32 *vs* 25%, and median TTP was 5.7 *vs* 3.6 months, respectively (Jones *et al*, 2005). The activity demonstrated in the present study does not appear to arise from the mechanism proposed, by which bortezomib reduces AAG concentrations through inhibition of IL-6 and consequently increases docetaxel efficacy, as mean AAG concentrations increases from baseline at nearly all time points across bortezomib dose levels. Other cellular and molecular effects of bortezomib may be involved; recently published results demonstrating its differential effects in breast cancer cells may be relevant in designing mechanism-based combination treatments (Codony-Servat *et al*, 2006).

Bortezomib has been studied in combination with trastuzumab in HER2-positive breast cancer cell lines (Cardoso *et al*, 2006). Although its value in HER2-postive cells is well established, the response rate with single-agent trastuzumab in metastatic breast cancer is $<40\%$ (Vogel *et al*, 2002). A preclinical study in four cell lines demonstrated that bortezomib acts synergistically to increase the effect of trastuzumab in HER2-positive cells (Cardoso *et al*, 2006). The potential clinical application of this combination is currently under investigation in a phase I trial. Additionally, a phase II study is underway to investigate bortezomib plus pegylated liposomal doxorubicin in patients with anthracycline-pretreated metastatic breast cancer.

The baseline characteristics of patients in the present study were typical of patients with anthracycline-pretreated advanced/metastatic breast cancer. The p53 and estrogen receptor status were not recorded but may be of interest in future trials, as *in vitro* studies suggest proteasome inhibition is at least partially dependent on the p53 status in breast cancer (MacLaren *et al*, 2001), and

estrogen-receptor-negative status plus a dysregulated IκBα/NF-κB system is associated with greater bortezomib antitumour activity (Tapia *et al*, 2005).

In conclusion, the study demonstrated that bortezomib and docetaxel combination therapy is feasible, tolerable, and active in anthracycline-pretreated metastatic breast cancer.

ACKNOWLEDGEMENTS

We thank Gardiner Caldwell London for their assistance in drafting this research paper. This research was supported by Millennium Pharmaceuticals Inc. and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

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