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Bortezomib plus gemcitabine/carboplatin as first-line treatment of advanced non-small cell lung cancer: A phase II Southwest Oncology Group study (S0339)

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Abstract

Purpose—Bortezomib is a small-molecule proteasome inhibitor with single-agent activity in patients with non-small cell lung carcinoma (NSCLC) and synergy with gemcitabine in preclinical studies. This phase II study of bortezomib in combination with gemcitabine/carboplatin was conducted in chemotherapy-naïve advanced NSCLC patients to assess efficacy and safety.

Patients and Methods—Patients with selected stage IIIB/IV NSCLC, performance status 0–1, and no history of brain metastasis received up to six 21-day cycles of gemcitabine 1,000 mg/m^2, days 1 and 8, carboplatin AUC 5.0, day 1, and bortezomib 1.0 mg/m^2, days 1, 4, 8, and 11.

Results—114 patients (52% adenocarcinoma, 85% stage IV) received a median of 3.6 treatment cycles. Median follow-up was > 3 years. Median overall survival (OS) was 11 months; 1-year and 2-year survival rates were 47% and 19%, respectively. Median PFS was 5 months; 1-year PFS rate was 7%. Response rate was 23%, and disease control rate (responses + stable disease) was 68%. The most common grade 3/4 toxicities were thrombocytopenia (63%) and neutropenia (52%). One patient experienced febrile neutropenia. Grade 3/4 neuropathy occurred in 4%.

Conclusions—Bortezomib plus gemcitabine/carboplatin resulted in a notable survival benefit in patients with advanced NSCLC, with the anticipated primary toxicity of myelosuppression. Further studies designed to investigate the role of bortezomib in advanced NSCLC are warranted.

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Keywords

advanced NSCLC; bortezomib; carboplatin; gemcitabine; proteasome; stage IV

INTRODUCTION

For the past decade, doublet chemotherapy with cisplatin or carboplatin plus a third-generation drug (paclitaxel, docetaxel, vinorelbine or gemcitabine) has been considered the standard of care for first-line treatment of advanced NSCLC.[1-8] Gemcitabine/carboplatin is a commonly used regimen due to its favorable toxicity profile.[4,9-11 5,7,12] Despite the benefits of chemotherapy, prognosis for these patients remains poor,[1,8,13] with median overall survival (OS) of typically 8–10 months and 1-year survival rates of 35–40%.[1,8] Thus, integrating novel agents into front-line therapy is of tremendous interest and importance in advancing the field of lung cancer and patient outcomes.

Bortezomib (VELCADE®, Millennium Pharmaceuticals, Inc. and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) inhibits the 26S proteasome, thereby affecting the levels of numerous proteins involved in processes such as cell-cycle control, apoptosis, cell adhesion, angiogenesis, and chemoresistance.[14,15] Bortezomib disrupts multiple cellular pathways shown to be important in NSCLC (Table 1).[14-16] In particular, most NSCLC cells have a dysregulated apoptotic pathway involving activated nuclear factor-κB (NF-κB).[17] NF-κB activates the transcription of anti-apoptotic and proliferation genes, mediating tumor cell survival in response to cytotoxic stress and resulting in chemoresistance. Bortezomib attenuates this pathway by preventing proteasomal degradation of IκB, the inhibitor of NF-κB.[14,15] Bortezomib also modulates levels of the anti-apoptotic gene Bcl-2 and the tumor suppressor p53.[14-16] Overexpression of Bcl-2, a key mediator of resistance to apoptosis following chemotherapy, is evident in 70–80% of NSCLC cases, while mutations leading to functional loss or decreased expression of p53 are present in up to 50% of cases.[14-16]

Bortezomib has demonstrated single-agent anti-tumor activity in NSCLC, both in preclinical [18-20] and in early-phase clinical studies.[21-23] In preclinical studies, bortezomib sensitized NSCLC and pancreatic cancer cells to gemcitabine-induced apoptosis *in vitro* and *in vivo*,[24,25] and sequence-dependent enhanced activity was observed with bortezomib plus gemcitabine/carboplatin in NSCLC cells.[26] A phase I California Cancer Consortium study demonstrated bortezomib plus gemcitabine/carboplatin to be well tolerated in patients with advanced NSCLC, with the primary toxicity being myelosuppression. The maximum tolerated dose (MTD) was determined to be bortezomib 1.0 mg/m^2 days 1, 4, 8, and 11, gemcitabine 1,000 mg/m^2 days 1 and 8 and carboplatin AUC 5.0 on day 1.[27] The combination showed encouraging activity. Here, we report the subsequent Southwest Oncology Group (SWOG) phase II study to evaluate the efficacy and toxicity of this regimen as first-line treatment in patients with advanced NSCLC.

Methods

Patients

Chemotherapy-naïve patients with histologically or cytologically proven selected stage IIIB (T4 lesion due to malignant pleural effusion) or stage IV NSCLC were eligible. Patients were required to have measurable or assessable disease, and to have a SWOG performance status of 0–1. Patients with recurrent disease following previous surgery and/or radiation were also eligible. Recurrent disease had to be outside previous radiation fields or have a new lesion inside the field. Patients with brain metastases were not eligible. Adequate organ

function was required: serum creatinine less than or equal to the institutional limit of normal, or calculated creatinine clearance of ≥ 60 cc/min (Cockcroft-Gault formula28); absolute neutrophil count (ANC) ≥ 1,500 cells/μL; platelets ≥ 100,000 cells/μL; and adequate hepatic function. Patients with grade ≥ 2 peripheral neuropathy (based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 3.0) were excluded. No other prior malignancies were allowed except adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other cancers from which the patient had been disease-free for 5 years. Eligibility criteria were consistent with previous SWOG trials in advanced NSCLC.[12,29-31] The Institutional Review Board at each participating institution approved the study; all patients gave written informed consent in accordance with institutional and federal guidelines before undergoing any study-related procedures.

Study design

Patients were accrued at 33 SWOG institutions between February and September 2004. Data cut-off for this report was October 11, 2007. Dosing was based on the MTD in the California Cancer Consortium phase 1 study of this combination.[27] Patients received gemcitabine 1,000 mg/m^2 on days 1 and 8, carboplatin AUC 5.0 on day 1, and bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11, in 21-day treatment cycles. Bortezomib was administered 60 minutes after gemcitabine/carboplatin on days 1 and 8, based on preclinical data demonstrating sequence specificity.[26] Patients without progression could receive up to six treatment cycles of the triplet regimen; those tolerating treatment and without disease progression could continue receiving bortezomib alone for up to 1 year.

Gemcitabine/carboplatin dose reductions were required for treatment delays of > 7 days due to neutropenia and/or thrombocytopenia, or significant hematologic or non-hematological toxicities in the preceding cycle. Bortezomib dose reductions (to 0.8 mg/m^2, then 0.6 mg/m^2) were required for unacceptable hematologic toxicities that persisted following gemcitabine/carboplatin dose reduction, and for any grade ≥ 2 neurological toxicities.

Supportive care, including use of anti-emetics, was at the discretion of the treating physician. Routine use of granulocyte colony stimulating factors (GCSFs) was not permitted; administration had to follow American Society of Clinical Oncology (ASCO) guidelines and be discontinued 48 hours prior to the start of the next cycle.

Evaluations

The primary objective of this phase II study was to assess OS. Progression free survival (PFS), response rate, and safety were secondary objectives. Patient archival specimens and blood samples were submitted for exploratory molecular analyses. Radiological investigations occurred at baseline and every 6 weeks during treatment, and responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST).[32] Safety was assessed throughout the study; toxicities were graded according to NCI CTCAE version 3.0.

Statistical analyses

Target accrual was 99 patients, to provide 85% power to rule out the null hypothesis of an 8-month median OS at the .05 alpha level versus an alternative of a 12-month median OS. Median OS of ≥ 10 months was considered as warranting phase III testing of gemcitabine/carboplatin ± bortezomib. The target accrual allowed for estimation of response and toxicity rates to within ± 10% (95% confidence interval [CI]). OS and PFS were evaluated by Kaplan–Meier methods.

Results

Of 121 patients accrued, 6 were ineligible due to the following: timing of registration following surgery, elevated SGOT and bilirubin levels, low creatinine clearance, lack of stage information, and timing of disease assessment (2). One additional patient did not receive treatment. Of the 114 patients that were treated, 2 patients completed planned treatment with 6 cycles of gemcitabine/carboplatin/bortezomib and single-agent bortezomib for a total of one year; 112 patients discontinued treatment due to progression/relapse (n=55), adverse events (AEs, n = 44), refusal unrelated to AEs (n = 6), death (n = 3; all unrelated to treatment), and other non-specified reasons (n = 4). Baseline patient characteristics are shown in Table 2. Slightly more than half of patients had adenocarcinoma, and 85% had stage IV NSCLC. Patients received a median of 3.6 treatment cycles. Median follow-up was > 3 years.

Efficacy

Median OS was 11 months (95% CI: 8.2–13.4 months) (Figure 1). Survival rates at 1 and 2 years were 47% and 19%, respectively. Median PFS was 5 months (95% CI: 3.5–5.3 months) (Figure 2). The 1-year PFS rate was 7%. Best response to therapy is shown in Table 3. The overall response rate (ORR) for all 114 registered patients was 23%, with a disease control rate (ORR + stable disease) of 68%.

Safety

A total of 113 patients were evaluable for safety; AEs were not reported for one patient. The most common grade 3 and 4 AEs are shown in Table 4. While the incidences of grade 3/4 thrombocytopenia and neutropenia were 63% and 52%, respectively, only 3 patients (3%) had grade 3 hemorrhage (associated with grade 4 thrombocytopenia, grade 3 thrombocytopenia, and no thrombocytopenia, respectively) and 1 patient (1%) had febrile neutropenia. Sensory neuropathy was seen in 26 patients (23%), including 3 (3%) with grade 3/4 toxicity. In total, 99 (87%) patients were reported as requiring dose reductions during the first six cycles of treatment. The most common AEs resulting in dose reduction were neutropenia and thrombocytopenia. There were four deaths possibly related to treatment, one due to multi-organ failure, one due to pneumonitis, one due to diarrhea and dehydration, and one sudden death in a patient with grade 4 thrombosis/embolism and grade 4 thrombocytopenia.

Discussion

Modern platinum-based chemotherapy is associated with benefits in survival, symptom palliation and quality of life in patients with advanced NSCLC. Nevertheless, the overall impact is modest at best, and novel approaches are needed. Bortezomib both potentiates chemotherapy in NSCLC cell lines and has demonstrated single-agent activity in clinical trials. Gemcitabine/carboplatin was selected as the chemotherapeutic backbone for S0339 because it is largely devoid of neuropathy, a potential overlapping toxicity with other agents commonly employed in NSCLC, and because of encouraging data in *in vitro* and *in vivo* models with this three drug regimen. Indeed, the median OS of 11 months and 1 year survival of 47% achieved in this phase 2 study surpass results of prior SWOG trials (S9509, S9806, S0003) in advanced NSCLC.[12,29,31] Historically, recent SWOG studies in advanced NSCLC have maintained consistent eligibility criteria and therefore patient populations have been relatively comparable from study to study.[12,29-31] In addition, all studies were conducted in the era of PET scanning for disease staging, minimizing the possibility that the prolonged survival seen in this study compared with historical data may be related to stage-migration effects. The survival data reported here are further validated by

the multi-institutional, cooperative-group nature of our study, and by the large number of patients enrolled.

While our survival results exceeded the predefined statistical end point for proceeding with phase III investigation of gemcitabine/carboplatin plus bortezomib compared with gemcitabine/carboplatin alone, it is important to note that changes in the therapeutic landscape for advanced NSCLC have occurred since our study was initiated. Most notably, the Eastern Cooperative Oncology Group (ECOG) 4599 study of paclitaxel/carboplatin alone or in combination with bevacizumab, which demonstrated a significant survival advantage with the triplet regimen (12.3 vs 10.3 months),[33] has established this combination as a new first-line standard of care in selected patients with advanced NSCLC. Results from studies in this setting must now be considered in the context of the ECOG 4599 data. However, it is worth noting that the patient populations in the current study and the ECOG 4599 trial differ somewhat due to eligibility limitations for patients receiving bevacizumab. The ECOG 4599 trial did not enroll patients with a histology of squamous cell carcinoma, hemoptysis, history of hemorrhagic diathesis, or coagulopathy due to the risk of serious hemorrhagic events, which limits the widespread applicability of this triplet regimen.33

An additional reason for improved survival in S0339 may be the more widespread use of second-line therapy in NSCLC, such as docetaxel, pemetrexed, and erlotinib. The median PFS of 5 months is similar to that reported previously, 4–5 months,[12,29-31] as is the overall response rate of 23% and disease control rate of 68%.[12,29-31]

Therapy with bortezomib plus gemcitabine/carboplatin was generally well tolerated. As expected the most common grade 3/4 AEs were hematologic. Bortezomib-induced thrombocytopenia and neutropenia have been described as transient and cyclical, with rapid recovery of platelet count and neutrophils toward baseline during the rest period of each cycle, in studies in relapsed and/or refractory multiple myeloma.34-36 While the hematologic toxicity was not clinically significant in terms of AEs (bleeding and febrile neutropenia), it resulted in a substantial number of dose reductions (87%), which limited dose intensity. Due to the conservative criteria for dose reductions for thrombocytopenia and neutropenia specified in the protocol, they were commonly implemented and may have affected efficacy by reducing the ability to deliver full-dose gemcitabine/carboplatin.

Another common toxicity associated with bortezomib in multiple myeloma studies is peripheral sensory neuropathy.[37,38] The overall incidence of grade 3/4 sensory neuropathy seen in this study was lower than in studies of bortezomib 1.3 mg/m^2 in relapsed/refractory multiple myeloma;[37,38] this may be attributed to the lower dose of bortezomib (1.0 mg/m^2) used and the different patient population.

Lastly, a biomarker for bortezomib sensitivity has yet to be established. Considering the large number of potential molecular targets of proteasome inhibition, it may be unlikely that a single predictive biomarker will be identified. The results of our study suggest that bortezomib-based combinations could prove promising for advanced NSCLC, particularly if a biomarker for efficacy could be identified to predict which patients are most likely to benefit.

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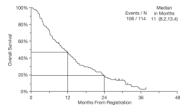

Figure 1.
Kaplan–Meier curve for overall survival (N = 114).

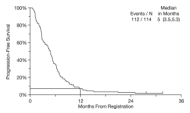

Figure 2.
Kaplan–Meier curve for progression-free survival (N = 114).

Table 1

Effect of bortezomib on protein targets of relevance to lung cancer.[16]

Protein and effect of bortezomib	Function of protein	Protein role in lung cancer
$p27^{kip1}$ stabilization	Cell-cycle inhibition, apoptosis	Tumor suppressor
p53 stabilization	DNA damage repair, cell-cycle inhibition, apoptosis	Tumor suppressor, therapy resistance
NF-κB downregulation	Transcription factor, apoptosis suppressor	Cell survival, therapy resistance
Bcl-2, Bcl-xL downregulation	Anti-apoptosis	Cell survival, therapy resistance
Bax stabilization	Pro-apoptosis	Promote apoptosis
Cyclin D, E, A stabilization	Cell-cycle progression	Oncogenic

Table 2

Baseline patient characteristics (N = 114). Percentages in categories do not necessarily total 100% due to rounding.

Parameter	n	%
Median age, years (range)	64 (28–79)	
Male	69	61
Race		
White	103	90
Black	4	4
Asian	3	3
Native American	1	1
Multi-racial	1	1
Unknown	2	2
Histology		
Adenocarcinoma	59	52
Squamous cell	23	20
Large cell	7	6
Bronchioloalveolar	4	4
NSCLC, NOS	1	1
Other	20	18
Performance status		
0	50	44
1	64	56
Disease stage		
IIIB	14	12
IV	97	85
Recurrent	3	3
Weight loss during past 6 months		
< 5%	79	69
≥ 5%	32	28
Missing	3	3

NOS, not otherwise specified; NSCLC, non-small cell lung cancer

Table 3

Response to therapy by RECIST.

	Measurable disease (N = 108)		Non-measurable disease (N = 6)		All patients (N = 114)	
Response	**n**	**%**	**n**	**%**	**n**	**%**
CR/CRu	2	2	0	0	2	2
PR/PRu	24	22	0	0	24	21
ORR (CR + PR)	26	24	0	0	26	23
SD	49	45	3	50	52	46
Disease control rate (ORR + SD)	75	69	3	50	78	68
PD	19	18	2	33	21	18
Assessment inadequate	14	13	1	17	15	13

CR, complete response; CRu, unconfirmed CR; ORR, overall response rate; PD, progressive disease (includes assessments of increasing disease and symptomatic deterioration); PR, partial response; PRu, unconfirmed PR; SD, stable disease.

Table 4

Most common grade ≥3 hematologic and non-hematologic toxicities (N = 113).

	Total grade ≥ 3		Grade 3		Grade 4	
Adverse event	**N**	**%**	**N**	**%**	**N**	**%**
Hematologic toxicities						
Thrombocytopenia	71	63	30	27	41	36
Neutropenia	59	52	37	33	22	19
Anemia	15	13	13	12	2	2
Non-hematologic toxicities						
Fatigue	15	13	12	11	3	3
ALT/AST	14	12	13	12	1	1
Neuropathy	5	4	3	3	2	2
Dehydration	5	4	5	4	–	–
Hypokalemia	4	4	3	3	1	1
Pneumonitis	4*	4	3	3	–	–
Anorexia	3	3	3	3	–	–
Diarrhea	3	3	3	3	–	–
Dyspnea	3	3	3	3	–	–
Hyponatremia	3	3	3	3	–	–
Hypotension	3	3	2	2	1	1
Lung infection	3	3	3	3	–	–
Nausea	3	3	3	3	–	–
Thrombosis/embolism	3	3	2	2	1	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Includes one grade 5 event.