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Vorinostat and bortezomib as third-line therapy in patients with advanced non-small cell lung cancer: a Wisconsin Oncology Network Phase II study

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Ethical standard The conduction of this study complies with the current laws of the United States.

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Summary

Introduction—The primary objective of this phase II trial was to evaluate the efficacy and tolerability of vorinostat and bortezomib as third-line therapy in advanced non-small cell lung cancer (NSCLC) patients.

Methods—Eligibility criteria included recurrent/metastatic NSCLC, having received 2 prior systemic regimens, and performance status 0–2. Patients took vorinostat 400 mg PO daily days 1–14 and bortezomib 1.3 mg/m2 IV day 1, 4, 8 and 11 in a 21-day cycle. Primary endpoint was 3-month progression free survival (3m-PFS), with a goal of at least 40 % of patients being free of progression at that time point. This study followed a two-stage minimax design.

Results—Eighteen patients were enrolled in the first stage. All patients had two prior lines of treatment. Patients received a median of two treatment cycles (range: 1–6) on study. There were no anti-tumor responses; stable disease was observed in 5 patients (27.8 %). Median PFS was 1.5 months, 3m-PFS rate 11.1 %, and median overall survival 4.7 months. The most common grade 3/4 toxicities were thrombocytopenia and fatigue. Two patients who had baseline taxane-related grade 1 peripheral neuropathy developed grade 3 neuropathy. The study was closed at its first interim analysis for lack of efficacy.

Conclusions—Bortezomib and vorinostat displayed minimal anti-tumor activity as third-line therapy in NSCLC. We do not recommend this regimen for further investigation in unselected patients.

Keywords

Non-small cell lung cancer; Vorinostat; Bortezomib; Third-line

Introduction

Despite improvements with chemotherapy and molecularly targeted drugs, current treatment for advanced non-small cell lung cancer (NSCLC) is inadequate. Erlotinib is the only drug approved for third-line treatment in the US. In a phase IV study, third-line erlotinib in unselected Australian patients resulted in a response rate, progression free and overall

survival of only 2.4 %, 2.5 months and 5.3 months, respectively [1]. Therefore, new therapies are clearly needed.

Vorinostat is an inhibitor of class I and II histone deacetylases that regulate the transcription of various genes involving in cell survival and apoptosis. Its anti-proliferative activity has been demonstrated in several NSCLC cell lines [2]. Stable disease was observed in 57.1 % of patients in a phase II trial of single agent vorinostat in relapsed NSCLC [3]. Bortezomib is a proteasome inhibitor that caused G2/M cell cycle arrest, apoptosis and growth inhibition in several NSCLC cell lines [4]. Early clinical data had shown encouraging activity of bortezomib in NSCLC, particularly in combination with other anti-cancer agents [5].

Preclinical data have demonstrated apoptotic and anti-tumor augmentation with the vorinostat and bortezomib combination [6]. A patient receiving fourth-line therapy for his advanced NSCLC attained a partial response in our dose escalation phase I study of vorinostat and bortezomib [7]. Therefore, we conducted this single arm phase II trial to investigate the efficacy and tolerability of this regimen as third-line therapy in advanced NSCLC patients through the Wisconsin Oncology Network (WON), a 17 member research consortium of community and academic practices based at the University of Wisconsin.

Materials and methods

Eligible patients were required to have pathologically confirmed NSCLC; recurrent disease, stage IIIB with pleural effusion or stage IV; to have received two prior systemic anti-cancer regimens for recurrent/metastatic disease, including at least one platinum-based doublet; measurable disease; ECOG performance status (PS) of 0–2; age ≥18 years; and adequate bone marrow, liver and kidney function. Patients with treated brain metastases were allowed. Main exclusion criteria included prior therapy with vorinostat or bortezomib; and pre-existing grade ≥2 neuropathy. Patients signed an informed consent for study participation. This protocol was approved by institutional review boards of accruing WON sites.

Patients received the combined regimen with vorinostat 400 mg orally daily on days 1–14 and bortezomib 1.3 mg/m^2 IVon day 1, 4, 8 and 11, every 3 weeks [7]. Disease evaluation with imaging took place after every other cycle. Patients were treated until disease progression or intolerability of side effects. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (version 3.0).

The primary endpoint of this study was the 3-month progression free survival (3m-PFS). Secondary endpoints included objective response, median progression free survival (PFS), overall survival (OS), and toxicities. A two-stage minimax design was used. The plan was to accrue 18 patients in the first stage. If at most 4 patients were free of progression at month 3, the study would be terminated and the regimen considered ineffective. Otherwise, an additional 15 patients were to be enrolled during the second stage for a total of 33 patients. The design tested the null hypothesis that the probability of 3m-PFS is at most 0.20 versus an alternative hypothesis that it is at least 0.40, with a 0.05 significance level and 0.80 power.

Results

Between January 2009 and March 2010, 18 patients enrolled during the first stage of the study. All patients were evaluable for toxicity and efficacy. They were followed until death. Because the primary endpoint of 3-m PFS rate was not met, the study was closed at the first interim analyses.

Patient characteristics and response to prior treatment are presented in Table 1. Despite this trial being in the third-line setting, most patients had a good PS, including 27.8 % with PS 0 and 66.7 % with PS 1.

All 18 patients received at least one cycle of vorinostat and bortezomib, with a median of 2 cycles administered per patient (range 1–6). The most common cause for treatment discontinuation was disease progression (66.7 %), followed by intolerable toxicity (22.2 %) and consent withdrawal (11.1 %).

There were no anti-tumor responses (Table 2). Stable disease was seen in 5 patients (27.8 %). The 3m-PFS rate was 11.1 % (95 % CI 0.8–25.6 %). Median PFS and OS was 1.5 months (95 % CI 1.2–2.0 months) and 4.7 months (95 % CI 3.2–8.6 months), respectively (Fig. 1a, b). All patients have died from their disease.

Grade 3 and 4 toxicities (in at least 2 patients) are presented in Table 3. There were no treatment related deaths. 77.8 % of patients required dose reduction, primarily related to non-hematologic toxicities. The most common adverse event was thrombocytopenia of grade 3 (38.9 %) or 4 (5.6 %), but no clinically significant bleeding occurred. The most common non-hematologic event was grade 3 (22.2 %) or grade 4 (5.6 %) fatigue. Grade 3 peripheral neuropathy was reported in 2 patients (11.1 %); these patients enrolled with baseline grade 1 sensory neuropathy from a prior taxane.

Discussion

Despite demonstrating activity of the novel combination of vorinostat and bortezomib in a heavily pretreated patient with advanced NSCLC in a phase I trial [7], our multicenter phase II evaluation of this regimen in the third-line setting was closed at its first interim analyses due to lack of efficacy.

Much recent effort in lung cancer research has focused on developing molecularly targeted therapies. Identification of somatic sensitizing EGFR mutations and EML4-ALK rearrangements in patients with NSCLC has yielded the most impressive efficacy outcomes following treatment with EGFR TKIs (erlotinib, gefitinib) [8] and crizotinib [9], respectively, demonstrating the critical importance of enriching populations based upon favorable biologic aspects of their tumors.

Unfortunately, the clinical development of additional novel molecularly targeted drugs, including the two agents used in our study, has been hampered by the inability to consistently identify biomarkers predictive of drug activity. Vorinostat has been investigated as single agent [3], and in combination with chemotherapy in NSCLC. A randomized phase

II first-line study showed a higher response rate by adding vorinostat to chemotherapy with paclitaxel and carboplatin (34 % vs. 12.5 %, p=0.02), but no statistical improvement in PFS (6.0 months vs. 4.1 months, p=0.48) or OS (13.0 months vs. 9.7 months, p=0.17) [10]. Among other HDAC inhibitors, the selective class I HDAC inhibitor HBI-8000 is currently being tested in combination with an EGFR-TKI in previously treated, EGFR wild-type NSCLC. Several trials were conducted to evaluate bortezomib alone or with chemotherapy such as docetaxel, pemetrexed, platinum plus gemcitabine in advanced NSCLC. Bortezomib did not show single activity and results with combined therapy were mostly unimpressive. For example, a randomized three-arm phase II study comparing bortezomib alone, pemetrexed alone, and pemetrexed plus bortezomib resulted in response rates (primary endpoint) of 0 %, 4 % and 7 %, respectively [11]. The difference in overall survival (7.8 months, 12.7 months, and 8.6 months) was not statistically different. MLN9708, a second-generation, small molecule proteasome inhibitor is currently under investigation in multiple myeloma and solid tumors, in parallel with the development of an assay based on the activating transcription factor-3 (ATF-3) as a candidate pharmacodynamic bio-marker for this drug. Overall, the lack of significant efficacy seen in any of these completed trials demonstrates the need to develop and validate biomarkers of drug efficacy through preclinical and translational research.

The clinical evaluation of potential biomarkers predictive of drug activity may be best suited for the pre-operative setting, where pre- and post-treatment specimens are available for comparison. For example, Jones and colleagues treated 21 NSCLC patients with induction vorinostat and bortezomib prior to surgical resection [12]. Nineteen patients (90.5 %) achieved stable disease, while the remaining two progressed. Post-treatment serum 20S proteasome activity decreased in half the patients. Changes in the protein expression of several markers of apoptosis and cell cycle kinetics (including p21, Bcl-xl, and RAD23b) were inconsistent in 11 paired pre- and post-treatment tumor specimens. Gene expression analyses of these 11 paired specimens demonstrated intratumoral up-regulation of 174 genes, including *CXCL2* and *RBM6*, and down-regulation of 116 genes, including *Decorin* and *MMP1*. These comparative translational assays represent an excellent example of the work needed to identify biomarkers for targeted therapy.

In conclusion, we found that the combination of bortezomib and vorinostat had no meaningful anti-tumor activity as third-line therapy in our unselected NSCLC population. Our results suggest that the prior paradigm of moving forward with phase II testing based upon clinical results seen in phase I trials is not relevant when using biologically targeted therapies, and that the evaluation of potential bio-markers predictive of drug activity, such as through pre-resection studies, should drive clinical development.

Acknowledgments

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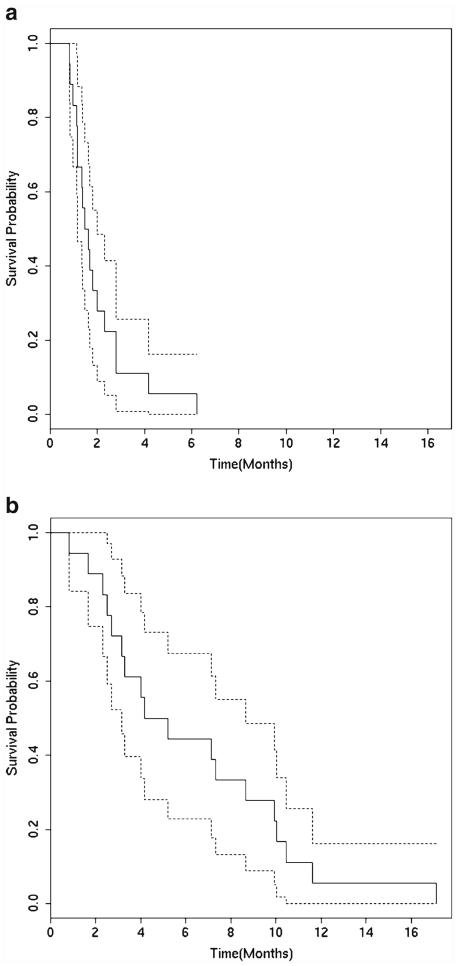

Fig. 1.

Survival. **a** Progression free survival (with 95 % confidence intervals). **b** Overall survival (with 95 % confidence intervals)

Table 1
Patient characteristics and response to prior therapies

Characteristics	Total (*n*=18)
Age—yr	
Median	57
Range	45–78
Sex—*n* (%)	
Male	9 (50.0)
Female	9 (50.0)
Race—*n* (%)	
White	17 (94.4)
Black	1 (5.6)
Histology—*n* (%)	
Adenocarcinoma	9 (50.0)
Squamous cell	2 (11.1)
NSCLC, NOS[a]	7 (38.9)
Performance Status—*n* (%)	
0	5 (27.8)
1	12 (66.7)
2	1 (5.6)
Disease stage—*n* (%)	
Metastatic	16 (88.9)
Recurrent	2 (11.1)
Brain metastases—*n* (%)	6 (33.3)
Prior first-line systemic therapy—*n* (%)	
Paclitaxel/Platinum	10 (55.5)
Paclitaxel/Platinum/Bevacizumab	2 (11.1)
Paclitaxel/Platinum/Investigational drug	2 (11.1)
Pemetrexed/Platinum	3 (16.7)
Vinorelbine/Platinum	1 (5.6)
Response to first-line therapy—*n* (%)	
Partial response	7 (38.9)
Stable disease	4 (22.2)
Progressive disease	6 (33.3)
Not reported	1 (5.6)
Prior second-line systemic therapy—*n* (%)	
Pemetrexed	10 (55.5)
Pemetrexed/Investigational drug	1 (5.6)
Docetaxel/Investigational drug	1 (5.6)
Erlotinib	4 (22.2)
Platinum doublets	2 (11.1)
Response to second-line therapy—*n* (%)	

Characteristics	Total (*n*=18)
Partial response	1 (5.6)
Stable disease	3 (16.7)
Progressive disease	13 (72.2)
Not reported	1 (5.6)
Prior thoracic radiation therapy—*n* (%)	6 (33.3)

[a] NSCLC, NOS, non-small cell lung cancer, not otherwise specified

Table 2

Treatment outcome

Variable	Total (*n*=18)
Response—*n* (%)	
Partial response	–
Stable disease	5 (27.8)
Progressive disease	13 (72.2)
3-month progression free survival (%)	11.1
95 % confidence interval	(0.8, 25.6)
Progression free survival—mo	
Median	1.5
95 % confidence interval	(1.2, 2.0)
Overall survival—mo	
Median	4.7
95 % confidence interval	(3.2, 8.6)

Table 3
Grade 3/4 toxicities occurring in at least two patients

Toxicity (*n*=18)	Grade 3 *n* (%)	Grade 4 *n* (%)
Hematological		
Thrombocytopenia	7 (38.9)	1 (5.6)
Lymphopenia	3 (16.7)	–
Non-Hematological		
Fatigue	4 (22.2)	1 (5.6)
Vomiting	2 (11.1)	–
Dizziness	2 (11.1)	–
Syncope	2 (11.1)	–
Neuropathy	2 (11.1)	–
Hyponatremia	3 (16.7)	–