Published in final edited form as:
J Thorac Oncol. 2009 April ; 4(4): 522–526.

Vorinostat (NSC# 701852) in Patients with Relapsed Non-Small Cell Lung Cancer: A Wisconsin Oncology Network Phase II Study

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Introduction

Treatment of relapsed non-small cell lung cancer (NSCLC) remains discouraging. Results from clinical trials yield median survivals that range from 6 to 9 months, and rates of toxicities, particularly with the use of cytotoxic agents, are not negligible (1-4). Investigation of more effective, or at least less toxic, agents and combinations remains paramount.

Histone deacetylases (HDACs) represent an emerging therapeutic target in NSCLC and other malignancies since the extent of histone acetylation impacts gene expression, including those genes involved in the pro-survival signaling cascades, regulation of apoptosis, and control of the cell cycle (5-7). Histone deacetylase inhibitors effect cell death by activating apoptotic pathways, mitotic failure, or autophagic cell death (5,8,9). Normal cells are relatively resistant to cell death induced by HDAC inhibitors. This specificity may be related to protection from generation of reactive oxygen species found in the normal cell. As such, HDAC inhibitors may offer an appealing therapeutic index in cancer therapy (10).

Vorinostat (suberoylanilide hydroxamic acid, SAHA, Zolinza™, NSC# 701852) is a small molecule inhibitor of class I and II HDACs. It has yielded anti-proliferative and pro-apoptotic results in multiple cancer cell lines (including NSCLC) and xenograft mouse models (11-13). Preclinical studies using NSCLC and other cell lines confirmed the ability of vorinostat to enhance the cytotoxicity of radiation, targeted agents, and traditional DNA-directed chemotherapeutics (14-16).

Phase I trials with oral vorinostat identified the maximum tolerated dose to be 400 mg once daily or 200 mg twice daily in patients with solid tumors or hematologic malignancies, or

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300 mg twice daily for 3 consecutive days per week for patients with solid tumors (17,18). Dose limiting toxicities included anorexia, dehydration, diarrhea, and fatigue. Drug-related adverse events were constitutional (fatigue), gastrointestinal (anorexia, diarrhea, nausea, and vomiting), metabolic (hyperglycemia and hypocalcemia), and hematologic (thrombocytopenia, anemia, and some neutropenia). Antitumor activity was seen in patients with Hodgkin's and non-Hodgkin's lymphoma, mesothelioma, differentiated thyroid cancer, bladder cancer, and laryngeal cancer. Accumulation of acetylated histones H3 and H4 was demonstrated 4 hours after treatment with vorinostat in peripheral blood mononuclear cells and in 3 of 5 paired tumor biopsies (17,18).

Two schedules of vorninostat (400 mg once daily for 14 days and 300 mg twice daily for 7 days) were tolerated well when combined with carboplatin and paclitaxel (19). This phase I combination study yielded surprisingly robust antitumor activity in patients with advanced NSCLC: 10 of 19 patients obtained a partial response (19). Vorinostat obtained Food and Drug Administration (FDA) approval in refractory cutaneous T cell lymphoma resulting from a nearly 30% response rate (20,21). Disease activity has also been seen in a phase II trial of mesothelioma, such that a randomized trial is underway for patients who have progressed through pemetrexed (22). Phase II trials in advanced ovarian cancer, head and neck cancers, and relapsed diffuse large-B-cell lymphoma were negative (23-25).

The objective of our multicenter phase II trial was to establish the single agent activity of vorinostat in the second line setting of advanced NSCLC. Additional objectives included examining the safety profile of vorinostat in this population, and estimating survival of treated patients.

Materials and Methods

Patient Selection

Patients at least 18 years of age with pathologically confirmed advanced (stage IIIB with pleural or pericardial effusion, stage IV, or recurrent) NSCLC whose disease had progressed during or after treatment with no more than 1 prior cytotoxic combination chemotherapy regimen and who gave informed consent according to institutional and FDA guidelines were eligible for this study provided that the following criteria were met: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; brain metastases, if present, must have been clinically stable after treatment with surgery and/or radiotherapy; adequate bone marrow, liver and renal function; life expectancy of at least 3 months; measureable disease per RECIST criteria; peripheral neuropathy less than or equal to grade 1 per the NCI CTCAE version 3.0; no prior therapy with valproic acid within 2 weeks of enrollment; no treatment with chemotherapy or radiotherapy within 3 weeks of enrollment; no other active malignancy in the past 5 years except non-melanoma skin cancer; absence of HIV positivity; and no uncontrolled intercurrent illness that would limit compliance with study requirements. This protocol was approved through institutional ethics review boards of each participating center in the Wisconsin Oncology Network.

Treatment Plan

Vorinotstat (NSC# 701852) was supplied by the Cancer Therapy Evaluation Program of the National Cancer Institute as gelatin capsules containing either 100 mg or 300 mg of drug. Vorinostat was self-administered with food, continuously, at 400 mg orally, once daily, in a 21 day cycle. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. The vorinostat dose was reduced according to prestudy-defined adverse event criteria to 400 mg or 300 mg once daily on days 1-14 of the 21 day cycle. Patients who required more than two dose reductions due to toxicity were removed from the

study. All toxicities (except alopecia) must have resolved to grade 1 or less prior to the start of the next cycle. All dose reductions were permanent. Patients completed a standardized capsule calendar to document treatment compliance.

Disease Assessment

The objective antitumor response rate (RR) was determined using computed tomography imaging at baseline and after every other cycle of treatment. Bone scans and brain imaging were performed only if clinically indicated. Additional baseline assessment included a history and physical, complete blood count, comprehensive chemistry panel, ECOG PS, and an electrocardiogram if clinically indicated.

Statistical Considerations

The primary endpoint of this study was the overall confirmed objective RR, defined as the percentage of patients experiencing complete responses (CRs) and partial responses (PRs) per RECIST criteria. Secondary objectives included time to disease progression (TTP), overall survival (OS), the 1-year survival rate, and safety. All patients were evaluable for survival and toxicity assessments per the NCI CTCAE version 3.0. Patients must have completed one cycle of therapy to be evaluable for response.

A two-stage minimax design was used to allow the possibility of early stopping due to lack of efficacy. It was assumed that a true RR of less than 5% would not warrant further study of vorinostat treatment in this setting. It was also assumed that a RR of at least 20% would be considered promising for further evaluation. In the first stage, 14 evaluable patients were to be accrued. If no response was observed, then accrual would be stopped with the conclusion that vorinostat treatment was not promising for further study. If at least one response was observed in the first 14 patients, than an additional 9 patients were to be accrued during the second stage of the study. The probability of falsely declaring the regimen with a 5% response probability as warranting further study was 10% (type I error), and the probability of correctly declaring the regimen with a 20% response probability as warranting further study was 85%.

Categorical variables were summarized by frequencies and percentages, while continuous variables were summarized in terms of medians and ranges. Overall survival, TTP and duration of stable disease (SD) were analyzed using the Kaplan-Meier methodology.

The University of Wisconsin Paul P. Carbone Comprehensive Cancer Center (UWCCC) Data and Safety Monitoring Committee was responsible for monitoring data quality and patient safety according to UWCCC guidelines. In addition, each patient's treatment was reviewed weekly by the UWCCC Lung Cancer Research Disease Oriented Working Group.

Results

Patient Characteristics

A total of 16 patients were enrolled between January 2006 and April 2007 at 3 participating sites. Table 1 displays the patient demographics. Eighty-one percent of the patients were female. Most patients experienced SD from their prior treatment. All patients were evaluable for toxicity and survival assessments, including time to progression. Two patients were not evaluable for response due to not completing one cycle of treatment, both due to progressive disease. The median follow-up is 7.1 months (range 1.4 – 27).

Treatment

Treatment compliance was calculated as the percentage of vorinostat taken each cycle, based upon study drug accountability (i.e., capsules returned each cycle). Compliance with vorinostat was good, at 97.4 %. The median number of cycles administered was 3 (range 1 - 27).

Toxicities

Table 2 lists grade 2, 3, and 4 toxicities at least possibly related to treatment.

One patient experienced an acute ischemic stroke and died while on study; this event was deemed possibly related to treatment with vorinostat. The patient had no prior history of hypertension or prior thromboembolic events. She tolerated her first cycle of vorinostat without complication. During the first week of cycle 2 of treatment, she experienced confusion, headaches, and aphasia. Magnetic resonance imaging of the brain detected an acute infarction in the distribution of the right middle cerebral artery, as well as new evidence of leptomeningeal and parenchymal brain metastases. She was hospitalized and evaluated by neurologic consultation, who felt that her symptoms were related to her ischemic infarction. The family elected to pursue supportive care and the patient died within two weeks.

Grade 4 toxicities attributed as at least possibly related to treatment included two patients with pulmonary emboli and one episode of neutropenia. Grade 3 toxicities attributed as at least possibly related to treatment found in at least two patients included three occurrences of asymptomatic lymphopenia and two episodes of fatigue. Three patients had their treatment delayed due to toxicity not resolving to grade 1 or less prior to the start of the next cycle.

Three patients discontinued treatment due to adverse events experienced while on study. One patient came off study due to dyspnea from a pulmonary embolism experienced following two cycles of vorinostat. Her CT scan performed 30 days after stopping treatment showed progressive disease. A second patient was taken off study following 4 cycles of treatment. She had stable disease but unfortunately experienced multiple injuries from a life-threatening motor vehicle accident. Lastly, a third patient developed delirium after completing 7 cycles of vorinostat. This patient also had stable disease at the time. A neurologic consultation diagnosed the patient with Alzeheimer's disease, and she was started on donepezil. Two additional patients had their vorinostat dose reduced due to grade 3 toxicity (asymptomatic lymphopenia and fatigue) possibly related to treatment.

Treatment Efficacy

No objective antitumor responses were seen in the 14 evaluable patients. Over half the patients (8 patients, 57%) experienced SD as their best response to treatment, with a median duration of 3.7 months (range 1.4 - 19.4 months). Two patients (12.5%) were not evaluable for response due to not completing one cycle of treatment, both due to progressive disease, and were therefore classified as non-responders. Median TTP for the study population measured 2.3 months (range 0.9 - 19.4 months). Median OS was 7.1 months (range 1.4 - 30+ months), and, to date, 15 patients have died. The estimated 1 year OS rate was 19% (standard error 10%). Thirteen patients discontinued treatment due to disease progression, and three due to toxicity (one of which, a pulmonary embolism, was possibly treatment related). Of the seven patients who received subsequent systemic therapy, five were treated with pemetrexed and two received erlotinib.

Discussion

This multicenter, open-label, non-randomized single-arm phase II study was conducted based upon the biologic rationale of HDAC inhibitors as cancer therapeutics, and due to the efficacy of vorinostat seen in preclinical NSCLC models. Unfortunately, none of our patients experienced an objective response to treatment per RECIST criteria. Despite this, our rate of stable disease, median time to disease progression, and overall survival were commensurate with results seen using other agents in this setting (1-4). It may be that RECIST criteria are not the best means to gauge the efficacy of vorinostat, or other targeted agents, and that patients may still accrue clinical benefit from nonprogressive disease (26,27). As such, low rates of early progressive disease may more accurately describe the clinical performance of this class of therapeutics (28). However, any consideration of our efficacy with vorinostat must take into account that 81% of our patients were female, a population with improved efficacy outcomes in NSCLC, compared to men, irrespective of treatment (29).

The low rate of antitumor response with single agent vorinostat may have been expected, since it was suggested that vorinostat be classified as a biologic response modifier, rather than as a traditional cytotoxic drug (23). Combining HDAC inhibitors in preclinical models with either cytotoxic or targeted anticancer agents has yielded synergistic results (5,16,30,31). Clinically, this potentiation was suggested by the surprisingly high response rate (53% in NSCLC patients) seen when carboplatin and paclitaxel were combined with vorinostat (19). Sensitization to paclitaxel may be related to the ability of HDAC inhibitors to stabilize microtubules (32). Further clinical exploration of this modulatory capability of vorinostat will result from the outcomes of two large clinical trials presently underway that randomize patients with advanced NSCLC to carboplatin and paclitaxel with or without vorinostat.

The range of toxicities in this trial mirrored that seen with other clinical experiences with vorinostat, including primarily fatigue, dehydration, hyperglycemia, and mild myelosuppression (17,22-24). Two prior vorinostat trials in CTCL reported patients who experienced pulmonary emboli and deep vein thromboses (20-21). The incidence of thromboembolic complications in patients with lung cancer is estimated at 10% (33). No association is described in the literature between histone deacetylase inhibitors and thromboembolism. Not unexpectedly, two of our patients experienced pulmonary emboli, both when their disease was very advanced, within a few weeks of their deaths. A third patient, with no prior history of thrombosis, was diagnosed with a deep vein thrombosis in cycle 3 of treatment when she had stable disease. Evaluation of any possible association of treatment in advanced NSCLC with thromboembolic complications is difficult, but more information will be forthcoming from large randomized trials of vorinostat in front-line disease.

In addition, one of our patients died during cycle 2 with an acute ischemic stroke. Olsen et al. also reported a patient with CTCL receiving vorinostat who experienced an ischemic stroke and died on day 227 (21). Our patient's experience is complicated by her concurrent diagnosis of leptomeningeal and parenchymal brain metastases. A review of stroke in cancer patients from Memorial Sloan Kettering found that 30% of those patients carried a diagnosis of lung cancer, and half of those strokes were “non-embolic,” the category that included ischemic strokes (34). Recent laboratory data using rat models with middle cerebral artery occlusion demonstrated that HDAC inhibitors, including vorinostat, exert a neuroprotective effect in this setting, decreasing histone deacetylation in the brain, reducing infarct size, and in one report, yielding improved neurofunctional outcomes (35-37). These studies concluded

by recommending the study of HDAC inhibitors in this clinical setting, so any relation between ischemic stroke and vorinostat in our patient is unclear.

Eighty-one percent of our patients were female. We believe this disproportionate gender enrollment occurred due to chance. Accrual to this trial started off briskly (10 patients enrolled in the first 4 months), but then declined thereafter for reasons that are not clear. Ironically, only two community practice sites in our Wisconsin Oncology Network opened this trial due to the brisk initial accrual at the University of Wisconsin. It is likely that more sites would have participated in this trial had the initial enrollment at the University of Wisconsin not been so rapid.

In conclusion, vorinostat as a single agent in our patients with relapsed NSCLC did not exert disease activity per RECIST criteria. Stable disease resulted in over half our patients, but efficacy conclusions are limited by our small number of patients and the fact that 81% were female. Toxicities were similar to other disease studies of vorinostat. Due to potential capabilities as a biologic response modifier, vorniostat may prove most beneficial in combination therapy. A patient with advanced NSCLC experienced a PR when receiving treatment with vorinostat combined with bortezomib in an NCI-sponsored phase I study at the University of Wisconsin; as such, and given preclinical evidence supporting this combination, we are developing a phase II study of these agents to be run through our Wisconsin Oncology Network (38-40). Additional clinical trials in NSCLC are underway combining vorinostat with erlotinib and cytotoxic chemotherapeutics.

Acknowledgments

The authors acknowledge our patients, their families, and our clinic staff in the completion of this trial, as well as the UWCCC Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics, & Pharmacogenetics for support of this research. This trial was supported by the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center K12 CA087716, the NCI Early Clinical Trials of Anti-Cancer Agents with Phase I Emphasis U01 CA062491, the UWCCC 2 P30 CA014520-34, and by the NCI/CTEP, with CTEP Translational Research Initiative Funding, Contract 24XS097.

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Table 1

Patient Demographics

Total enrolled	16
Patients evaluable for efficacy	14
Males/females	3/13
Median age (range)	59.5 years (47-79 years)
ECOG PS 0/1	10/6
Histology	
Adenocarcinoma	6
Bronchoalveolar carcinoma	3
NSCLC NOS	5
Squamous cell	1
Large cell	1
Prior treatment	
1 prior chemotherapy regimen	15
1 prior erlotinib regimen	1
Median time since prior treatment	2.7 months (0.2-78.5 months)
Best response to prior treatment	
Partial response	1
Stable disease	12
Progressive disease	3

Table 2
Grade 2, 3, and 4 Toxicities at Least Possibly Related to Treatment

Toxicity	Grade	Number of Patients
Cerebrovascular accident	5	1
Pulmonary embolism	4	2
Neutropenia	3/4	1/1
Deep vein thrombosis	3	1
Lymphopenia	3	3
Fatigue	3	2
Dehydration	3	1
Elevated alkaline phos	3	1
Hypokalemia	3	1
Neutropenia	4	1
	3	1
	2	2
Fatigue	3	2
	2	2
Hyperglycemia	2	5
Lymphopenia	2	3
Diarrhea	2	2
Anemia	2	1
Anorexia	2	1
Neuropathy – motor	2	1
Palpatations	2	1
Pneumonia	2	1
Thrombocytopenia	2	1