Published in final edited form as:
J Thorac Oncol. 2011 May ; 6(5): 951–953. doi:10.1097/JTO.0b013e31820db227.

Phase I Study of Sunitinib and Erlotinib in Advanced Nonsquamous Non-small Cell Lung Cancer

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Abstract

Introduction—Erlotinib has prolonged survival in unselected patients with advanced non-small cell lung cancer, whereas sunitinib has yielded promising rates of disease control in previously treated patients. We conducted a dose escalation study of this combination to determine the maximum tolerated dose of sunitinib in combination with a fixed dose of erlotinib and to evaluate the toxicities of this combination.

Methods—Patients with advanced nonsquamous non-small cell lung cancer were treated at two dose levels: sunitinib at either 25 mg or 37.5 mg, with erlotinib 150 mg. Both drugs were given once daily, continuously.

Results—Eleven patients enrolled from November 2007 to October 2009. No dose-limiting toxicities occurred. Grade 3/4 adverse events at least possibly related to treatment were seen in seven patients (64%). Six patients (54%) required dose modifications, and three (27%) discontinued study treatment due to toxicity. Rates of grade 3 diarrhea and mucositis exceeded those seen with single-agent erlotinib or sunitinib. One patient (9%) attained a partial response lasting 16.3 months.

Conclusions—Although no dose-limiting toxicities occurred, it is difficult to recommend erlotinib 150 mg and sunitinib 37.5 mg daily as the phase II dose for this combination due to the high rate of adverse events. Because of the overlapping toxicity profile of each agent, this combination was poorly tolerated in our population.

Keywords

Phase I clinical trial; Non-small cell lung cancer; Epidermal growth factor receptor; Vascular endothelial growth factor receptors; Receptor protein-tyrosine kinases

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Disclosure: Anne M. Traynor, MD, received clinical trial research funding from Pfizer, Genentech Novartis, and Lilly. Toby C. Campbell, MD, received clinical trial research funding from Bayer, Geron, Lilly, and GlaxoSmithKline. Tien Hoang, MD, received clinical trial research funding from Lilly and Pfizer. KyungMann Kim, PhD, received travel honorarium from OSi and Bayer.

Treatment with erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has prolonged survival and improved symptom control in unselected patients with advanced non-small cell lung cancer (NSCLC).[1] Sunitinib, an oral multitargeted TKI of vascular endothelial growth factor (VEGF) receptor (VEGFR) -1, -2, and -3, and platelet-derived growth factor receptor-α and -β, has demonstrated modest efficacy as a single agent in advanced NSCLC.[2,3]

Both preclinical and clinical evidence support simultaneous blockade of EGFR and VEGFR pathways. Laboratory evidence has shown that both tumor- and host-derived VEGF expression were elevated in models of EGFR TKI primary and acquired resistance and that exposure of these resistant models to the dual VEGFR and EGFR TKI vandetanib significantly inhibited tumor growth.[4,5] Clinically, progression-free survival was lengthened when bevacizumab was added to erlotinib in the maintenance[6] and second-line settings of advanced NSCLC,[7] compared with single-pathway suppression. Similarly, vandetanib prolonged progression-free survival compared with EGFR blockade alone using gefitinib.[8] Therefore, we sought to assess the safety of the combination of sunitinib and erlotinib in patients with advanced nonsquamous NSCLC.

PATIENTS AND METHODS

Patients of good performance status with advanced nonsquamous NSCLC were eligible, provided they had not previously been treated with prior EGFR or VEGFR inhibitors. Patients with squamous cell histology were excluded due to concerns regarding the potential risk of hemorrhage in this population using sunitinib.[9] Each patient gave written informed consent, according to institutional and federal guidelines. The protocol was approved by the University of Wisconsin-Madison Institutional Review Board.

This dose escalation trial was designed to determine the safety, tolerability, and maximum tolerated dose (MTD) of sunitinib combined with erlotinib in patients with advanced nonsquamous NSCLC of any line of therapy. Patients received erlotinib, 150 mg, and sunitinib at either 25 mg (dose level 1) or 37.5 mg (dose level 2). Both drugs were given once daily, continuously, during a 21-day cycle.

Dose escalation followed a traditional 3 + 3 phase I trial design, with the MTD defined as the highest dose level at which 0 or 1 of 6 evaluable patients experienced dose-limiting toxicities (DLTs) and was expanded to six patients to more fully characterize safety of this combination. DLTs were assessed through cycle 1 of treatment, were judged to be probably or definitely related to either sunitinib or erlotinib, and included febrile neutropenia, neutropenic infection, ≥ grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia lasting ≥7 days, and ≥ grade 3 nonhematologic toxicities lasting ≥7 days, other than nausea, vomiting, or diarrhea unresponsive to maximal supportive therapy. Toxicities were evaluated per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.

The primary objective of the study was determination of the MTD. Secondary objectives included measurement of antitumor response. Demographics, toxicities, and tumor responses were summarized with descriptive statistics such as frequencies, percentages, median, and range of minimum and maximum. The 95% confidence interval (CI) for the response rate at the MTD was constructed using Wilson's score method, and the Kaplan-Meier (product limit) method was used to estimate the survival function for overall survival. All patients were evaluable for safety and toxicity. The efficacy analysis was based on the intent-to-treat principle.

RESULTS

Eleven patients enrolled from November 2007 to October 2009. Median follow-up duration of this study was 9.3 months. Pretreatment characteristics are summarized in Table 1. The dose escalation schema is given in Table 2. Four patients were enrolled on dose level 1 (sunitinib 25 mg daily), whereas seven were enrolled on dose level 2 (sunitinib 37.5 mg daily). One patient at each of the two dose levels were replaced due to not completing cycle 1 of therapy for reasons other than toxicity: one patient in dose level 1 was removed from the study due to investigator discretion when a subsequent review of his screening imaging revealed multiple cavitary pulmonary lesions, and one patient on dose level 2 withdrew consent. Pill diaries revealed that treatment compliance with this combination measured 90.6%.

No DLTs were observed. Per protocol definition, the MTD was dose level 2 (sunitinib 37.5 mg with erlotinib 150 mg).

There were no deaths on study. Four serious adverse events occurred. Two patients died within 30 days of coming off treatment, both due to disease progression. A 70-year-old male patient enrolled on dose level 1 was hospitalized during cycle 2 for grade 3 abdominal pain and ileus possibly related to treatment. In addition, a 75-year-old male patient enrolled on dose level 2 was admitted during cycle 1 of treatment with grade 2 rapid atrial fibrillation and grade 3 left ventricular dysfunction possibly related to treatment. The atrial fibrillation occurred after a protocol-mandated change in the patient's rate control agent. Three patients (27%) discontinued study treatment due to toxicities, six patients due to progressive disease, one due to withdrawal of consent, and one due to investigator discretion.

Six patients (54%) had their treatment doses held or reduced due to adverse events, four of whom never resumed treatment. Grade 3 and grade 4 adverse events at least possibly related to treatment occurred in seven patients (64%), as seen in Table 3. Rates of grade 3 diarrhea and mucositis exceeded those seen with single-agent erlotinib or sunitinib.

The most common toxicities encountered with this regimen were dermatologic (eight episodes of acneiform rash and three of hand-foot reaction), diarrhea (including two grade 3 occurrences), fatigue, mucositis, and lymphopenia. One asymptomatic patient experienced the radiographic incidental finding of a grade 4 pulmonary embolism. Six patients experienced grade 3 toxicity as their worst grade of toxicity, and four patients experienced grade 2 toxicity as their worst grade.

One patient (9%) attained a partial response lasting 16.3 months, whereas two patients (18%) experienced stable disease for four cycles, and one patient (9%) had stable disease for two cycles. The disease control rate was 36% (95% CI: 15– 65%). The median overall survival and 1-year estimated overall survival were 9.3 months (95% CI: 1.7–23.9 months) and 46% (95% CI: 17–71%), respectively.

DISCUSSION

Toxicity was increased using this regimen in our limited patient sample. Sixty-four percent of patients experienced grade 3 and grade 4 adverse events, resulting in 54% of patients reducing and/or holding their doses, a frequency exceeding the rate of dose modifications with either agent alone.[1–3] Our rates of grade 3 mucositis and diarrhea were increased compared with rates seen with single-agent erlotinib or sunitinib.[1–3] No new, unexpected toxicities were encountered, but rather, they mirrored the overlapping off-target toxicity profiles of fatigue, dermatologic, and gastrointestinal adverse events seen with each agent

alone. It is difficult to conclude if toxicities in our population were dose dependent, as seven patients enrolled in dose level 2, whereas only four enrolled in dose level 1.

Our increased rate of off-target adverse events with combination targeted treatment was not unique. Ryan et al.[10] detected higher rates of dose reductions and interruptions, compared with each single agent, when using this same combination in patients with advanced renal cell carcinoma. Similarly, published studies using the combination of erlotinib and sorafenib found higher frequencies of dose modifications compared with each agent alone, with toxicities consisting primarily of increased rates of dermatologic and gastrointestinal adverse events.[11–13] Thus, it seems that combining targeted agents with overlapping off-target toxicity profiles, as was the case with our combination, leads to enhanced rates of dose delays and reductions due to adverse events.

A significant limitation of our study is that we did not perform pharmacokinetic analyses. The need for pharmacokinetic evaluation is especially critical when using oral agents, in which absorption may be variable,[14] and when combining agents characterized by similar toxicity profiles that may then result in increased rates of dose reductions. Additional limitations of our study include the small sample size and the absence of predictive biomarkers that could have enriched our population for response from dual pathway inhibition.

Efficacy outcomes were secondary endpoints in this small dose escalation study, so although promising, it is not appropriate to draw conclusions from them. A goal of dual EGFR and VEGFR pathway inhibition is that simultaneous blockade may reverse both primary and acquired resistance to EGFR TKIs.[4,5] We cannot conclude from our limited patient population that this rationale was verified. The clinical relevance of dual pathway inhibition will remain uncertain in NSCLC, in either EGFR mutation-positive or -negative patients, until both efficacy and toxicity outcomes from a phase III study of this combination are analyzed completely.[15]

In conclusion, our rates of dose modifications due to treatment-related toxicities suggest that this combination was poorly tolerated at either dose of sunitinib. The impact of our frequent dose modifications on potential target modulation is unknown as pharmacokinetic analyses were not performed and as our study was not designed to estimate efficacy. Future evaluation of this combination in advanced NSCLC should be performed in a biomarker-determined population.

Acknowledgments

Supported by Pfizer, Inc., New York City, NY, and Genentech, Inc., South San Francisco, CA.

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TABLE 1

Patient Demographics

No. of patients	**11**
Median age (range)	64 yr (48–78 yr)
Sex	
Male	5
Female	6
Performance status	
0	5
1	6
Histology	
Adenocarcinoma	9
NSCLC (not otherwise specified)	2
Prior cytotoxic regimens	
0	1
1	10
Median time since prior treatment (range)	4.3 mo (1–21 mo)
Best response to prior cytotoxic treatment	
Complete response	1
Partial response	3
Stable disease	4
Progressive disease	2
Unknown	1
Patients evaluable for	
Safety	11
Efficacy	11

TABLE 2

Dose Escalation Schema

Dose Level	Sunitinib (mg/d)	Erlotinib (mg/d)	*N*	No. of Cycles
−2	25	50		
−1	25	100		
1[a]	25	150	4	9
2	37.5	150	7	36

[a]Dose escalation started with dose level 1.

TABLE 3

Grade 3 and Grade 4 Toxicities, At Least Possibly Related to Treatment

		Dose Level	
Toxicity	**No. of Patients (*N* = 11)**	**Sunitinib 25 mg/d**	**Sunitinib 37.5 mg/d**
Pulmonary embolism[a]	1	0	1
Diarrhea	2	1	1
Hand-foot skin reaction	1	0	1
Mucositis	1	0	1
Hypertension	1	0	1
Left ventricular dysfunction	1	0	1
Leukopenia	1	1	0
Abdominal pain with ileus	1	1	0

[a]Grade 4 toxicity; all other toxicities were grade 3.