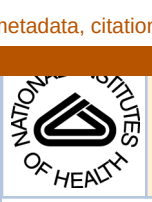

Published in final edited form as:

Lung Cancer. 2011 February ; 71(2): 151–155. doi:10.1016/j.lungcan.2010.05.022.

A phase I trial of sorafenib combined with cisplatin/etoposide or carboplatin/pemetrexed in refractory solid tumor patients

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Abstract

Introduction—Sorafenib has demonstrated single agent activity in non-small cell (NSCLC) and small cell lung cancer (SCLC). Carboplatin/pemetrexed (CbP) and cisplatin/etoposide (PE) are commonly used in the treatment of these diseases.

Methods—A phase I trial escalating doses of sorafenib in combination with fixed doses of PE (Arm A) or CbP (Arm B) was performed using a 3-patient cohort design to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT); DLT were assessed in the first cycle. The trial was subsequently amended with closure of Arm B and to include Arm C with a reduced dose of carboplatin.

Results—Between 9/2007 and 9/2008, 20 pts were treated on the trial; median age 62 (range 42-73), male/female ratio 12/8, PS 0/1 ratio 6/14, and median number of prior therapies 2 (range 1-4). The most common tumor types were NSCLC and SCLC. On Arm A at dose level 0 (sorafenib 200 mg BID), 2 of 4 patients experienced DLT; 2 patients were enrolled at dose level -1 (sorafenib 200 mg QD) without DLT, but this arm was closed due to slow accrual. On Arm B, 2 of 3 patients experienced DLT at dose level 0 (sorafenib 200 mg BID). On Arm C at dose level 0 (sorafenib 200 mg BID), 1 of 6 patients experienced DLT, and at dose level +1 (sorafenib 400 mg BID) 2 of 5 patients experienced a DLT.

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Conflicts on Interest: Dr. Stinchcombe received research funding from Bayer Pharmaceuticals, Inc., and was on the speakers bureau of Lilly Oncology and Genentech

Conclusions—The MTD of sorafenib was 200 mg BID continuously in combination with carboplatin (AUC of 5) and pemetrexed 500 mg/m^2 every 3 weeks. However, only 6 patients were treated at this dose level, and the results should be interpreted cautiously.

Keywords

Sorafenib; non-small cell lung cancer; small cell lung cancer; safety and toxicity; phase I

Introduction

In lung cancer, multiple signal pathways such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and vascular endothelial growth factor receptor (VEGFR) are dysregulated.[1] The Ras/Raf pathway is an important mediator of angiogenesis and tumor proliferation.[1] Sorafenib is a multi-targeted tyrosine kinase inhibitor that inhibits Raf-1, VEGFR, and platelet derived growth factor receptor (PDGFR) pathways, and the process of angiogenesis.[2] At the time this trial was developed, preliminary results of phase II trials had demonstrated single agent activity of sorafenib in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[3,4] Phase II trials revealed promising activity and favorable toxicity profile with the combination of carboplatin and pemetrexed (CbP) in advanced NSCLC.[5,6] A randomized phase II trial revealed a favorable toxicity profile of carboplatin and pemetrexed in SCLC, and a phase III trial comparing carboplatin and pemetrexed to carboplatin and etoposide in SCLC had been initiated.[7,8] An interim analysis of the phase III subsequently revealed that carboplatin and pemetrexed was inferior to carboplatin and etoposide, and trial enrollment was discontinued. The combination of cisplatin and etoposide (PE) is the standard first-line therapy for SCLC and an accepted therapy for advanced NSCLC.[9-12] We were interested in integrating sorafenib into two commonly used chemotherapy combinations for the treatment of NSCLC and SCLC. This interest led to the development of a two arm phase I trial to determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of sorafenib in combination with these chemotherapy combinations.

Materials and Methods

Patient selection

Eligible patients included those with histologically or cytologically confirmed advanced solid tumors, with adequate organ function, good performance status, and able to provide informed consent. The complete eligibility criteria are presented in Table 1. Study evaluations prior to each cycle included: complete blood count, electrolytes including magnesium, creatinine, and liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase, and total bilirubin]. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST)[13] every two cycles with computed tomography (CT) or magnetic resonance imaging (MRI) scans, and tumor markers, if applicable. After trial enrolment had begun, it was amended to exclude patients with NSCLC with squamous histology. This trial was approved by the Protocol Review Committee of the Lineberger Comprehensive Cancer Center and the Institutional Review Board of the University of North Carolina. The trial was registered with United States National Institutes of Health (trial number: NCT00573690).

Study Design

The primary objective of this phase I non-randomized single center clinical trial was to determine the MTD of sorafenib in combination with fixed doses of PE or CbP. The secondary objectives were to identify the DLT and the efficacy of these combinations. The

treatment arms were performed in parallel, with no intent to compare the two treatment arms. Toxicity was assessed after each treatment cycle using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. DLT were assessed in cycle 1, defined as ≥ grade 3 non-hematological toxicities (except nausea, vomiting, and alopecia), grade 4 anemia or thrombocytopenia, grade 4 neutropenia lasting > seven days, and a > two week delay in initiating cycle 2 due to toxicities.

The initial study design included two treatment groups (Arms A and B) with three dose levels of sorafenib (sorafenib 200 mg daily, sorafenib 200 mg BID, sorafenib 400 mg BID) for each treatment arm. Sorafenib dose escalation was not pursued beyond the currently approved single agent dose of 400 mg po BID. However, due to toxicities attributed to the carboplatin dose of area under the curve (AUC) of 6 using the Calvert equation[14] in Arm B, the study was amended: Arm B was closed to accrual and Arm C was added with a lower dose of carboplatin (AUC=5) while maintaining three sorafenib dose levels. Arm A included a pharmacokinetic evaluation of the sorafenib and etoposide. However, enrollment in that treatment arm was slow and the trial was amended to eliminate the pharmacokinetic investigations in an attempt to facilitate enrollment.

A standard “3+3” trial design was used. Three patients were treated at the initial dose level for each treatment group, and if no DLTs were observed in cycle 1, then three patients were treated at the next dose level. If one of three patients experienced a DLT, then three additional patients were enrolled at that dose level. If a DLT occurred in two or more patients at a given dose level (i.e. DLT rate ≥33%), the MTD would be exceeded and three additional patients were enrolled at the previous dose level. A maximum of six patients were enrolled at any dose level. The MTD (or recommended phase II dose) was defined as the highest dose with an observed toxicity rate ≤ 1 in 6 patients.

Study Treatment

Patients on Arm A were treated with cisplatin 60 mg/m^2 over 1 hour on day 1 and etoposide 120 mg/m^2 over 30 minutes on days 1, 2 and 3, in a three week cycle with sorafenib continuously. For cycle 1 only, cisplatin was given on day 2 in order to assess the pharmacokinetics of sorafenib and etoposide. Sorafenib was taken orally on a daily basis starting on day 2 for cycle 1, and taken continuously thereafter. For all patients, dose level “0” (starting dose) was sorafenib 200 mg po BID, dose level “-1” was sorafenib 200 mg po daily, and dose level “+1” was sorafenib 400 mg po BID. All patients were treated with the following premedication regimen: aprepitant, ondansetron, dexamethasone, and mannitol 25 g IV, 0.9% Normal Saline with 20 mEq KCl/L, and magnesium sulfate 2 g/L at 250 mL/h for 2 hours prior to and after cisplatin, all on cycle 1 day 2 and day 1 thereafter. On Arm B, patients were treated with pemetrexed 500 mg/m^2 over 10 minutes followed by carboplatin AUC=6 using the Calvert[14] equation, over 30 minutes on day 1 of a 3 week cycle. Due to excessive toxicity, the trial was amended such that the carboplatin dose was lowered to AUC=5 (Arm C). Sorafenib was taken orally on a daily basis starting on day 1. Patients receiving pemetrexed received folic acid, vitamin B12 and dexamethasone as per the package insert.[15]

Following cycle 1, the following criteria had to be met prior to treatment for each subsequent cycle on both treatment arms: ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and creatinine clearance ≥ 45 mL/min. If hematologic parameters were not met, treatment was delayed to allow sufficient time for recovery. If the creatinine clearance had not returned to ≥ 45 mL/min within 42 days of last treatment, the patient was discontinued from study. The use of growth colony stimulating factors was prohibited during the first cycle, but could be used thereafter in accordance with the American Society of Clinical Oncology guidelines. [16] The use of erythropoietin stimulating agents was permitted, based on standard

guidelines available at the time the study was conducted. [17] A second episode of a DLT despite dose reduction or initiation of growth factor support resulted in the patient discontinuing the treatment and protocol. Patients were treated until disease progression, unacceptable toxicity, or investigator discretion.

Results

Patient Characteristics

Between September 2007 and September 2008, 31 patients provided informed consent for trial participation and 20 patients were treated on the trial. Eleven patients did not participate in the trial due to decline in performance status related to disease progression (n=5), withdrawal of informed consent (n=2), pursuit of hospice care (n=1), ineligibility due to increased liver function tests (n=1), squamous histology (n=1), and interval development of hemorrhagic brain metastases (n=1). The median age was 62 (range 42-73), 12 were male, 14 had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Patients received a median of two prior therapies (range 1-4). The most common tumor types were NSCLC (n=7), SCLC (n=4), and head/neck malignancies (n=2).

Toxicities

At dose level 0 of Arm A, 2 of 4 patients experienced DLT (grade 4 thrombocytopenia, grade 3 fatigue, and grade 3 febrile neutropenia in one patient; grade 4 neutropenia for > 7 days, grade 3 febrile neutropenia, diarrhea, hypokalemia, and hyponatremia in the other). Two of the required six patients were then enrolled at dose level -1 without a DLT. However, this arm was closed due to slow accrual.

On Arm B at dose level 0, two of three treated patients had grade 4 thrombocytopenia attributed to carboplatin (AUC=6). Subsequently, on Arm C (carboplatin AUC=5) at dose level 0, 1 of 6 patients experienced DLT (grade 3 hyponatremia, dehydration, and hypoglycemia). Enrollment continued at dose level +1, but 2 of 5 pts experienced DLT (both grade 3 fatigue and anorexia). As such, the MTD was exceeded and the recommended phase II dose was sorafenib 200 mg po BID continuously with carboplatin AUC=5 and pemetrexed 500 mg every three weeks. The hematologic toxicities observed in each of the treatment arms are presented in Table 3, electrolyte and renal toxicities in Table 4, and other non-hematological toxicities in Table 5. One grade 5 toxicity, gastrointestinal perforation, was observed on Arm C after cycle 2 which was possibly treatment-related.

Treatment Administration

The median number of treatment cycles on all arms was 2; range for Arms A, B and C was 1 to 2, 1 to 4, and 1 to 4 respectively. The reasons for treatment discontinuation were progressive disease (n=5), adverse events (n=9), and death (n=1). Five patients received four cycles of therapy and then discontinued treatment at the discretion of the treating physician. After excessive toxicity was observed in Arm B, one patient who did not experience toxicity underwent a dose reduction and received four cycles of treatment on Arm B. Four patients received four cycles on Arm C.

Response

Of the 20 patients treated on the trial, ten patients were evaluable for response. Two patients experienced a partial response (SCLC and squamous cancer of the head and neck) and three patients experienced stable disease of ≥ 12 weeks duration (thymoma, atypical carcinoid, and NSCLC). Five patients experienced progressive disease. Of the remaining ten patients, nine were not evaluable due to the fact that they discontinued therapy related to toxicity, and one patient died from a gastrointestinal perforation. Four of the patients who experienced a

partial response or stable disease received treatment on Arm C, and one patient who had stable disease was treated on Arm B.

Discussion

An unacceptable rate of toxicity was observed in this previously treated patient population with the combination of cisplatin and etoposide with sorafenib 200 mg po BID. Enrollment at dose level -1 was slow, and in order to facilitate accrual the trial was amended to eliminate the pharmacokinetic investigation, which required an inpatient admission to our clinical research center. However, this was not successful. Several factors probably contributed to the slow accrual including the fact that only a limited number of patients with progressive solid tumors who are candidates for cisplatin-based chemotherapy, physician and patient hesitancy about treatment with a novel three drug combination, and restrictions related to trial eligibility. The continuous schedule of sorafenib with cisplatin and etoposide may have contributed to the rate of toxicity observed, and investigations of an alternative schedule of sorafenib administration may be considered for further investigation with appropriate pharmacokinetic evaluation.

An excessive rate of thrombocytopenia was observed with sorafenib 200 mg BID with the combination of carboplatin AUC=6 and pemetrexed 500 mg/m2 every three weeks. The explanation of the unexpectedly severe thrombocytopenia seen in Arm B is unclear. Decreased excretion of sorafenib as a result of carboplatin is unlikely to explain this as less than 20% of sorafenib is excreted in the urine, predominantly as the inactive glucuronide metabolite.[18] A potential explanation is the synergistic effect of both sorafenib and carboplatin on the platelets. Platelets and megakaryocytes express VEGFRs and VEGF, as well as other growth factors, which have been shown to be important in their production, maturation, and function.[19] The current action of carboplatin causing direct toxicity to the platelets and sorafenib further inhibiting production may have resulted in the more pronounced thrombocytopenia seen in these pretreated patients with lower megakaryocte reserves. Episodes of grade 3 or 4 neutropenia were observed in all arms, and three episodes of febrile neutropenia were observed. Of the three patients who experienced febrile neutropenia, two patients did not receive any further therapy on trial and one patient received growth colony stimulating factor on the following cycle and then discontinued treatment due to progressive disease. Since only patient received colony growth factor for a single cycle it is not possible to determine the impact of colony growth stimulating factors on the rate of neutropenia or febrile neutropenia.

The combination of sorafenib 200 mg twice daily and carboplatin AUC=5 and pemetrexed 500 mg/m2 was moderately well tolerated; however, excessive toxicity was observed with the sorafenib 400 mg twice daily. It should be noted that the median number of cycles observed on this treatment arm was 2 (range 1 to 4). The fact that a pretreated patient population with refractory disease was enrolled on this trial may have contributed to the low number of median cycles. If a phase II trial of this combination is pursued, then patients should be monitored for cumulative toxicity. It is possible that a treatment naïve patient population may better tolerate this three drug combination.

While this trial was ongoing, the results of a phase III trial comparing carboplatin and paclitaxel with and without sorafenib revealed a similar overall survival in the intent-to-treat patient population, and a statistically significant inferior survival among patients with NSCLC with squamous histology on the sorafenib-containing arm compared to the carboplatin and paclitaxel alone arm.[20] Subsequent to the development of this trial, the combination of carboplatin and pemetrexed was found to be inferior to the combination of carboplatin and etoposide in patients with extensive stage SCLC, [8] and the activity of

pemetrexed in NSCLC was found to be limited to NSCLC tumors with non-squamous histology.[21]

The future development of sorafenib in combination with standard chemotherapy in NSCLC is in doubt; however a phase III trial in patients with advanced NSCLC with non-squamous histology of cisplatin and gemcitabine with and without sorafenib is ongoing. A previous phase III trial revealed the superiority of cisplatin and pemetrexed compared to cisplatin and gemcitabine in patients with advanced NSCLC with non-squamous histology.[22] If the phase III trial of cisplatin and gemcitabine with and without sorafenib reveals an improvement in overall survival with the addition of sorafenib, then the combination of carboplatin, pemetrexed, and sorafenib may be of interest in non-squamous NSCLC.[22]

The combination of cisplatin and pemetrexed is a standard therapy for malignant mesothelioma, and the combination of carboplatin and pemetrexed has also shown activity.[23,24] Single agent sorafenib has demonstrated modest activity in malignant mesothelioma, but the trial did not meet the primary objective for further study as a single agent.[25] The combination of carboplatin, pemetrexed, and sorafenib may have activity in malignant mesothelioma. Single agent pemetrexed has demonstrated activity in squamous cell cancer of the head and neck, [26] single agent sorafenib has demonstrated modest activity, [27] and platinum- agents are a standard agent in this disease. We observed a response in this patient population, and the carboplatin, pemetrexed, and sorafenib combination may be considered for further investigation in squamous cancer of the head and neck.

The MTD of sorafenib is 200 mg po BID in combination with carboplatin (AUC=5) and pemetrexed 500 mg every 3 weeks; however, these results should be interpreted cautiously since the number of patients treated at this dose level was small (n=6) and the number of cycles was limited. Further evaluation of sorafenib scheduling when used in combination with carboplatin and pemetrexed may help to ameliorate the toxicity profile.

Acknowledgments

This study was supported by grant RR00046. Funding for this study was provided by Bayer Pharmaceuticals, Inc. Eli Lilly and Company provided pemetrexed. JMD was supported by an Alberta Heritage Foundation for Medical Research Clinical Fellowship and Canadian Association of Medical Oncology Fellowship.

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Table 1
Inclusion and Exclusion Criteria and Dose Limiting Toxicities

Inclusion criteria

1 Histologically or cytologically confirmed metastatic solid tumor

2 Measurable disease by RECIST criteria

3 Progressed on at least one standard therapy or who have a disease for which there is no standard therapy

4 Age ≥ 18 years old

5 Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1

6 Adequate organ function defined as:

- Bone marrow: hemoglobin ≥ 9.0 g/dL, ANC ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L

- Hepatic: total bilirubin ≤ 1.5 × ULN, ALT and AST ≤ 2.5 × ULN, INR < 1.5 or a PT/PTT within normal limits. Patients receiving warfarin or heparin were allowed to participate. For patients on warfarin, the INR should be measured prior to initiation of sorafenib and monitored at least weekly, or as defined by the local standard of care, until INR is stable

- Renal: Cockcroft calculated creatinine clearance (CrCL) ≥ 45 mL/min

7 Asymptomatic brain metastases were permitted if treated ≥ 6 months before study entry, and clinically stable without steroid treatment for 1 week

8 Women of childbearing potential: negative serum pregnancy test performed within 7 days prior to the start of treatment

9 Women of childbearing potential and men must agree to use adequate contraception (barrier method of birth control) prior to study entry and for the duration of study participation. Men and women should use adequate birth control for at least 2 weeks after the last administration of sorafenib

10 Able and willing to provide written informed consent

Exclusion Criteria

1 Histological or cytological diagnosis of squamous cell carcinoma of the lung.

2 Congestive heart failure > class II NYHA; unstable angina, new onset angina (began within the last 3 months), or myocardial infarction within the past 6 months.

3 Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.

4 Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic > 90 mmHg) despite optimal medical management.

5 Known severe hypersensitivity to sorafenib or any of the excipients, etoposide, pemetrexed, cisplatin, or carboplatin.

6 Known human immunodeficiency virus (HIV) infection or chronic Hepatitis B or C.

7 Active clinically serious infection > CTCAE Grade 2.

8 Thrombolic or embolic events within the past 6 months.

9 Pulmonary hemorrhage/bleeding event > CTCAE Grade 2 or any other hemorrhage/bleeding event > CTCAE Grade 3 within the past 4 weeks.

10 Serious non-healing wound, ulcer, or bone fracture.

11 Evidence or history of bleeding diathesis or coagulopathy

12 Major surgery, open biopsy or significant traumatic injury within the past 4 weeks.

13 Use of St. John's Wort or rifampin.

14 Any condition that impairs patient's ability to swallow whole pills

15 Any malabsorption problem or uncontrolled inflammatory bowel disease or gastrointestinal disorder causing ≥ 5 bowel movements in 24 hour period at baseline

16 For Arms B/C (carboplatin/pemetrexed):

- Clinically relevant pleural effusions or ascites which cannot be controlled by drainage

- Non-compliance or inability to take vitamin B12 and folic acid supplementation

- Inability to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) for 2 days before (5 days for long-acting NSAIDs), the day of, and the 2 days after pemetrexed administration

17 Prior exposure to > 3 cytotoxic therapies for metastatic disease

Table 2

Patient Characteristics

Characteristics	
Total Number of Patients	20
Age (years)	62 (range 42-73)
ECOG Performance Status	
0	6
1	14
Gender	
Male	12
Female	8
Race	
White	17
Black	3
Median Number of Pervious Therapies	2 (range 1-4)
Malignancy	
Non-Small Cell Lung Cancer	7
Small Cell Lung Cancer [A]	4
Esophageal Cancer	1
Thymoma	1
Atypical Carcinoid Lung Cancer	1
Salivary Gland Mucoepidermoid	1
Gastric Cancer	1
Renal Cell Cancer	1
Squamous Cancer of Head and Neck	1
Hurthle cell	1
Melanoma	1

[A] One patient had small-cell of the esophagus

Table 3

Hematological toxicity per treatment arm

Treatment cohort	Patients (N)	Cycles (N)	Neutropenia				Anemia				Thrombocytopenia				Febrile neutropenia			
			Grade				Grade				Grade				Grade			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Arm A	6	10	0	0	0	6	1	2	1	0	1	0	1	1	0	0	2	0
Arm B	3	7	0	1	2	0	0	2	0	0	0	0	0	2	0	0	1	0
Arm C	11	31	4	1	4	1	0	4	2	0	2	2	3	3	0	0	0	0

Numbers represent episodes of toxicity observed during all cycles

Table 4

Renal and Electrolyte Toxicities

Treatment cohort	Patients (N)	Cycles (N)	Hyperglycemia				Hypoglycemia				Hypokalemia				Hyponatremia				Hypomagnesmia				Hypophospahtemia				Renal toxicity			
			Grade				Grade				Grade				Grade				Grade				Grade				Grade			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Group A	6	10	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0
Group B	3	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group C	11	31	0	1	0	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0	0	0	1	0	0	0	1	0	0	0

Numbers represent episodes of toxicity observed during all cycles

Table 5

Select non-hematological toxicities

Treatment cohort	Patients (N)	Cycles (N)	Fatigue				Anorexia				Dehydration				Gastrointestinal Perforation					Nausea Vomiting				Diarrhea				Hypertension			
			Grade				Grade				Grade				Grade					Grade				Grade				Grade			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	1	2	3	4	1	2	3	4
Group A	6	10	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	1	0	0	1	0	0
Group B	3	7	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	1	0	0	0
Group C	11	31	1	6	3	0	3	1	3	0	0	2	1	0	0	0	0	0	1	8	1	0	0	3	0	0	0	0	0	0	0

Numbers represent episodes of toxicity observed during all cycles