Phase II Study of Sorafenib in Combination With Docetaxel and Cisplatin in the Treatment of Metastatic or Advanced Gastric and Gastroesophageal Junction Adenocarcinoma: ECOG 5203

Weijing Sun, Mark Powell, Peter J. O'Dwyer, Paul Catalano, Rafat H. Ansari, and Al B. Benson III

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From the University of Pennsylvania, Philadelphia, PA; Dana Farber Cancer Institute, Boston, MA; Memorial Hospital of South Bend, South Bend, IN; and Northwestern University, Chicago, IL.

Submitted December 23, 2009; accepted March 19, 2010; published online ahead of print at www.jco.org on May 10, 2010.

Supported in part by Public Health Service Grants No. CA23318, CA66636, CA21115, CA15488, and CA17145 from the National Cancer Institute.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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Corresponding author: Weijing Sun, MD, 16 Penn Tower, 3400 Spruce St, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA 19104-4283; e-mail: weijing.sun@uphs.upenn.edu.

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0732-183X/10/2818-2947/\$20.00

DOI: 10.1200/JCO.2009.27.7988

ABSTRACT

Purpose

The combination of sorafenib with chemotherapy is well-tolerated and is associated with encouraging response rates in several malignancies. Both docetaxel and cisplatin are active in gastric cancer. A phase II study was conducted to determine the efficacy and toxicity of combined sorafenib, docetaxel, and cisplatin in patients with metastatic or advanced adenocarcinoma of stomach or gastroesophageal junction (GEJ).

Patients and Methods

Forty-four chemotherapy-naïve patients with Eastern Cooperative Oncology Group performance status 0 or 1, of whom 80% had metastatic disease and two thirds had poorly differentiated gastric or GEJ adenocarcinoma, were enrolled. The treatment regimen was sorafenib 400 mg orally twice a day for 21 days, docetaxel 75 mg/m² intravenously on day 1, and cisplatin 75 mg/m² intravenously on day 1, repeated every 21 days. The primary end point was response rate to the combination. Toxicity, overall survival, and progression-free survival were assessed as secondary end points.

Results

Eighteen of the 44 eligible and treated patients showed partial responses (41%; 90% CI, 28% to 54%). The median progression-free survival was 5.8 months (90% CI, 5.4 to 7.4 months). The median overall survival was 13.6 months (90% CI, 8.6 to 16.1 month). The major toxicity of this regimen was neutropenia, which reached grade 3 to 4 in 64% of patients. One patient experienced hemorrhage at the tumor site.

Conclusion

The combination of sorafenib, docetaxel, and cisplatin has an encouraging efficacy profile with tolerable toxicity. Additional studies of sorafenib with chemotherapy are warranted in gastric cancer.

J Clin Oncol 28:2947-2951. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Gastric cancer remains one of the leading causes of death worldwide. In 2009, approximately 21,130 cases of gastric cancer will be diagnosed in the United States, with 10,620 deaths.¹ There has been a worldwide increase in proximal gastric and gastroesophageal junction (GEJ) adenocarcinoma. Overall prognosis is poor, in that only 40% of patients are eligible to undergo potentially curative surgery, and the majority of patients present with advanced metastatic or surgically unresectable disease. Even for patients who have undergone potentially curative resection, the rate of recurrence is high. Although many cytotoxic agents show activity in advanced gastric cancer, either as single agents or in combina-

tion, with response rates at approximately 20% to 40%, the overall benefit is still disappointing, and median survival is approximately 10 months.²⁻⁴ Against this background, the development of targeted therapies is an important priority.

The targeted agents that inhibit the signal transduction pathways central to tumorigenesis have provided new options for the combination therapy of advanced malignancies.⁵⁻⁸ Sorafenib targets several tyrosine kinases, including Raf-1, wild-type and mutant Braf, vascular endothelial growth factor (VEGFR) 1, VEGFR2, VEGFR3, platelet-derived growth factor receptor- β , and Mcl-1.⁹ Antitumor efficacy of sorafenib has been demonstrated against a broad range of human tumors in both preclinical models and clinic studies.¹⁰ On the basis

of data from large randomized phase III studies, sorafenib has been approved as the first-line therapy for renal cell carcinoma and hepatocellular carcinoma.^{11,12} Sorafenib can be safely combined with a variety of standard cytotoxic cancer chemotherapy agents, including paclitaxel, irinotecan, gemcitabine, and cisplatin, with no significant increase in the toxicity associated with those agents and with promising antitumor efficacy in different cancer models.¹³⁻¹⁵

Docetaxel and cisplatin are cytotoxic chemotherapy agents commonly administered in gastric cancer therapy. A randomized phase II trial showed that a combination of docetaxel and cisplatin seemed to be as effective as triple-agent combinations.¹⁶ In this trial, the median overall survival times were 8.3, 11.0, and 10.4 months for the combination of epirubicin, cisplatin, and fluorouracil; docetaxel and cisplatin; and docetaxel, cisplatin, and fluorouracil, respectively. The toxicity profiles were comparable with these three regimens (grade 3 or 4 neutropenia rates of 34%, 49%, and 57%, respectively). The current Eastern Cooperative Oncology Group (ECOG) single-arm, open-label phase II study was designed to determine the efficacy and toxicity of the combination of sorafenib with docetaxel and cisplatin in metastatic and advanced gastric and GEJ adenocarcinoma.

PATIENTS AND METHODS

Eligibility

Patients enrolled onto this study had measurable, histologically confirmed advanced or metastatic gastric or GEJ adenocarcinoma. Baseline imaging studies were conducted within 4 weeks of study entry. The tumor location for each patient entered onto the study was specified using the Siewert classification.¹⁷ Patients were required to have an ECOG performance status of 0 or 1 and to be at least 18 years old. Previous adjuvant chemo- or chemoradiotherapy was allowed. Any other radiotherapy, chemotherapy, or investigational therapies, particularly inhibitors of tyrosine kinases, signal transduction, or angiogenesis for metastatic or advanced disease, were not permitted. Adequate organ function was required, as defined by absolute granulocyte count $\geq 1,500/\text{mm}^3/\text{dL}$, platelet count $\geq 100,000/\text{mm}^3/\text{dL}$, WBC $\geq 3,000/\mu\text{L}/\text{dL}$, serum creatinine $\leq 1.5 \text{ mg/dL}$, total bilirubin $\leq 2.0 \text{ mg/dL}$, and AST/ALT/alkaline phosphatase $\leq 2.5\times$ the upper limit of normal. Patients were required to not have acute active infection. Previous or concurrent other malignancies were not allowed, except nonmelanoma skin cancer and in situ cervical cancer or treated cancer from which the patient had been continuously disease-free for more than 5 years. Women could not be pregnant or breast-feeding, and women of childbearing potential and sexually active males were strongly advised to use an accepted and effective method of contraception. Patients with HIV infection receiving combination antiretroviral therapy and patients with known brain metastases were excluded from the study. Patients with concurrent uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, significant cardiac arrhythmia, or severe psychiatric illness or unstable social situation were not eligible. All patients must have been able to take oral medication without crushing, dissolving, or chewing tablets. All patients gave written informed consent. Approval from institutional ethic review boards of each participating center was obtained. Stratification was performed on the basis of disease site or tumor location (the Siewert classification type I, II, or III) and locally advanced unresectable disease versus distal metastatic disease.

Treatment Plan

Sorafenib was administered orally at a fixed dose of 400 mg twice a day for 21 days continuously. Patients were allowed to have sorafenib as a single agent when the combination therapy was discontinued because of docetaxel- or cisplatin-related toxicities in the absence of disease progression. Docetaxel 75 mg/m² was administered intravenously over 1 hour on day 1, and cisplatin 75 mg/m² was administered intravenously over 1 to 2 hours on day 1 of each

21-day cycle (approximately 30 to 60 minutes after docetaxel). Cycles were to be repeated until progression. All doses were to be based on actual rather than ideal body weight.

The primary goal of this single-arm, phase II study was to evaluate the objective response (complete response plus partial response) rate in patients with gastric and GEJ adenocarcinoma treated with sorafenib combined with docetaxel and cisplatin. Toxicity of the regimen, overall survival (OS), and progression-free survival (PFS) were the secondary end points.

Imaging studies for disease measurement were performed after every two cycles of treatment for assessment of response. Responders were defined as patients in whom changes in tumor measurements were confirmed by a repeat assessment conducted no less than 4 weeks after the criteria for response were first met. Response definitions were according to Response Evaluation Criteria in Solid Tumors (RECIST).¹⁸

The target response rate for the combination of sorafenib with docetaxel and cisplatin was defined as 40% to be viewed as promising. A true response rate of $\leq 20\%$ was to be deemed ineffective. The planned sample size of 36 eligible patients (allowing for 5% ineligibility) would then provide a maximum width of a 90% CI for the response rate of 29%. Data for all eligible and treated patients were used and hence included in the denominator. Point estimates and exact 90% CIs were shown for the primary end point of objective response (complete response plus partial response) as well as toxicity severity groupings. Kaplan-Meier estimates were used for OS and PFS.

RESULTS

Demographic information for all 44 eligible and treated patients is summarized in Table 1. Among all eligible patients, ages ranged from 28 to 85 years (median, 58 years) and most were male (84%) and white, non-Hispanic (89%). All patients had good performance status, with approximately 61% having ECOG performance status of 0. Thirty-five patients (80%) had distal metastatic disease, and nine had locally advanced unresectable disease. Among those nine patients, four had undergone a surgical procedure, and two had prior chemoradiotherapy. All 44 patients had adenocarcinoma, 66% of whom had poorly differentiated (grade 3) disease. A majority of patients (74%) had GEJ adenocarcinoma (71% with Siewert class type I). These features together establish these patients as a particularly poor-prognosis group.

The median number of treatments administered was 4.5 cycles (range, one to 28 cycles). Twenty patients (45%) received six or more cycles of therapy. Nine percent withdrew voluntarily from therapy.

Toxicity

Toxicity information is available for all 44 treated patients. Forty patients reported a treatment-related toxicity of grade 3 or worse

Table 1. Patient Characteristics at Registration

Characteristic	No. of Patients (N = 44)	%
Sex		
Male	37	84.1
Female	7	15.9
Race		
Black	1	2.3
White, Hispanic	4	9.1
White, non-Hispanic	39	88.6
Performance status		
0	27	61.4
1	17	38.6

Table 2. Grade 3 and 4 Toxicities of the Combination of Docetaxel, Cisplatin, and Sorafenib (N = 44)

Toxicity	Grade 3 (n = 20)	Grade 4 (n = 18)
Leukopenia	8	10
Lymphocytopenia	1	1
Neutropenia	11	17
Febrile neutropenia	3	—
Infection	3	1
Thrombocytopenia	2	—
Hemorrhage	—	1
Thrombosis/thromboembolism	1	2
Rectal perforation	1	—
Hypotension	2	—
Hand-foot reaction	7	—
Rash/desquamation	2	2
Fatigue	7	—
Anorexia	6	—
Dehydration	8	1
Diarrhea	6	—
Nausea	7	—
Vomiting	2	—

(91%; 90% CI, 80.4% to 96.9%) while on the treatment protocol. The most common grade 3 or worse toxicity was neutropenia, with 28 patients (64%) reporting grade 3 or worse neutropenia (90% CI, 50.1% to 75.7%; Table 2). Toxicity is considered to have led to death in two patients. One patient died as a result of infection with normal absolute neutrophil counts during the eighth cycle of treatment. The cause of death was cancer-related sepsis, deemed by the investigator to be probably related to treatment. The other patient died of tumor hemorrhage 3 days after completing four cycles of therapy; sorafenib was deemed a possible cause and the GEJ adenocarcinoma a definite cause. Other grade 3 and worse toxicity included hand-foot syndrome (23%), dehydration (20%), fatigue (16%), anorexia/nausea (16%), and rash/desquamation (10%). Grade 3 electrolyte disturbances (hypomagnesemia, hypokalemia, hyponatremia) were reported in 20% of patients.

The tolerability of combined sorafenib with docetaxel and cisplatin was analyzed. A total of 10 patients (23%) had their treatment terminated before four cycles of therapy because of chemotherapy-related toxicity. An additional 10 patients (23%) had either cisplatin or docetaxel dose reductions to 75%, and one patient had both medications reduced to 50% of initial doses. Of the 44 patients, 35 had their sorafenib dose held or modified per protocol at some point during their treatment. Nineteen patients needed a sorafenib dose interruption or modification during the first cycle. Eleven patients required two or more such sorafenib modifications.

Efficacy

Eighteen of the 44 eligible and treated patients achieved a partial response, for a rate of 41% (90% CI, 28.4% to 54.4%). An additional 14 patients (32%) achieved stabilization of their disease. Only three patients had confirmed disease progression at their initial disease assessment. There were nine patients whose disease status was unevaluable for response to therapy, mainly because of noncompliant imaging schedules (five patients).

PFS was defined as the time from registration to progression or the time from registration to death without documentation of progression. Patients not meeting either of the criteria for a PFS event were censored at the date of last disease assessment without progression (or registration, whichever is more recent). At the time of data analysis, 38 of 44 eligible and treated patients had experienced disease progression. The median PFS was 5.8 months (90% CI, 5.4 to 7.4 months). Overall survival was defined as time from registration to death from any cause. As the time of data analysis, 32 (72.7%) of the 44 eligible and treated patients were known to have died. The median overall survival is 13.6 months (90% CI, 8.6 to 16.1 month), with 11.3 months in those with distal metastatic disease and 17.6 months in those with locally advanced unresectable disease.

DISCUSSION

In this single-arm phase II study, we evaluated the efficacy and tolerability of sorafenib, an inhibitor of multiple tyrosine kinases, in combination with docetaxel and cisplatin, one of several active cytotoxic drug regimens in advanced gastric cancer. It has been suggested that the docetaxel and cisplatin combination has similar survival benefits compared with triple cytotoxic drug combinations (docetaxel, cisplatin, and fluorouracil or epirubicin, cisplatin, and fluorouracil).¹⁶ All 44 patients included in this study had relatively good performance status (ECOG 0 or 1). A substantial majority (80%) had distal metastatic disease, and 66% had poorly differentiated adenocarcinoma, which represents an advanced and relatively aggressive population of patients with gastric and GEJ cancer. Despite these attributes, the outcome of this trial was notable for a favorable response profile.

For this initial screening trial, we chose response rate as the primary end point, and wished to observe in addition a favorable PFS and/or OS. The combination of sorafenib with docetaxel and cisplatin achieved the primary end point of the study with response rate of 41%. This response rate in a cooperative group setting compares favorably to the response rate of 37% with docetaxel, cisplatin, and fluorouracil in a large European trial⁴ and to the response rates with three-drug combinations of epirubicin, fluoropyrimidine, and platinum cytotoxics investigated by Cunningham et al.³ (response rates ranging from 42% to 48%) in another large multicenter trial. Furthermore, the secondary end points were similarly encouraging. The PFS at 5.8 months was in the range identified with three-drug regimens in these trials, whereas OS at 13.6 months compares favorably to the 11 to 12 months reported by Cunningham et al.³ The survival with the sorafenib-containing combination studied here (11.3 months in those with distal metastatic disease and 17.6 months in the locally advanced unresectable population) compares favorably to reported double or triple cytotoxic chemotherapy combinations in such patient populations.^{3,4,19} The results of this study suggest that sorafenib may contribute additional antitumor effects to the combination of docetaxel and cisplatin in the treatment of metastatic and advanced unresectable gastric and gastroesophageal junction adenocarcinoma cancer. Although this is a single-arm phase II trial, these results in the broad cooperative group setting argue strongly for a randomized phase II trial of the incorporation of sorafenib with chemotherapy in gastric cancer.

The basis of the favorable results in this population is not known; although sorafenib inhibits multiple kinases in the achievable plasma

concentration range, several lines of evidence point to the importance of VEGFR-2 receptor inhibition as a major contributor: selective single-agent activity in renal cell cancer, hypertension as a frequent toxic effect, together with dynamic contrast-enhanced magnetic resonance imaging findings of decreased tumor perfusion and vascular permeability. A recent study presented in abstract form supports a role for angiogenesis inhibition along with chemotherapy in gastric cancer.²⁰ Here bevacizumab added to a modified triple-agent regimen of docetaxel, cisplatin, and fluorouracil yielded a response rate of 54%. It may be considered that the potential contribution of sorafenib may be broader than angiogenesis inhibition on the basis of its inhibition of raf isoforms. It has been shown that in murine models, sorafenib inhibits proliferation in endothelial cells, though less in tumor cells. The putative marrow origin of some gastric cancers should prompt more detailed analysis of pharmacodynamic effects as part of the further development of sorafenib in this disease.

We were encouraged that adding sorafenib to the docetaxel/cisplatin regimen did not show extra or unexpected toxicity. The toxicity profile of the combination was manageable and similar to that previously reported for the docetaxel and cisplatin combination. Neutropenia was the most common grade 3 to 4 toxicity (63.3%) and is expected with the docetaxel and cisplatin combination. Roth et al¹⁶ reported that 76% of patients developed grade 3 to 4 neutropenia with docetaxel/cisplatin in their randomized phase II study. The grade 3 to 4 neutropenia rate was 82% with the combination of docetaxel, cisplatin, and fluorouracil from the V325 phase III study and was also common in other commonly used regimens: 57% with cisplatin and fluorouracil; 42% with epirubicin, cisplatin, and fluorouracil; and 51% with epirubicin, cisplatin, and capecitabine combination.^{3,4} It is important to point out that prophylactic growth factor was not permitted initially in the protocol so as not to confound evaluation of the bone marrow suppression from the combination. Nevertheless, less toxic cytotoxic chemotherapy regimen (eg, the combination of docetaxel with oxaliplatin) may be preferable in the future study. Hand-foot reaction is an expected adverse effect of sorafenib. The tolerability of sorafenib in combination with docetaxel and cisplatin is similar as when it is administered as a single agent.^{21,22} Somewhat surprisingly, there were no hypertension or vascular events reported.

The success of biologically targeted agents in colorectal, lung, breast, renal cell, and liver cancers support the idea that similar approaches may benefit patients with gastric and GEJ cancers. These findings suggest that sorafenib may have a role in this disease. Moreover, with an effective biologic agent in the combination therapy, we may be able to have not only more effective, but also less toxic regimens.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Weijing Sun, Bayer/Onyx; Al B. Benson III, Bayer/Onyx **Research Funding:** Peter J. O'Dwyer, Bayer/Onyx **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Weijing Sun, Paul Catalano, Peter J. O'Dwyer, Al B. Benson III

Financial support: Al B. Benson III

Administrative support: Weijing Sun, Peter J. O'Dwyer, Al B. Benson III

Provision of study materials or patients: Weijing Sun, Peter J. O'Dwyer, Rafat H. Ansari, Al B. Benson III

Collection and assembly of data: Weijing Sun, Mark Powell, Paul Catalano

Data analysis and interpretation: Weijing Sun, Mark Powell, Paul Catalano, Peter J. O'Dwyer, Al B. Benson III

Manuscript writing: Weijing Sun, Mark Powell, Peter J. O'Dwyer, Al B. Benson III

Final approval of manuscript: Weijing Sun, Mark Powell, Paul Catalano, Peter J. O'Dwyer, Rafat H. Ansari, Al B. Benson III

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