A phase II study of bevacizumab, oxaliplatin, and docetaxel in locally advanced and metastatic gastric and gastroesophageal junction cancers

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Background: Bevacizumab has demonstrated antitumor activity in multiple diseases. This phase II study was undertaken to determine the effects of adding bevacizumab to a regimen of docetaxel and oxaliplatin in patients with advanced adenocarcinoma of the stomach or gastroesophageal junction.

Patients and methods: Previously untreated patients with locally advanced or metastatic disease and a performance status (PS) of 0–1 were eligible for this study. Patients received bevacizumab at 7.5 mg/kg, docetaxel at 70 mg/m^2, and oxaliplatin at 75 mg/m^2 administered on day 1 of a 21-day cycle. The primary end point of the study was progression-free survival (PFS).

Results: A total of 38 eligible patients (median age 57 years, 45% gastric, 55% PS 0) were enrolled on to the study. Median PFS was 6.6 months [95% confidence interval (CI) 4.4–10.5] and median survival 11.1 months (95% CI 8.2–15.3). Complete responses were documented in 2 (5%) patients, partial responses in 14 (37%), and stable disease in 14 (37%). No treatment-related deaths were observed. The most commonly reported grade 3–4 toxicity was neutropenia (34%), and gastrointestinal perforation occurred in three patients (8%).

Conclusion: The combination of bevacizumab, docetaxel, and oxaliplatin has promising activity for further evaluation in randomized trials.

Key words: bevacizumab, docetaxel, gastric cancer, oxaliplatin

introduction

Gastric cancer is the second leading cause of cancer death worldwide [1–2]. In the USA, the incidence of gastroesophageal junction (GEJ) cancer has increased threefold, making it among the cancers with the fastest rising incidence [3]. Therapeutic research in gastric and GEJ cancers has focused on screening cytotoxic agents. Despite decades of research, the impact of conventional chemotherapy combinations on advanced gastric and GEJ cancers has reached a plateau. Combinations of two or three cytotoxic drugs demonstrate objective response rates and median progression free-survival (PFS) estimates of 21%–47% and 3.4–7.4 months, respectively[4–6]. Median survival generally remains <1 year.

Cytotoxic agents commonly used in this disease include platinum compounds, fluoropyrimidines, taxanes, irinotecan, and anthracyclines. The addition of docetaxel to cisplatin and 5-fluorouracil (5-FU) resulted in a significantly higher response rate (39% versus 23%), a longer time to progression (5.2 versus 3.7 months), and an improved median overall survival (OS; 10.2 versus 8.5 months) [4]. Cunningham et al. [5] evaluated the impact of substituting oxaliplatin for cisplatin and capecitabine for 5-FU in the epirubicin, cisplatin, and 5-FU (ECF) regimen. Oxaliplatin as compared with cisplatin demonstrated comparable efficacy, with a lower incidence of myelosuppression, thromboembolic complications, and nephrotoxicity. The combination of docetaxel and oxaliplatin has been evaluated in gastric cancer in four phase II trials [7–10]. The observed response rates, median PFS, and median OS were 34%–55%, 4.3–8.9 months, and 8.5–12.7 months, respectively. These results indicated that the oxaliplatin–docetaxel combination is an active and a safe platform for incorporation of targeted agents.

Angiogenesis is an essential step for tumor growth and metastasis [11]. The vascular endothelial growth factor (VEGF) promotes the proliferation and migration of endothelial cells [12]. In gastric cancer, overexpression of the VEGF is associated

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with increasing microvascular density, advancing stage, and reduced survival [13–15]. Inhibition of VEGF in preclinical models of gastric cancer resulted in increased apoptosis and reduction in metastases [16]. Furthermore, inhibition of VEGF by bevacizumab is thought to improve the efficacy of cytotoxic therapy in colorectal [17], breast [18], and non-small-cell lung cancers [19]. Two phase II trials in patients with advanced gastric and GEJ cancers reported increased median PFS (8.3 and 12 months) and OS (12.3 and 16.2 months) with the addition of bevacizumab to cisplatin-based chemotherapy [20, 21] The rationale of this multi-institutional study was to evaluate the efficacy and tolerability of bevacizumab in combination with oxaliplatin and docetaxel in patients with advanced gastric and GEJ cancers.

materials and methods

patient eligibility

Patients were required to have a histological or cytological diagnosis of locally advanced unresectable or metastatic adenocarcinoma of stomach or GEJ, Southwest Oncology Group performance status of 0–1, measurable disease, and adequate hematological, renal, and hepatic function defined by the following criteria: neutrophil count $\geq$1500/mm^3, platelet count $\geq$100 000/mm^3, serum creatinine $\leq$1.5 mg/dl, total serum bilirubin less than or equal to the upper limit of the institutional normal range (ULN), and serum alkaline phosphatase and aspartate transaminase $\leq$2.5 times ULN. Patients were excluded if they had other active malignancy within the preceding year except for adequately treated basal cell cancer, squamous cell skin cancer, or *in situ* cervical cancer. Additional exclusion criteria included uncontrolled hypertension, brain metastases, history of deep venous thrombosis (DVT) requiring anticoagulation, or arterial thrombotic events including angina, myocardial infarction, or cerebrovascular accident within 1 year. Patients were also ineligible if they had a major surgery within 4 weeks, incompletely healed surgical wounds, or an active peptic ulcer disease. Previous chemotherapy for gastric or GEJ cancer was not allowed except for patients relapsing >6 months after the completion of adjuvant chemotherapy that did not include a taxane or platinum compound. All patients provided written informed consent in accordance with the institutional Human Investigation Committee guidelines before enrolment on the study.

study design and treatment plan

Oxaliplatin (Eloxatin; Sanofi-Aventis, Bridgewater, NJ) 75 mg/m^2 i.v. and docetaxel (Taxotere; Sanofi-Aventis) 70 mg/m^2 i.v. were administered on day 1 of a 21-day treatment cycle. Bevacizumab (Avastin; Genentech Inc., San Francisco, CA) was administered at a dose of 15 mg/kg i.v. on day 1 of the treatment cycle. After the occurrence of two gastrointestinal (GI) perforations in the first five patients, the dose of bevacizumab was reduced to 7.5 mg/kg for the remainder of the study.

A new cycle of therapy could begin only if the neutrophil count was $\geq$1500/mm^3, platelet count was $\geq$100 000/mm^3, and all relevant non-hematological toxic effects were grade 1 or lower. Dose reductions were based on the toxicity in the preceding cycle. The docetaxel and oxaliplatin doses were reduced by 20% for any grade 3 or 4 hematological toxicity, except anemia. A 20% dose reduction of oxaliplatin was carried out for grade 3 neuropathy lasting >7 days but resolving before the next treatment cycle. Dose reduction of 20% for oxaliplatin and docetaxel was carried out for grade 2 neuropathy present at day 1 of a treatment cycle. No dose reduction was carried out for grade 3 or lower neuropathy lasting <7 days. Oxaliplatin and docetaxel were discontinued for grade 3 neuropathy

present at day 1 of a treatment cycle or for grade 4 neuropathy regardless of duration. Treatment was held for grade 3 or 4 non-hematological toxic effects (excluding nausea or vomiting), until resolution to grade 1 or lower, and resumed at a 20% reduction of docetaxel and oxaliplatin doses. No dose adjustments for bevacizumab were planned. Bevacizumab was discontinued for grade 4 hypertension, grade 3 or 4 hemorrhage, grade 4 venous thromboembolic event (VTE), grade 4 proteinuria, or any grade of GI perforation, wound dehiscence, or arterial thromboembolic event. Patients requiring a delay in therapy of longer than 2 weeks because of toxicity or requiring more than two dose reductions were removed from the study. In addition, patients were removed from study for disease progression, unacceptable toxicity, or withdrawal of consent.

on-study evaluation

Efficacy end points of objective response, PFS, and OS were assessed. Imaging studies were carried out at baseline and repeated after every two cycles of therapy or whenever there was any clinical suspicion of disease progression. Objective tumor responses were determined and categorized by the RECIST criteria [22] as complete response, partial response, disease progression, or stable disease. Objective responses required at least one additional confirmatory follow-up scan to be carried out at $\geq$3 weeks after the first documentation of response. OS was measured from study registration to the date of death or last follow-up. PFS was measured from study registration to the date of first documented progressive disease or death. Time to treatment failure (TTF) was measured from study registration to the date of first documented progressive disease or date off treatment due to toxicity, patient refusal, or death, whichever occurred first. Response duration (RD) was measured from the start of objective response to the date of first evidence of relapse or censored at the last tumor assessment for those patients still responding. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [23].

statistical methods

The primary end point was PFS. A single-stage, one-sample survival-type study design was planned. The primary goal was to detect evidence (with 90% power and one-sided type I error of 0.15) that patients on this new regimen had a median PFS of at least 6 months, in contrast to an assumed population reference value of 4 months. Due to the lack of reasonably effective treatments for this disease, we purposely relaxed the type I error probability to $\leq$0.15 but limited the type II error probability to $\leq$0.10. Under the assumptions of exponential PFS times and uniform accrual rate, the required sample size was $N = 38$ patients via the method of Lawless.

Baseline patient characteristics, response, and toxic effects were described using summary statistics. Wilson's method was used to compute a 95% confidence interval (CI) for a proportion. Standard Kaplan?Meier (K–M) estimates of the censored RD, TTF, PFS, and OS distributions were computed. PFS was the primary end point of the study. Due to modest sample sizes (or numbers of events), time-to-event (TTE) statistics (e.g. median, 6-month rate) were estimated more conservatively using linear interpolation between successive event times on the K?M curves [24]. All point estimates of TTE statistics were accompanied by a 95% CI. Censored PFS was compared by disease site using the log-rank test.

results

patient characteristics

Study patients were enrolled from 25 July 2005 until 14 July 2009. Patient characteristics are shown in Table 1. Thirty-nine patients were enrolled on to the study. One patient was ineligible. Twenty-one patients had cancer of GEJ and 17

Table 1. Characteristics of the 38 eligible patients with advanced gastroesophageal junction (GEJ) or gastric cancer treated with bevacizumab, docetaxel, and oxaliplatin

Characteristic	n	%	Years
Age: median (range)			57 (22–73)
Sex			
Male	29	76	
Female	9	24	
Race			
African American	4	11	
Caucasian	32	84	
Other	2	5	
Prior surgery			
No	37	97	
Yes	1	3	
Performance status			
0	21	55	
1	17	45	
Site of primary tumor			
Stomach	17	45	
GEJ	21	55	
Stage			
Locally advanced	2	5	
Metastatic disease	36	95	
Liver	19	50	
Lung	14	37	
Peritoneum	4	11	
Other (bone, lymph nodes)	27	71	

patients had primary gastric cancer. One patient had prior surgery for localized disease, and none had received adjuvant chemotherapy. Of the 36 patients with metastatic disease, 22 had more than one site of metastasis including liver (19 patients), lung (14), lymph nodes (23), peritoneum (4), and bone (3).

efficacy

A total of 208 cycles were administered, with a median of 6 cycles given per patient (range 1–12). Thirteen patients (34%) are still receiving therapy. Reasons for removal from the study included disease progression (12 patients), neuropathy (5), GI perforation (3), tracheoesophageal (TE) fistula (1), DVT (1), worsening dysphagia (1), and patient preference (2). Eleven patients subsequently went on to receive second-line therapy.

The median PFS for all 38 eligible patients was 6.6 months (95% CI 4.4–10.5 months). Twenty patients were still without progression, and their median follow-up for progression was 3.0 months. The K–M estimate of the probability of PFS is given in Figure 1. No significant difference in PFS was observed between patients with gastric and GEJ tumors ($P = 0.435$). The median TTF was 4.5 months (95% CI 3.6–6.3 months). The median OS was 11.1 months (95% CI 8.2–15.3 months). Twenty-four patients were still alive, and their median follow-up for survival was 3.9 months. The K–M estimate of the probability of OS is shown in Figure 2.
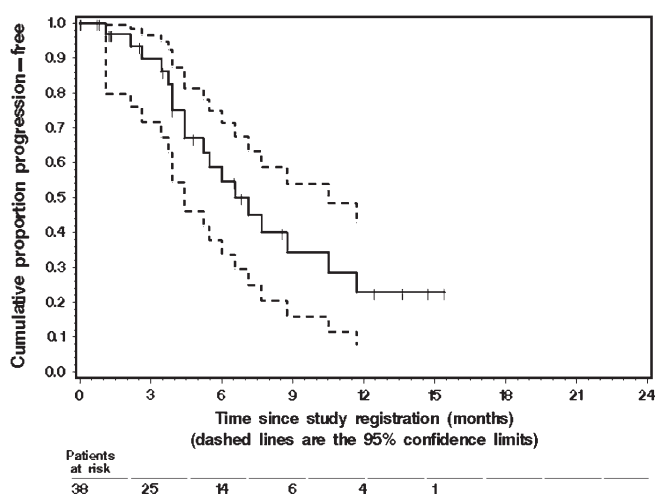

Figure 1. The Kaplan–Meier estimate of progression-free survival (PFS) in the 38 eligible patients with metastatic gastroesophageal junction cancer or gastric cancer who were treated with docetaxel, oxaliplatin, and bevacizumab. The dashed lines represent the 95% confidence interval (CI) about each successive estimate of the progression-free rate. The median PFS was 6.6 months (95% CI 4.4–10.5 months). The 6-month PFS rate was 55% (95% CI 35% to 74%).
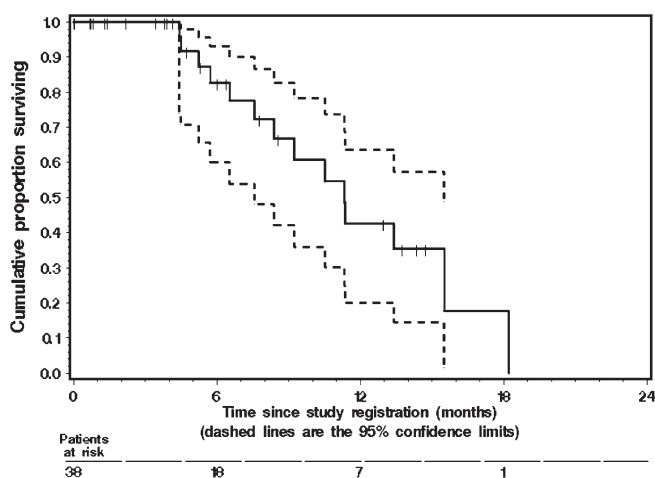

Figure 2. The Kaplan–Meier estimate of overall survival (OS) in the 38 eligible patients with metastatic gastroesophageal junction cancer or gastric cancer enrolled in the study. The dashed lines represent the 95% confidence interval (CI) about each successive estimate of the survival rate. The median OS was 11.1 months (95% CI 8.2–15.3 months). The 12-month OS rate was 40% (95% CI 17% to 63%).

Objective tumor responses were seen in 16 patients (42%, 95% CI 28% to 58%) including two complete responses. Stable disease as the best response was seen in an additional 14 patients. The median RD was 4.0 months (95% CI 1.3–10.8 months). Seven patients were still in remission, and their median follow-up for relapse was 1.9 months.

toxicity

The treatment was generally well tolerated in the outpatient setting. No treatment-related deaths were reported. Table 2 summarizes the grade 3 and 4 toxic effects observed in the

study. The most common grade 3–4 toxic effects were hematological. Thirteen patients had grade 3–4 neutropenia. Two patients had a grade 3 febrile neutropenia. Five patients had grade 2 or 3 neuropathy. The median number of cycles before development of neuropathy was 8 (range 6–10 cycles).

Table 2. The frequency of treatment-related toxic effects in 38 treated patients with gastric or gastroesophageal junction cancer expressed as the worst toxicity per patient

Toxicity type	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Bevacizumab related				
GI perforation	0 (0)	0 (0)	1 (3)	2 (5)
Tracheoesophageal fistula	0 (0)	0 (0)	0 (0)	1 (3)
Hypertension	4 (11)	1 (3)	2 (5)	0 (0)
Venous thromboembolism	1 (3)	0 (0)	1 (3)	0 (0)
Proteinuria	1 (3)	1 (3)	0 (0)	0 (0)
Hematological				
Neutropenia	0 (0)	1 (3)	5 (13)	8 (21)
Anemia	1 (3)	2 (5)	0 (0)	0 (0)
Leukopenia	2 (5)	0 (0)	1 (3)	0 (0)
Neuropathy				
Acute	3 (8)	6 (16)	2 (5)	0 (0)
Chronic	5 (13)	0 (0)	3 (8)	0 (0)
GI-related toxic effects				
Stomatitis	1 (3)	0 (0)	0 (0)	0 (0)
Nausea	7 (18)	3 (8)	4 (11)	0 (0)
Vomiting	3 (8)	1 (3)	2 (5)	0 (0)
Diarrhea	7 (18)	5 (13)	3 (8)	0 (0)
Hepatotoxicity				
Aspartate transaminase	1 (3)	0 (0)	0 (0)	0 (0)
Alanine transferase	1 (3)	0 (0)	0 (0)	0 (0)
Alkaline phosphatase	0 (0)	1 (3)	0 (0)	0 (0)
Other				
Dehydration	0 (0)	0 (0)	4 (11)	0 (0)
Fever	1 (3)	0 (0)	2 (5)	0 (0)
Infection	0 (0)	1 (3)	0 (0)	0 (0)
Fatigue	7 (18)	7 (18)	2 (5)	0 (0)
Anorexia	2 (5)	1 (8)	2 (5)	0 (0)
Myalgia	1 (3)	0 (0)	0 (0)	0 (0)
Alopecia	0 (0)	1 (3)	0 (0)	0 (0)

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 scale for toxicity grading.
GI, gastrointestinal.

Bevacizumab-related toxic effects included hypertension, VTEs, GI perforation, and TE fistula. No arterial thrombotic events, wound dehiscence, hemorrhage, or grade 4 proteinuria was observed. Bevacizumab-related grade 3 hypertension occurred in two patients (5%). One patient (3%) developed a grade 3 DVT after the first cycle of therapy.

GI perforation occurred in three (8%) patients each of whom had intact primary tumors and two of whom also had peritoneal metastases. GI perforation developed following the second cycle of chemotherapy in each patient. In one, the perforation was at a gastric ulcer site and the patient required surgery. The site of perforation could not be ascertained in the second patient who was managed medically. The third patient had the perforation in the sigmoid colon and underwent successful surgical repair. One additional patient had a TE fistula develop after an 11th cycle of therapy. This patient had previously received chemoradiotherapy to the mediastinum and had surgical resection of the primary tumor. All four patients went on to receive additional alternate systemic therapy. Two perforations occurred in the first five patients enrolled in the study raising safety concerns and leading to a reduction in the bevacizumab dose from 15 to 7.5 mg/kg in the remaining cohort of patients.

In total, 20 patients required hospitalization for listed reasons during study therapy [neutropenia (6), fever (2), dehydration (4), GI perforation (3), infection (2), pain (2), TE fistula, DVT].

discussion

The impact of conventional cytotoxic therapy on gastric and GEJ adenocarcinoma remains modest at best. An increase in efficacy gained by the use of a triplet cytotoxic combination (e.g. with docetaxel, cisplatin, and 5-FU or ECF) has been offset by increased toxic effects associated with these regimens. The inclusion of a targeted agent such as bevacizumab into a cytotoxic regimen might improve antitumor activity with less of an increase in toxicity. In this multi-institutional study, we evaluated the impact of adding bevacizumab to oxaliplatin and docetaxel in patients with advanced gastric and GEJ cancers. The regimen resulted in an objective response rate, median PFS, and median OS of 42%, 6.6 months, and 11.1 months, respectively. Three other phase II trials have evaluated bevacizumab in combination with cytotoxic chemotherapy in untreated gastric and GEJ cancers [20, 21, 25]. These trials differed in the patient selection and the chemotherapy regimens used and are summarized in Table 3 with our trial. In total, the reported response rates, PFS, and OS in these trials indicate that

Table 3. Phase II trials of bevacizumab + chemotherapy in gastric and GEJ tumors

Regimen	Disease site	n	ORR (%)	Median PFS (months)	Median OS (months)	Reference
Cisplatin/irinotecan	GEJ/gastric	47	47	8.3	12.3	Shah et al. [20]
Docetaxel/cisplatin/5-FU	GEJ/gastric/esophagus	44	67	12.0	16.2	Kelsen et al. [21]
Docetaxel/cisplatin/ irinotecan	GEJ/gastric/esophagus	26	68	N/A	N/A	Enzinger et al [25]
Oxaliplatin/docetaxel	GEJ/gastric	38	42	6.6	11.1	Current trial

GEJ, gastroesophageal junction; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; 5-FU, 5-fluorouracil; N/A, not available.

bevacizumab is active in gastric and GEJ tumors. The definition and magnitude of that benefit with bevacizumab in this disease will require randomized trials.

The bevacizumab, oxaliplatin, and docetaxel combination in general was well tolerated. The addition of bevacizumab did not significantly change the side-effect profile associated with oxaliplatin and docetaxel. However, bevacizumab-related toxicity in this trial, including GI perforations observed in three patients (8%), warrants comment. The perforations appear to occur early in the course of therapy, which is similar to the pattern reported in advanced colorectal cancer (CRC) treated with bevacizumab. Although the perforations resulted in significant morbidity, there were no deaths due to perforations in our study. The incidence rates of GI perforation observed in two previous trials of bevacizumab in gastric and GEJ cancers were 2.5% and 6% [20, 21]. The reported rates of GI perforation in patients with gastric cancer receiving systemic chemotherapy without bevacizumab and in patients with CRC treated with bevacizumab were 1.1% and 1.8%, respectively [26, 27]. These results clearly indicate that there is a higher likelihood of GI perforation in patients with gastric and GEJ tumors treated with bevacizumab. This may be attributed to a higher proportion of patients with an unresected primary tumor or peritoneal metastases. A recent meta-analysis of GI perforations in randomized trials of bevacizumab revealed an increased risk for perforation in patients receiving the 5 mg/kg per week dose as compared with those receiving the 2.5 mg/kg per week dose [28]. Strategies to address the higher risk for GI perforations in future clinical trials of bevacizumab in gastric or GEJ tumor could include consideration of a lower dose of bevacizumab [28] or exclusion of patients with clinical risk feature for perforation such as diffuse peritoneal metastasis or unresected primary tumor. One patient who had previously received radiation to the chest developed a TE fistula. The safety of administering bevacizumab after thoracic radiation therapy in patients with GEJ cancers requires further evaluation.

The incidence of other bevacizumab-related side-effects appeared to be lower in our study as compared with previously reported trials in patients with gastric and GEJ cancers. Grade 3 hypertension was observed in only 5% of the patients and was lower than the 28% rate previously reported in gastric and GEJ cancer trials [20]. VTEs were observed in one patient (3%) in the current study. The incidence of grade 3–4 VTE observed with bevacizumab in other gastric and GEJ cancer trials was 25%–31% [20, 21]. This difference in the toxicity profile between the current study and previously reported data may be related to the use of a lower dose of bevacizumab and/or the concurrent chemotherapy regimen. In CRC trials, the incidence of bevacizumab-related side-effects was similar in trials that used 2.5 and 5 mg/kg per week dose of bevacizumab [17, 29], and therefore, the reduction in the dose of bevacizumab in our study is unlikely to explain the difference in the observed rate of grade 3 hypertension and VTE. Instead, the lower incidence of these toxic effects observed in our study may be related to the substitution of oxaliplatin for cisplatin. This is supported by the results of the REAL-2 (Randomized ECF for Advanced and Locally advanced Esophagogastric cancer) trial where the incidence rates of VTE with cisplatin and oxaliplatin arms were

13.3%–16.9% and 7.5%–7.7%, respectively [5]. Similarly, the impact of cisplatin on renal function may explain the increased incidence of hypertension.

In conclusion, the results of this trial support the development of and need for further evaluation of bevacizumab in gastric and GEJ adenocarcinoma. In addition and perhaps more importantly, the identification and validation of predictive biomarkers for response or resistance to anti-VEGF therapies in gastric or GEJ cancer is vital to help select those patients most likely to benefit from this type of therapy.

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