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Invest New Drugs (2011) 29:1449–1458
DOI 10.1007/s10637-010-9438-y

PHASE II STUDIES

Phase II study of sunitinib as second-line treatment for advanced gastric cancer

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Received: 9 February 2010 / Accepted: 19 April 2010 / Published online: 12 May 2010

Summary *Purpose.* This phase II, open-label, multicenter study assessed the oral, multitargeted, tyrosine kinase inhibitor sunitinib in patients with advanced gastric or gastroesophageal junction adenocarcinoma who had received prior chemotherapy. *Experimental design.* Patients received sunitinib 50 mg/day on Schedule 4/2 (4 weeks on treatment, followed by 2 weeks off treatment). The primary endpoint was objective response rate; secondary endpoints included clinical benefit rate, duration of response, progression-free survival (PFS), overall survival (OS), pharmacokinetics, pharmacodynamics, safety and tolerability, and quality of life. *Results.* Of 78 patients enrolled,

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most had gastric adenocarcinoma (93.6%) and metastatic disease (93.6%). All were evaluable for safety and efficacy. Two patients (2.6%) had partial responses and 25 patients (32.1%) had a best response of stable disease for ≥6 weeks. Median PFS was 2.3 months (95% confidence interval [CI], 1.6–2.6 months) and median OS was 6.8 months (95% CI, 4.4–9.6 months). Grade ≥3 thrombocytopenia and neutropenia were reported in 34.6% and 29.4% of patients, respectively, and the most common non-hematologic adverse events were fatigue, anorexia, nausea, diarrhea, and stomatitis. Pharmacokinetics of sunitinib and its active metabolite were consistent with previous reports. There were no marked associations between baseline soluble protein levels, or changes from baseline, and measures of clinical outcome. *Conclusions*. The progression-delaying effect and manageable toxicity observed with sunitinib in this study suggest that although single-agent sunitinib has insufficient clinical value as second-line treatment for advanced gastric cancer, its role in combination with chemotherapy merits further study.

Keywords Sunitinib · Gastric cancer · Tyrosine kinase inhibitor · Pharmacokinetics · Pharmacodynamics

Introduction

Gastric cancer is the fourth most common cancer globally, with an estimated 934,000 new cases in 2002 [1]. Patients presenting or relapsing with metastatic disease have a poor prognosis, and with 700,000 deaths annually, gastric cancer is the second most common cause of death from cancer worldwide [1]. In Japan and Korea, mass screening has led to a shift towards diagnosis at earlier stages of the disease, and the 5-year survival rate is relatively high at 40–60% [2, 3]. Globally, 5-year survival is lower, at approximately 20% [2]. In clinical trial patients with advanced gastric cancer, reported median survival commonly ranges from 8 months to 11 months in the first-line treatment setting and approximately 5 months to 6 months in the second-line treatment setting [4–6].

Combination chemotherapy prolongs survival and improves quality of life in patients with gastric cancer, compared with best supportive care [7, 8]. Recently, a meta-analysis showed a small but significant survival benefit for combination chemotherapy versus single-agent chemotherapy, though at a cost of higher toxicity [8]. There is no globally accepted standard regimen for first-line treatment of advanced gastric cancer, though a 5-fluorouracil-based regimen in combination with a platinum analog is reported to be the most widely accepted regimen [9]. As yet, there are no data showing acceptable efficacy for gastric cancer in the second line setting. New treatment strategies are still needed to improve the survival of patients with advanced gastric cancer, both in the first-line treatment setting and in those patients whose disease has progressed during or after chemotherapy.

Tumor angiogenesis, growth, and metastasis can be inhibited by blocking receptor tyrosine kinases (RTKs), including vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs), which are both expressed or overexpressed in gastric cancer [10–12]. VEGF and PDGF-A expression have been linked to tumor progression and poor survival in gastric cancer [13, 14], and both VEGF and VEGFR expression have been correlated with increasing stage of disease [15]. Treatments that specifically interrupt RTK signalling pathways have been investigated in phase II studies in advanced gastric cancer, including a study of single-agent gefitinib [16, 17] and targeted therapies such as bevacizumab [18], cetuximab [19, 20], and erlotinib [21] in combination with chemotherapy. These targeted agents act through a single receptor pathway. However, many gastric tumors co-express several RTKs [10] and drugs targeting multiple RTKs involved in angiogenesis may deliver additional benefits relative to single receptor target inhibition.

Sunitinib malate (SUTENT®; Pfizer Inc., New York, NY) is an oral, multitargeted tyrosine kinase inhibitor of VEGFR-1, -2, and -3, PDGFR-α and -β, and several other related RTKs [22–24]. In a murine xenograft model of gastric carcinoma, sunitinib exhibited antiangiogenic and antitumor activity at a dose of 40 mg/kg/day (Pfizer Inc. Data on file). At a dose of 50 mg/day given on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment), sunitinib has demonstrated superior efficacy to previous standard treatments and acceptable tolerability in gastrointestinal stromal tumors refractory or intolerant to imatinib, and advanced renal cell carcinoma [25, 26]. This phase II trial investigated the use of single-agent sunitinib in patients with previously-treated, advanced gastric carcinoma.

Materials and methods

Patients

Patients eligible for inclusion were males and females aged ≥18 years with histologically or cytologically confirmed

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diagnosis of gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (i.e. adenocarcinoma with >50% extension in the stomach) that was not amenable to surgery, radiation, or combined modality therapy with curative intent, and who had disease progression or recurrence after treatment with one prior chemotherapy regimen for advanced or metastatic disease (last dose ≥4 weeks before study entry).

Patients who had received prior adjuvant therapy were eligible if relapse occurred >6 months after completing adjuvant treatment and had received one regimen for relapsed disease. Those who had received prior palliative radiotherapy to metastatic lesions were also eligible, if at least one measurable lesion had not been irradiated. Patients were excluded if they had: major surgery or radiation therapy <4 weeks before starting study treatment; grade 3 hemorrhage (based on the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) <4 weeks before starting study treatment; presence of clinically relevant ascites (requiring paracentesis) and/or grade ≥2 weight loss; active inflammatory bowel disease, partial or complete bowel obstruction, or chronic diarrhea; known brain metastases, spinal cord compression, or carcinomatous meningitis; uncontrolled hypertension; clinically significant cardiovascular disease (severe/unstable angina, myocardial infarction, coronary artery bypass graft, symptomatic congestive heart failure), pulmonary embolism, or cerebrovascular accident within 12 months prior to study drug administration; ongoing cardiac dysrhythmias (NCI CTCAE grade ≥2), atrial fibrillation, or prolongation of the QTc interval; or any other severe acute or chronic medical or psychiatric condition making the patient inappropriate for entry into the study in the judgment of the investigator.

All patients had: measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST); Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1; adequate hepatic, renal, and hematologic function; and life expectancy of ≥3 months; and were required to provide written, informed consent.

Study design and treatment

In this phase II, open-label, 2-stage, multicenter study, patients received oral sunitinib 50 mg/day on Schedule 4/2 (4 weeks on treatment, followed by 2 weeks off treatment) in repeated 6-week cycles, until disease progression, unacceptable toxicity, or withdrawal of consent. Dose reduction to 37.5 mg/day and then to 25 mg/day was allowed, and therapy could be interrupted or delayed for up to 4 weeks according to individual tolerability.

The primary objective of this study was to determine the antitumor activity of single-agent sunitinib in this population. The primary endpoint was the overall objective response rate (ORR), defined as the percentage of all patients who experienced a confirmed complete response (CR) or partial response (PR), as defined by RECIST [27]. Secondary endpoints included duration of response (in those with an objective response of CR or PR); clinical benefit rate (CBR, defined as the percentage of patients with CR, PR, or stable disease [SD] ≥24 weeks); progression-free survival (PFS); time to progression (TTP); OS; one-year survival rate; safety and tolerability; health-related quality of life (HRQoL); and measurement of trough sunitinib and SU12662 (the major active metabolite of sunitinib) plasma levels, as well as levels of plasma biomarkers (VEGF, soluble (s) VEGFR2, sVEGFR3, and sKIT). This study was approved by the institutional review board of each participating center and was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, as well as applicable local laws and regulatory requirements.

Assessments

Tumor response was assessed according to RECIST version 1.0, with a minor modification such that lesions assessed using spiral computed tomography (CT) scan qualified as measurable if they were twice the reconstruction interval used (up to 8 mm) and at least 10 mm at baseline. Tumor response was assessed: on day 28 of every cycle; whenever disease progression was suspected; to confirm a CR or PR (at least 4 weeks after initial documentation of response); and at the end of study treatment or withdrawal from the study. Tumors were imaged using CT scan or magnetic resonance imaging.

Safety was assessed at regular intervals by monitoring and recording adverse events and by measuring hematology and clinical chemistries. Additional safety assessments included 12-lead electrocardiograms, vital signs, physical examination, and ECOG performance status. Adverse events were graded using NCI CTCAE, version 3.0.

Blood samples were taken for pharmacokinetic analysis of sunitinib and SU12662 prior to sunitinib treatment on study day 1, on days 14 and 28 of the first treatment cycle, on days 1 and 28 of cycles 2 and 3, and on day 28 of cycle 5. Sunitinib and SU12662 concentrations were analyzed using a validated, sensitive, and specific isocratic liquid chromatographic tandem mass spectrometric method, as previously described [28]. Blood samples for biomarker assessment were taken prior to sunitinib treatment on study day 1, on days 14 and 28 of the first treatment cycle, on days 1 and 28 of cycle 2, and on day 28 of cycle 5.

Patient-reported outcomes were assessed using the validated, self-administered European Organisation for Research and Treatment of Cancer (EORTC) Quality of

Life Questionnaire QLQ-C30, and the stomach cancer-specific questionnaire QLQ-STO22 [29, 30]. The questionnaires were completed on the first day of each cycle during a patient's clinic visit prior to other clinical activities including the administration of the study drugs, and at the end of treatment or withdrawal from the study.

Statistical considerations

This study followed a 2-stage Simon design. If ≤1 objective response (CR or PR) was observed in the first 38 eligible patients, then enrollment to the study would end. If ≥2 of these patients achieved a CR or PR, then the study was planned to proceed to Stage 2 by enrolling 25 additional patients. Based on Simon's 2-stage design, this study had 85% power to reject the null hypothesis of a 5% response rate (considered not clinically meaningful) when the true response rate for sunitinib was ≥15% (considered favorable in this patient population). With a significance level (α) of 5%, 63 eligible patients were required, and at the end of the study, the null hypothesis would be rejected if ≥7 objective tumor responses were observed.

The study population for all analyses was defined as the number of patients enrolled in the study who received at least one dose of sunitinib, and (for analysis of ORR, duration of response, CBR, TTP, and PFS) had measurable disease at baseline. The number (%) of patients who achieved an objective response was summarized along with the corresponding 95% exact confidence interval (CI). Time-to-event variables, 1-year survival rate, and a 2-sided 95% CI were estimated and summarized using the Kaplan-Meier method.

Results

Patient characteristics and study treatment

In total, 78 patients were enrolled in the study (Fig. 1), of whom 73 (93.6%) had a diagnosis of gastric adenocarcinoma, and 5 (6.4%) had adenocarcinoma of the gastroesophageal junction. A total of 73 patients (93.6%) had metastatic disease. Baseline characteristics are summarized in Table 1.

The median duration of treatment was 1.6 months (range, 0.1–15.4), and the median number of cycles started was 2 (range, 1–17). Fourteen patients (17.9%) required at least one dose reduction to 37.5 mg/day, mainly due to hematologic adverse events; three of these patients had ≥2 dose reductions. Median relative dose intensity was 93.5%. The relative dose intensity was highest during cycles 1 and 2 (96.4% and 100%, respectively) and ranged from 50.0% to 96.4% during cycles 3–17. Sixteen patients (20.5%) required one or more doses of sunitinib to be delayed, with 12 dose delays lasting for ≥1 week, 6 for ≥2 weeks, and 1 for ≥3 weeks. Reasons for study discontinuation were lack of efficacy (n=55), adverse events (n=11), death (n=8), and withdrawal of consent (n=2).

During follow-up, among 69 patients for whom data were available, 39 received post-study chemotherapy; the most common regimens were single-agent taxanes, FOLFIRI or FOLFOX, or cisplatin-based combinations. Japanese and Korean patients were most likely to receive later lines of chemotherapy (approximately 75% of enrolled patients) but no significant differences were noted in the types of chemotherapy delivered. Five patients received radiotherapy during the follow-up period, and one underwent surgical resection of metastatic ovarian cancer.

Efficacy

All 78 patients had measurable disease at baseline and were included in the efficacy analyses. Two patients achieved confirmed investigator-determined PR, with a response duration of 20 weeks in one patient and at least 6 weeks (before study discontinuation) in the other patient. Both patients achieving a PR were enrolled in Stage 1 of the study, hence the study proceeded to Stage 2. However, with no further responses seen during Stage 2, the primary endpoint of the study was not met, with an ORR of 2.6%. Twenty-five patients (32.1%) had stable disease (SD) for ≥6 weeks, including four patients (5.1%) experiencing SD lasting ≥24 weeks. The clinical benefit rate was 7.7%.

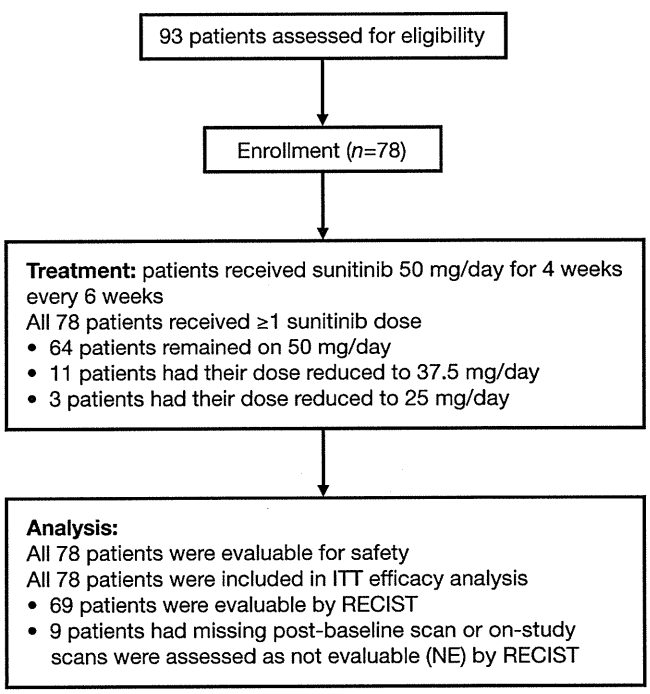

Fig. 1 Patient disposition. ITT, intention-to-treat. RECIST, Response Evaluation Criteria in Solid Tumors

Table 1 Patient baseline characteristics

	Patients receiving sunitinib (N=78)
Median age (range), years	56 (25–78)
Gender (male/female), *n* (%)	56 (71.8) / 22 (28.2)
ECOG PS, *n* (%)	
0	26 (33.3)
1	52 (66.7)
Histopathology, *n* (%)	
Gastric adenocarcinoma	73 (93.6)
Gastroesophageal junction adenocarcinoma	5 (6.4)
Histological grade, *n* (%)	
Well differentiated	9 (11.5)
Moderately differentiated	26 (33.3)
Poorly differentiated	35 (44.9)
Undifferentiated	3 (3.8)
Cannot be assessed	5 (6.4)
Extent of disease, *n* (%)	
Locally advanced	5 (6.4)
Metastatic	73 (93.6)
Prior treatment, *n* (%)	
Chemotherapy	78 (100.0)
Radiation therapy	6 (7.7)
Surgery	59 (75.6)

ECOG PS Eastern Co-operative Oncology Group performance status

Forty-two patients (53.8%) experienced disease progression; the remaining nine patients (11.5%) had missing evaluations or were not evaluable.

By intent-to-treat analysis (n=78), median TTP was 2.3 months (95% CI, 1.7–2.6 months), median PFS was 2.3 months (95% CI, 1.6–2.6 months; Fig. 2a), and median OS was 6.8 months (95% CI, 4.4–9.7 months; Fig. 2b). The probability of 1-year survival was 24.2% (95% CI, 14.4–34.1%).

Pharmacokinetics and pharmacodynamics

Steady-state observed trough concentrations (C_{trough}) were dose-corrected to the starting dose (i.e. reference dose) where appropriate, to adjust for individual dose changes during the study. Mean, dose-corrected, plasma C_{trough} on day 28 (steady state) of cycles 1, 2, 3, and 5 ranged from 62.2 ng/mL to 65.6 ng/mL for sunitinib, 26.0 ng/mL to 33.7 ng/mL for its active metabolite SU12662, and 90.7 ng/mL to 97.9 ng/mL for total drug (sunitinib + SU12662), respectively. The mean dose-corrected C_{trough} box plot of the total drug concentration versus cycle/day is displayed in Fig. 3. No unexpected accumulation of sunitinib and SU12662 was observed throughout the study.

Baseline soluble protein (biomarker) levels or changes from baseline at each time point were analyzed in patients stratified by tumor response category (clinical benefit [PR

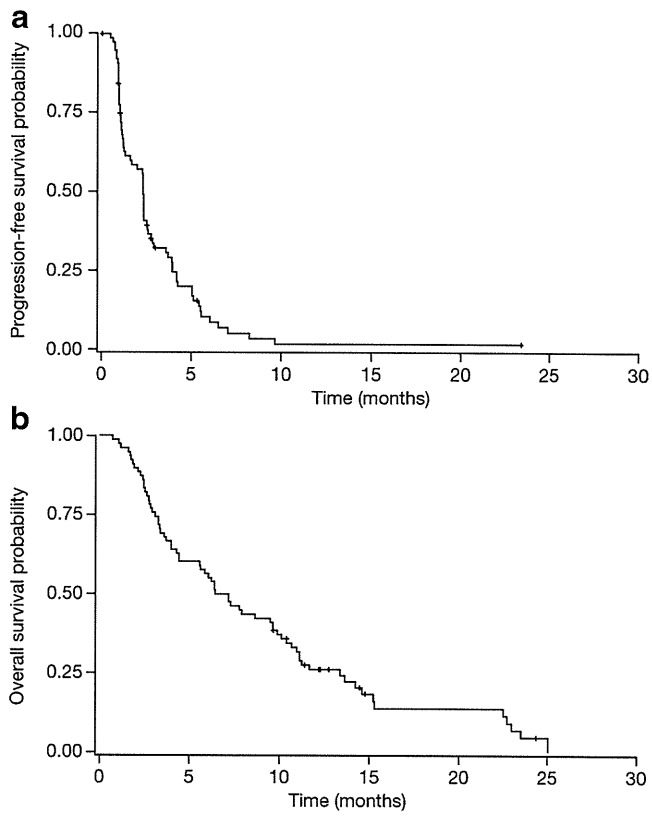

Fig. 2 Kaplan-Meier curve of a progression-free survival and **b** overall survival following treatment with sunitinib 50 mg/day on Schedule 4/2

or SD ≥24 weeks] versus progressive disease). Significant associations with clinical benefit were only observed between high sKIT ratio to baseline at cycle 1 day 28 (P=0.0081), and between low VEGF-C ratio at cycle 2 day 1 (P=0.0326), though the number of patients with clinical benefit was relatively small (n=6). Analysis of patients stratified according to whether they were above or below median time-to-event endpoints for PFS or TTP found no significant differences in any of the soluble proteins studied; there was a modest association between elevated baseline plasma VEGF-C levels and above-median OS (P=0.0241).

Safety

All 78 patients received at least one dose of sunitinib and were included in the safety analyses (Table 2). The most commonly reported treatment-emergent, all-causality, non-hematologic adverse events were fatigue, anorexia, nausea, diarrhea, and stomatitis (Table 2). Most non-hematologic adverse events were grade 1 or 2. Grade 3 or 4 events included fatigue (10.3%), anorexia, hand–foot syndrome, hyperbilirubinemia (6.4% each), and abdominal pain (5.1%). The most common hematologic toxicities were thrombocytopenia (61.5% of patients; 34.6% grade 3 or 4, and one patient with a grade 5 event) and neutropenia (52.6% of patients, 29.4% grade 3 or 4). Thirteen patients (16.7%) experienced grade 3 or 4 anemia. There were no cases of neutropenic fever. Of non-hematologic laboratory adverse events, blood alkaline phosphatase was increased in 10.3% of the study population and occurred at grade 3, the maximum grade reported, in only two patients. Increases in gamma glutamyl transferase were infrequent (2.6%) and of grade 2 severity.

Twenty-four patients (30.8%) permanently discontinued study treatment due to an adverse event; in 14 patients, the adverse events were judged by the investigators to be treatment related. Non-fatal, treatment-related adverse events leading to discontinuation were grade 3 fatigue (n=2) and grades 2 and 4 mucositis, grade 3 nausea, grade 1 ascites, grade 4 thrombocytopenia, grade 3 hand–foot syndrome, grade 4 abdominal pain plus grade 1 anorexia, and combined grade 2 thrombocytopenia and grade 1 nausea, stomatitis, fatigue, skin erosion and hand–foot syndrome (n=1 each). Non-treatment-related discontinuations due to adverse events were attributed by investigators to the disease under study (n=8) or other illness (n=2; stomach cancer perforation and infection, respectively).

Table 2 Treatment-emergent, all-causality adverse events (any cycle) reported in ≥15% of patients

	Number of patients (%) (N=78)	
	All-grade	Grades 3/4
Non-hematologic		
Fatigue	35 (44.9)	8 (10.3)
Anorexia	35 (44.9)	5 (6.4)
Nausea	32 (41.0)	3 (3.8)
Diarrhea	28 (35.9)	2 (2.6)
Stomatitis	28 (35.9)	1 (1.3)
Vomiting	24 (30.8)	3 (3.8)
Hand–foot syndrome	22 (28.2)	5 (6.4)
Pyrexia	22 (28.2)	
Abdominal pain	20 (25.6)	4 (5.1)
Skin discoloration	19 (24.4)	
Constipation	17 (21.8)	1 (1.3)
Hypoalbuminemia	15 (19.2)	
Rash	14 (17.9)	
Mucosal inflammation	13 (16.7)	2 (2.6)
Hyperbilirubinemia	13 (16.7)	5 (6.4)
Hematologic		
Thrombocytopenia	48 (61.5)[a]	27 (34.6)
Neutropenia	41 (52.6)	23 (29.4)
Leukopenia	30 (38.5)	9 (11.5)
Anemia	29 (37.2)	13 (16.7)

[a] Includes one grade 5 event

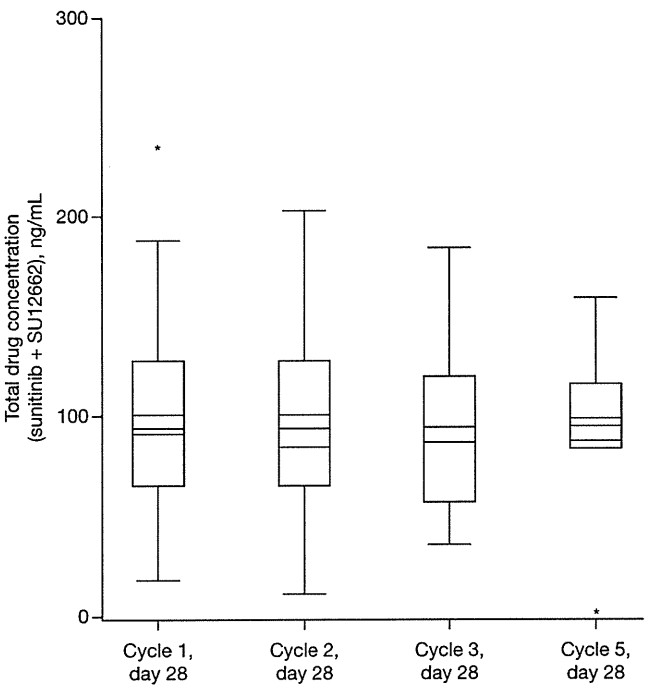

Fig. 3 Total drug (sunitinib + SU12662) dose-corrected (reference dose: 50 mg) plasma trough concentration versus cycle/day box plot. Box boundaries denote 25th and 75th percentiles; lines within the box show the median value and expected range of the median. Whiskers indicate the minimum and maximum data values; where outliers are present (asterisks), whiskers extend to a maximum of 1.5 times the interquartile range

Nine patients (11.5%) had a dose reduction due to treatment-emergent adverse events, all of which were treatment-related.

Eleven patients (14.1%) died during the reporting period (during treatment or within 28 days after the last dose of study drug), with eight of these patients having death as the reason for discontinuation of the study. Four of the 11 deaths were considered to be treatment-related adverse events (three during treatment and one within 28 days after the last dose of sunitinib) and seven due to adverse events unrelated to treatment (six due to disease progression; one due to hypotension, depressed level of consciousness and hypopnea). The deaths considered to be treatment-related were due to thrombocytopenia and pulmonary embolism; brain herniation (preceded by upper gastrointestinal bleeding at day 14); cardiac arrest; and brainstem hemorrhage occurring 21 days after the last dose of study drug, respectively.

HRQoL

QLQ-C30 questionnaires were completed by 64 patients at baseline (cycle 1, day 1); completion rates were generally high during treatment but upon withdrawal from the study the completion rate fell to 69.2%. From a mean baseline global health status/HRQoL of 62.3, HRQoL was maintained by sunitinib treatment during the first three cycles of this study, though the domains of diarrhea and reflux symptoms were noticeably worse compared to baseline. Beyond cycle 3, HRQoL data were available for <10 patients per cycle due to study discontinuations.

At patients' last evaluation (end of treatment or withdrawal from the study), noticeable changes (deterioration) were observed in most scales and measures of the EORTC QLQ-C30 and QLQ-STO22 compared to the baseline. The domains for perceived financial difficulties, body image, and hair loss did not change noticeably.

Discussion

In this study, sunitinib showed preliminary activity in the second-line treatment setting in patients with advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma. Following two objective responses in Stage 1, both stages of the study were enrolled, but overall the study did not meet its primary endpoint, with only two patients achieving a PR by RECIST for an overall RECIST-defined ORR of 2.6%. However, the clinical benefit rate was 7.7% and one-third of patients experienced a best response of SD. The median OS duration of 6.8 months, and the median PFS and TTP of 2.3 months with single-agent sunitinib in this study are comparable with those reported in the second-line treatment setting in similar phase II trials of single-agent chemotherapy, such as docetaxel [31, 32], paclitaxel [33, 34], irinotecan [35], or mitomycin C [36], as well as various chemotherapy combinations [4–6]. This level of efficacy is clearly insufficient to support further study of sunitinib as a single-agent in this population, although these data support the proof of concept that sunitinib does affect the late clinical course of gastric cancer.

Recently, the use of trastuzumab in combination with chemotherapy was found to significantly prolong survival when given as first-line treatment for patients with HER2-positive gastric or gastroesophageal cancer [37]—this is the first time that a regimen including a targeted agent has been shown to provide a survival benefit in patients with advanced gastric cancer. It can be hypothesized that the progression-delaying effects observed with sunitinib in our trial might be enhanced if sunitinib is given in combination with chemotherapy, and this is being investigated in the first-line treatment setting in phase I trials at present.

In general, the type and frequency of reported adverse events were consistent with those previously reported with sunitinib when administered as a single agent [25, 26, 38, 39]. Adverse events were generally manageable, as dose schedule modifications (mainly dosing delays) were required in less than half of the patients, though the incidence of permanent discontinuations due to treatment-related adverse events was 18%. This included four (5.1%) treatment-related deaths (thrombocytopenia/pulmonary embolism, brain herniation preceded by upper gastrointestinal bleeding, cardiac arrest, and one patient who died 21 days after the last dose of study drug from brainstem hemorrhage). The predominant non-fatal, treatment-related adverse events leading to discontinuation were fatigue and mucositis. Most non-hematologic adverse events were Grade 1 or 2 in severity. The most common Grade 3 or 4 non-hematologic events included fatigue, anorexia, hand–foot syndrome, hyperbilirubinemia, and abdominal pain, each reported in ≤10% of patients. However, the incidence and severity of hematologic adverse events during sunitinib treatment was higher in this population than in gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (mRCC) patients [25, 26]. Grade 3 or 4 neutropenia or thrombocytopenia was reported in approximately one-third of patients, but only one case of hemorrhagic thrombocytopenia was reported, and there were no cases of neutropenic fever. The majority of adverse events were managed by standard medical intervention and sunitinib dosing interruption, with or without dose reduction.

Analysis of the HRQoL endpoints measuring gastric cancer-related symptoms, general cancer-related symptoms, overall health status and quality of life shows that these scores were largely maintained during the first three cycles

of sunitinib treatment. Given that patients discontinued sunitinib treatment due to insufficient clinical response, the subsequent worsening in health status was more likely due to disease progression than to drug toxicity in this single-arm study of limited sample size.

Based on the dose-corrected C_{trough} data, the pharmacokinetics of sunitinib and its metabolite in advanced/metastatic gastric cancer patients were consistent with previous experience with sunitinib at 50 mg/day on Schedule 4/2 in patients with advanced solid tumors [40]. No unexpected accumulation of sunitinib or its metabolite was observed throughout the study. Assessment of soluble protein levels versus measures of clinical outcome only showed associations between clinical benefit and high sKIT ratio to baseline at cycle 1 day 28 (P=0.0081), and between clinical benefit and low VEGF-C ratio at cycle 2 day 1 (P=0.0326). However, there were a limited number of patients with clinical benefit to include in these analyses. In general, the patterns of pharmacodynamic changes in soluble protein levels observed were similar to those seen in previously reported sunitinib studies [41].

In exploring the potential of sunitinib in gastric cancer, several hypotheses can be proposed that may have had an impact on the limited efficacy observed in this trial. Firstly, in the absence of known predictive biomarkers, it was not possible in this trial to select a subset of gastric cancer patients who might be more likely to respond to sunitinib, which is in contrast to the ability to preselect HER2-positive patients likely to be sensitive to trastuzumab in the ToGA trial [37]. Further understanding of who may benefit from treatment could help to refine the target population for future studies. It is also notable that ORR assessed using RECIST was selected as the primary endpoint of this study. However, observations with targeted agents in other tumor types, for example imatinib in GIST [42] and sunitinib in RCC [43], suggest that one-dimensional RECIST measurements can miss important information about changes in tumor density and metabolic response. This raises the question as to whether ORR is the most suitable endpoint for assessing sunitinib in gastric cancer.

Dose selection and schedule could also be explored further. On the intermittent schedule used in this and other studies of sunitinib, pharmacodynamic modulation of several plasma proteins associated with angiogenesis was reversible during the off-treatment period [38, 43–45]. This raises the question of whether continuous administration of sunitinib might be of benefit, to ensure continuous suppression of angiogenesis. Ultimately, these hypotheses would all require testing in a trial setting.

In summary, the preliminary activity and manageable toxicity observed with sunitinib in this study suggest that although single-agent sunitinib has insufficient clinical value as second-line treatment for advanced gastric cancer, its role in combination with chemotherapy is worthy of further study. The results of ongoing phase I trials in the first-line treatment setting will provide more insight into the use of multiple-RTK inhibitors such as sunitinib in the treatment of advanced gastric cancer.

Acknowledgments Thanks to the global network of investigators who participated in this trial:

CHINA: Rongcheng Luo, Shukui Qin, Lin Shen, Yan Sun. HONG KONG: Wai-Tong Ng, Winnie Yeo. ITALY: Stefano Cascinu, Alberto Sobrero. JAPAN: Narikazu Boku, Toshihiko Doi, Kuniaki Shirao. PORTUGAL: José Evaristo Sanches. REPUBLIC OF KOREA: Yung-Jue Bang, Hyun-Cheol Chung, Won Ki Kang, Yoon-Koo Kang. TAIWAN: Jen-Shi Chen, Kun-Huei Yeh.

Editorial assistance was provided by Jenni Macdougall of ACUMED® (Tytherington, UK) and was funded by Pfizer Inc. The authors also acknowledge data analysis from Charles Harmon (an employee of Atrium Inc., and a paid consultant to Pfizer Inc.) and Zhixiao Wang (Outcomes Research, Pfizer Oncology, New York, NY, USA), and input and review of the manuscript from Richard Chao, Darrel Cohen, and Kristen Letrent (Pfizer Oncology, La Jolla, CA, USA, and New York, NY, USA).

This trial was sponsored by Pfizer Inc.

Conflict of interest Y-J Bang has received commercial research support, honoraria from speakers bureau, and compensation for consultation from Pfizer.

Y-K Kang has received honoraria from speakers bureau from Pfizer.

HC Chung has received research funding from Pfizer for the clinical trial.

T Doi has received compensation for consultation for Pfizer's Sutent GIST program.

JM Tursi, MJ Lechuga, DR Lu, and A Ruiz-Garcia are employees of Pfizer.

JM Tursi, MJ Lechuga, and DR Lu own stock in Pfizer.

A Ruiz-Garcia owns restricted stocks in Pfizer.

A Sobrero participated as chairman to advisory boards for Pfizer in 2009 and 2008.

WK Kang, N Boku, JS Chen, Y Sun, L Shen, SK Qin, and WT Ng have nothing to disclose.

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Gastric Cancer (2011) 14:226–233
DOI 10.1007/s10120-011-0030-8

ORIGINAL ARTICLE

A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial)

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Received: 26 October 2010 / Accepted: 24 January 2011 / Published online: 19 April 2011

Abstract
Background Preclinical studies have shown that mitomycin C (MMC) acts synergistically with irinotecan (CPT-11). In this phase II study, we evaluated the efficacy and toxicity of MMC/CPT-11 therapy as second-line chemotherapy for patients with fluoropyrimidine-resistant advanced gastric cancer.
Methods Eligible patients had evidence of tumor progression despite prior treatment with fluoropyrimidine-based regimens or had relapsed within 6 months after completion of therapy with adjuvant fluoropyrimidines. Treatment consisted of MMC (5 mg/m^2) and CPT-11 (150 mg/m^2) administered i.v. every 2 weeks. The primary endpoint was the response rate (RR). Our hypothesis was that this combination therapy was efficacious when the lower boundary of the 95% confidence interval (CI) of the RR exceeded 20% of the threshold RR.

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Results Between April 2002 and July 2003, 45 eligible patients were registered and analyzed. Among the 45 patients, 40 (89%) had previously received chemotherapy for metastasis and 24 (53%) had a performance status (PS) of 0. Thirteen partial responses were obtained among the 45 patients, resulting in an overall RR of 29% (95% CI, 16–42%). The median time to progression was 4.1 months, and the median survival time was 10 months, with a 1-year survival rate of 36%. Grade 4 neutropenia was observed in 29% of the patients, whereas febrile neutropenia occurred in 9%. The incidence rates of grade 3 nausea and diarrhea were 13 and 2%, respectively.

Conclusions Although this study did not achieve the per-protocol definition of activity, the progression-free survival and overall survival appeared to be promising, with acceptable tolerability. Thus, MMC/CPT-11 therapy as second-line chemotherapy for fluoropyrimidine-resistant advanced gastric cancer presents a potential treatment option in patients with a good PS.

Keywords Gastric cancer · Mitomycin-C · Irinotecan · Fluoropyrimidine-resistant · Second-line chemotherapy

Introduction

Gastric cancer is the most common malignancy in Asian countries, with approximately 50,000 deaths in Japan annually [1]. The treatment of choice for this malignancy is primary tumor resection. In patients with curatively resected stage I–III gastric cancer, the 5-year survival proportion is >50%; however, this proportion remains at <10% in stage IV or recurrent disease. Randomized trials have demonstrated that fluorouracil-based regimens improve survival proportions in patients with advanced gastric cancer (AGC) compared with best supportive care (BSC) alone as first-line chemotherapy [2–4]. Moreover, combination chemotherapy results in superior outcomes compared with monotherapy. In Japan, the efficacy and toxicity of the combination of an oral fluoropyrimidine (S-1) and platinum was previously evaluated in the phase III SPIRITS (S-1 plus cisplatin vs. S-1 alone for first-line treatment of AGC) trial. S-1 plus cisplatin resulted in superior overall survival (OS) compared with S-1 alone [hazard ratio (HR), 0.77; 95% confidence interval (CI), 0.61–0.98%; $P = 0.04$], with an impressive median OS of 13.0 months [5]. The Japan Clinical Oncology Group (JCOG) 9912 trial (5-fluorouracil [FU] alone vs. S-1 alone vs. irinotecan [CPT-11] plus cisplatin [CDDP] combination for the first-line treatment of AGC) was also conducted in Japan. S-1 showed significant noninferiority for progression-free survival (PFS) and OS compared with 5-FU alone; however, CPT-11 plus CDDP showed no significant superior effects on PFS and OS compared with 5-FU alone [6]. In Japan, S-1 plus CDDP combination therapy is considered the standard first-line treatment for AGC.

Thuss-Patience et al. [7] reported at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) that CPT-11 monotherapy significantly prolonged OS compared with BSC as second-line chemotherapy. Although that report was the first randomized phase III study investigating second-line chemotherapy for AGC, no objective responses were observed. Thus, a consensus regarding the standard regimen for second-line chemotherapy has not yet been obtained.

Many AGC patients who failed to respond to first-line chemotherapy showed symptoms of pain, weight loss, or nausea due to their progressive disease. Thus, the induction of a tumor response is as important as delaying tumor progression for as long as possible. Patients who received combination chemotherapy showed higher response rates than those who received single-agent chemotherapy alone. Therefore, combination chemotherapy is preferable to single-agent chemotherapy for palliation. Moreover, combination chemotherapy may prolong OS compared with single-agent chemotherapy alone.

CPT-11 is a potent topoisomerase I inhibitor and is effective against AGC. In a phase II trial, the response rate (RR) to CPT-11 alone was 16% in previously treated AGC patients [8]. The administration of a CDDP and CPT-11 combination in AGC patients resulted in a higher RR and longer time to progression (TTP) [9–11]. As mentioned above, CDDP/CPT-11 did not significantly prolong OS over 5-FU, but induced a significantly higher RR than 5-FU in the JCOG9912 trial [6]. A 5-FU, leucovorin (LV), and CPT-11 combination produced a higher RR and longer TTP than CDDP/CPT-11 in AGC patients [12]. In another randomized phase III trial, 5-FU/LV/CPT-11 showed a trend to have superiority in TTP over CDDP/5-FU (5.0 vs. 4.2 months, respectively; HR, 1.23; 95% CI, 0.97–1.57%; $P = 0.088$), and a better safety profile [13]. These results support the finding that CPT-11 is active against AGC.

Mitomycin C (MMC) is also effective against AGC. Preclinical studies have shown that a MMC and CPT-11 combination synergistically inhibits tumor growth in vitro [14]. This is due to the possible induction of topoisomerase I gene expression by MMC, thereby increasing tumor cell sensitivity to CPT-11. A phase I/II study of this combination recommended an MMC dose of 5 mg/m^2 and a CPT-11 dose of 150 mg/m^2 administered biweekly [15]. The dose-limiting toxicities of this combination regimen when administered at 10 mg/m^2 for MMC and 150 mg/m^2 for CPT-11 were grade 4 neutropenia with or without febrile neutropenia and grade 3 diarrhea. The overall RR was 50% (15/30 patients), and 5 of 14 patients (36%) with prior chemotherapy showed a partial response (PR). We

previously showed that MMC and CPT-11 combination chemotherapy was effective and well tolerated in patients with fluoropyrimidine-resistant metastatic colorectal cancer; the RR, median TTP, and median survival time (MST) were 34% (95% CI, 20–49%), 4.2 months, and 11.9 months [16], respectively.

These results led us to conduct the present phase II clinical trial to investigate the efficacy and toxicity of MMC/CPT-11 therapy in patients with AGC resistant to a fluoropyrimidine-containing regimen in the JCOG0109-DI study.

Patients and methods

Eligibility

A patient was considered eligible if there was evidence of a refractory response to one prior chemotherapy containing fluoropyrimidine, which was any of the following types of history of chemotherapy:

1. In the case of unresectable gastric cancer, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine, or confirmed immediately after the discontinuation for any reason other than disease progression.
2. In the case of recurrent gastric cancer, recurrence detected within 24 weeks from the last dose of postoperative adjuvant chemotherapy containing fluoropyrimidine, and further chemotherapy was not administered after recurrence.
3. In the case of recurrent gastric cancer detected 25 weeks after the last dose of postoperative adjuvant chemotherapy, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after the discontinuation for any reason other than progression.
4. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the effect of neoadjuvant chemotherapy containing fluoropyrimidine was stable disease, progressive disease, or not evaluated, and recurrence was identified after curative resection. Chemotherapy was not performed following recurrence.
5. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the chemotherapy effect was a complete response or PR, and progression was detected during one chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after discontinuation for any reason other than progression.

Disease progression and the nonefficacy of neoadjuvant chemotherapy were believed to represent clinical failure by treating physicians. Elevation of the level of a tumor marker, such as carcinoembryonic antigen (CEA), was not accepted as adequate evidence for treatment failure. Documentation of evidence of a refractory response by computed tomography (CT) and magnetic resonance imaging was required.

For the other eligibility criteria, patients must be between 20 and 75 years of age, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate baseline bone marrow function [white blood cell (WBC) and platelet counts $\geq$4,000 and 100,000/mm^3, respectively], adequate hepatic function (serum bilirubin level $\leq$1.5 mg/dl and both serum aspartate aminotransferase and alanine aminotransferase levels $\leq$100 U/l), adequate renal function (serum creatinine level $\leq$1.5 mg/dl), adequate respiratory function (arterial partial pressure of oxygen $\geq$70 mmHg), and have received no blood transfusion within 14 days before enrollment. All patients were required to have $\geq$1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Patients were excluded if they had symptomatic brain metastasis, symptomatic ascites and/or pleural effusion, previous history of MMC or CPT-11 chemotherapy, pre-existing diarrhea of >4 times/day, suspicion of existing active bleeding which needed blood transfusion at 14 days prior to registration in this study, or a high risk of a poor outcome due to concomitant nonmalignant disease (i.e., cardiac, pulmonary, renal, or hepatic disease; poorly controlled diabetes; or uncontrolled infection), or severe psychiatric disease. Pregnant or lactating women were excluded.

The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating hospital. All patients gave their written informed consent.

Treatment plan

The treatment schedule consisted of one MMC dose (5 mg/m^2, bolus injection), then CPT-11 (150 mg/m^2, 90-min i.v. infusion) repeated every 2 weeks, as described previously [16]. All patients were treated on an outpatient basis and were recommended to receive both a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone to prevent emesis. Subsequent treatment cycles were withheld until the WBC and platelet counts were $\geq$3,000 and 100,000/mm^3, respectively; diarrhea was $\leq$grade 1; and there were no infection symptoms such as pyrexia ($\geq$38°C). When the treatment course was delayed within 8 days from the planned schedule, the same dosage levels as those used previously were administered. When the treatment course was delayed beyond 8 days and within 21 days from the planned schedule, one lower dose level (CPT-11 level -1,

125 mg/m^2; level -2, 100 mg/m^2) than the previous level was administered, while the MMC dose was maintained at 5 mg/m^2. The treatment course was discontinued if it could not be started within 21 days from the planned schedule. When grade 4 leukopenia or thrombocytopenia occurred in a previous treatment course causing a delay within 8 days, the same dosage levels as those used previously were administered. When grade 2 diarrhea or higher was observed in a preceding course, dosages 1 level lower than the previous dosages were administered.

Treatment was repeated until disease progression or when severe toxicity was observed. The total MMC dose was limited to 50 mg/m^2, to prevent cumulative toxicity (e.g., interstitial pneumonia and hemolytic uremic syndrome), and thereafter CPT-11 alone was administered. This indicates that the maximum number of total treatment cycles of MMC/CPT-11 therapy is 10 cycles.

Evaluation of response and toxicity

During protocol treatment, the patient's signs and symptoms, as well as laboratory data (i.e., WBC with differential counts, liver function tests, urea nitrogen, creatinine, electrolytes, and urinalysis) were examined biweekly. Adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria version 2.0. Tumor response was assessed by CT every 4 weeks. The response of measurable and evaluable disease sites was assessed by each investigator in accordance with RECIST, and then reviewed by central review at the group meeting.

Statistical analysis

For this study, the primary endpoint was the RR and the secondary endpoints were OS and toxicity. Here, we used the standard design (attained design) of the Southwest Oncology Group [17]. Based on reports of RRs of 22% with paclitaxel alone [18] and 16% with CPT-11 alone [8] in the second-line setting and an RR of 36% in phase I/II studies of MMC/CPT-11 therapy [15], the RR in this study was expected to be within 30–40% for a future phase III trial. Here, the required sample size was calculated to be 45 patients, with the following parameters: $\alpha = 0.05$, $\beta = 0.10$, threshold response rate $(p_0) = 20\%$, and expected response rate $(p_a) = 40\%$. Interim analysis was performed when the number of enrolled subjects reached 25. The significance level for the interim analysis was set as $P < 0.02$. Furthermore, when the number of patients who reached RR was <5 at the interim analysis, the study was prematurely discontinued because it would have been difficult to exceed the expected RR despite further patient accumulation, or because it would not be worth advancing this regimen to an ensuing clinical study. When the study was not completed after the interim analysis, the number of patients was increased to 45 in order to allow the null hypothesis (threshold RR) to be tested. When α was <0.05, or when the lower boundary of the 95% CI of the RR exceeded 20% of the threshold RR, this therapy was considered to be efficacious as chemotherapy for gastric cancer patients who had received pretreatment. That is, when ≥16 of 45 patients had a PR, this study was judged to be positive. Here, patient enrollment was not temporarily discontinued.

OS was defined as the time from the registration date to death as a result of any cause. PFS was defined as the time from the registration date to the first documentation of objective tumor progression. Time-to-event and OS data were summarized using the Kaplan–Meier method.

Results

Patient population and study treatment

Between April 2002 and July 2003, 45 patients (33 men, 12 women) from 12 hospitals were enrolled and analyzed. Table 1 shows the demographic data, baseline disease, and regimens of prior chemotherapy. The median age was 64 years (range 36–75), and all patients had a good PS of 0 or 1. Eighteen patients (40%) had diffuse-type gastric cancer. As for prior chemotherapy, 40 (89%) had previously received chemotherapy for metastasis, whereas 5 had received adjuvant chemotherapy. In the first-line chemotherapy, 33 patients (73%) had received 5-FU or S-1 alone.

In all 45 patients, MMC/CPT-11 therapy was administered 281 times, and the median number of doses was 6 (range 1–10). Of the 45 patients, 10 (22%) completed the planned 10 chemotherapy cycles. In the remaining 35 patients, the reasons for treatment discontinuation were disease progression in 25, toxicity in 6, patient's refusal in 3, and death in 1. Regarding CPT-11 administration, 11 patients (24%) required -1 level dose reduction and 8 (18%) required -2 level reduction because of leukopenia and thrombocytopenia.

Efficacy

Of the 45 patients, 13 showed a PR (RR: 28.9%; 95% CI, 15.6–42.1%) (Table 2). The median PFS was 4.1 months (Fig. 1). The median OS time was 10.1 months (95% CI, 7.3–12.6 months), and the 1-year survival rate was 38% (Fig. 2).

Because the lower boundary of the 95% CI of the RR (15.6%) did not exceed the threshold RR (20%), the

Table 1 Patient characteristics ($n = 45$)

Age (years)	
Median	64
Range	36–75
Gender	
Male	33
Female	12
ECOG performance status	
0	24
1	21
2	0
Borrmann macroscopic type of primary cancer	
0	1
1	1
2	17
3	18
4	5
Unknown	3
Histological type	
Intestinal	25
Diffuse	18
Unclassified	2
Prior chemotherapy	
5-FU alone	18
S-1 alone	15
S-1 + CDDP	6
MTX + 5-FU	2
Others	4

ECOG Eastern Cooperative Oncology Group, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *MTX* methotrexate

Table 2 Evaluation of response ($n = 45$)

Tumor response	Patients	
	n	% (95% CI)
Complete response	0	0
Partial response	13	28.9 (15.6–42.1)
Stable disease	17	37.7 (23.6–51.9)
Progressive disease	14	31.1 (17.6–44.6)
Not evaluated	1	4.4 (0–6.5)
Survival	Months (95% CI)	
PFS	4.1 M (2.5–5.7)	
OS	10.1 M (7.3–12.6)	

CI confidence interval, *PFS* progression-free survival, *OS* overall survival

MMC/CPT-11 combination as second-line chemotherapy could not be definitively concluded as efficacious for further investigation.

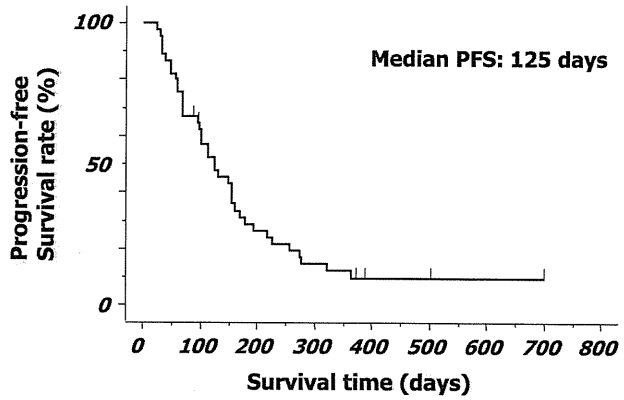

Fig. 1 Kaplan–Meier estimates of progression-free survival (*PFS*) rates

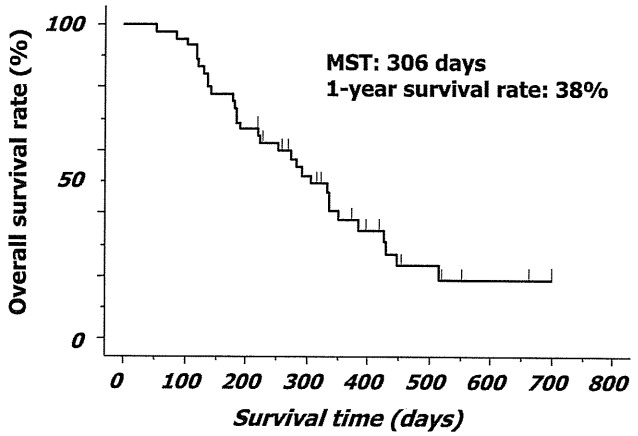

Fig. 2 Kaplan–Meier estimates of overall survival. *MST* Median survival time

Toxicity

The toxicities of the MMC/CPT-11 therapy are summarized in Table 3, with myelosuppression and gastrointestinal toxicity as major toxicities. Grade 3 and 4 neutropenia occurred in 24 and 29% of the patients, respectively, whereas grade 3 and 4 thrombocytopenia developed in only 7%. As for the nonhematological toxicities, the incidence rate of grade 3 diarrhea was 2%, and nausea and vomiting were mild. Early death due to interstitial pneumonitis within 30 days from the last chemotherapy occurred in 1 patient, which was considered by the JCOG Data and Safety Monitoring Committee to have been possibly related to the treatment.

Discussion

In second-line chemotherapy for AGC, the potential benefits remain unclear because of the few prospective studies that have been conducted thus far. These trials demonstrated that

Table 3 Grade 2–4 adverse events according to NCI-CTC ver. 2.0 ($n = 45$)

	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Hematological WBC	24	8	5	29
Neutrophils	10	11	13	53
Hb	25	3	3	13
Platelets	1	2	1	7
Febrile neutropenia	0	4	0	9
Non-hematological Anorexia	13	11	0	24
Nausea	11	6	0	13
Diarrhea	4	1	0	2
Infection with grade 3/4 neutropenia	0	2	0	4
Infection without neutropenia	4	2	0	4

NCI-CTC National Cancer Institute-Common Toxicity Criteria, *Hb* hemoglobin

the RRs to second-line chemotherapy in phase II trials for gastric cancer were similar to those observed for other cancers which are more commonly treated after the failure of first-line chemotherapy. Furthermore, 2 Japanese randomized trials (i.e., SPIRITS [5] and JCOG9912 [6]) achieved a median OS of 13.0 months despite the relatively short median PFS of about 4–6 months. Although both JCOG9912 and our previous phase III study (JCOG9205 [19]) utilized 5-FU continuous infusion (c.i.) and 5-FU/CDDP, the obtained median PFS was 2 months and the OS in JCOG9912 was much longer than that in JCOG9205. In the present study, the proportion of patients who received second-line chemotherapy was >70%, which is higher than that obtained in our previous study (53%). The results of previous phase II trials consistently suggest that patients treated with second-line chemotherapy may survive longer than those provided with BSC, although the survival benefit of the second-line chemotherapy has not yet been clarified.

According to the 26 prospective phase II studies reported in the literature, obtained using the search expressions "gastric cancer" and "second-line chemotherapy" in PubMed, the average and median RRs were 18.8 and 20.0% (0–34.6%), respectively [18, 20–44]. Although the present study did not disprove the null hypothesis about RR, it is suggested that MMC/CPT-11 therapy with an RR of 28.9% may possess some antitumor activity as second-line chemotherapy.

As for survival, the present study showed a median survival time of 10.1 months (95% CI, 7.3–12.9 months), and a 1-year survival proportion of 38%. These data are similar to those obtained in the first-line chemotherapy setting and appeared to be better than those obtained using several other regimens, showing a survival period of 3.5–13 months compared with the reported median survival period of 7–10 months in untreated patients. However, it is very difficult to compare phase II studies due to differences in patient background and subsequent therapy. One reason for improved survival may be good clinical selection of a patient. At the baseline evaluation, the median age of the patients in the present study was 64 years (range, 36–75), and all the patients had a good PS of 0 or 1. Another reason for the improved survival was the high proportion of tumor stabilization (66.7%) after the administration of the MMC/CPT-11 regimen. Therefore, it is considered that MMC/CPT-11 therapy may provide some survival benefit.

The toxicity of the MMC/CPT-11 regimen can be considered tolerable and manageable. Hematological toxicity was within the expected range, including grade 4 neutropenia, observed in 13 patients (29%) and grade 3 febrile neutropenia in 4 patients (9%). According to a Japanese prospective pharmacogenomic study of CPT-11, homozygotes and double heterozygotes of *6 and *28 (*6/*6, *28/*28 and *6/*28) were significantly associated with severe neutropenia. The UGT1A1 gene test prior to receiving this regimen may be useful to decide the starting dose of CPT-11 or to decide whether the patient should receive CPT-11 and MMC combination chemotherapy or CPT-11 monotherapy [45]. Although treatment-related death was observed in 1 patient (2%) in the present study, the occurrence of adverse events was similar to that in JCOG9911-DI, a phase II study of the same regimen for colon cancer; thus, MMC/CPT-11 therapy was considered tolerable. In the present study, the proportion of patients with toxicity was similar to that of patients where MMC/CPT-11 therapy was used as second-line treatment against colorectal cancer [16].

From the above results, the present phase II study of MMC/CPT-11 therapy for FU-based chemotherapy-refractory gastric cancer is judged to be negative on the basis of the decision rule defined in the protocol. This may be due to the threshold RR being set very high owing to the lack of data as the basis for setting the threshold level and expected RR, because of the small number of phase II studies of second-line treatment when this protocol was developed. In fact, the RR cannot be considered poor compared with that in phase II studies performed in other treated patients (as shown in Table 2), with a favorable

survival time of 10 months. In conclusion, the MMC/CPT-11 regimen might be one treatment option for pretreated AGC in patients with good PS.

Acknowledgments This study was supported by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare. We thank Ms. M. Kobayashi and Ms. M. Shinogi for data management and Ms. H. Orita for her secretarial assistance.

Conflict of interest None.

Appendix

Investigators in participating institutions: Yamagata Prefectural Central Hospital, H. Saito; Tochigi Cancer Center, H. Fuji; Saitama Cancer Center, K. Yamaguchi; National Cancer Center Hospital East, T. Doi; Chiba Cancer Center Hospital, T. Denda; National Cancer Center Hospital Tokyo, Y. Shimada; Kitasato University East Hospital, W. Koizumi; Aichi Cancer Center Hospital, Y. Inaba; Nagoya Medical Center, H. Iwase; Osaka Medical College, H. Takiuchi; National Hospital Organization Shikoku Cancer Center, J. Nasu; Kumamoto Regional Medical Center Hospital, M. Yoshida.

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Invest New Drugs
DOI 10.1007/s10637-011-9693-6

PHASE I STUDIES

Phase I results from a two-part Phase I/II study of cediranib in combination with mFOLFOX6 in Japanese patients with metastatic colorectal cancer

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Received: 12 March 2011 / Accepted: 17 May 2011

Summary *Background* Colorectal cancer (CRC) is the second most common malignancy in Japan. Inhibition of vascular endothelial growth factor (VEGF) signaling is a clinically validated therapeutic strategy in patients with metastatic CRC. Cediranib is an oral, highly potent VEGF signaling inhibitor of all three VEGF receptors. *Methods* This Phase I study investigated the safety, tolerability and pharmacokinetics of cediranib (20 or 30 mg) in combination with mFOLFOX6 in Japanese patients with previously untreated metastatic CRC. If the safety of the 20 mg dose was confirmed, a second cohort of patients was to be recruited to receive cediranib 30 mg + mFOLFOX6. *Results* Six patients received cediranib 20 mg + mFOLFOX6 and seven received cediranib 30 mg + mFOLFOX6. One patient in the initial cediranib 20 mg cohort experienced a dose-limiting toxicity (DLT; grade 3 bilirubin increase); no DLTs were observed in the 30 mg cohort. The most commonly reported adverse events were diarrhea, decreased appetite, peripheral neuropathy, hypertension and fatigue. Two patients in the 20 mg cohort and three in the 30 mg cohort experienced serious adverse events during all treatment courses. Cediranib was generally well tolerated in this patient population with no evidence to suggest any significant pharmacokinetic interactions between cediranib and fluorouracil or oxaliplatin. A preliminary evaluation showed that five of nine evaluable patients achieved a best response of partial response. *Conclusion* Cediranib (20 or 30 mg) in combination with mFOLFOX6 was considered tolerable according to the protocol-defined criteria, providing justification for the Phase II part of this study.

Keywords Cediranib · Colorectal cancer · mFOLFOX6 · Tolerability

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Published online: 25 May 2011