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PHASE II STUDIES

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

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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%.

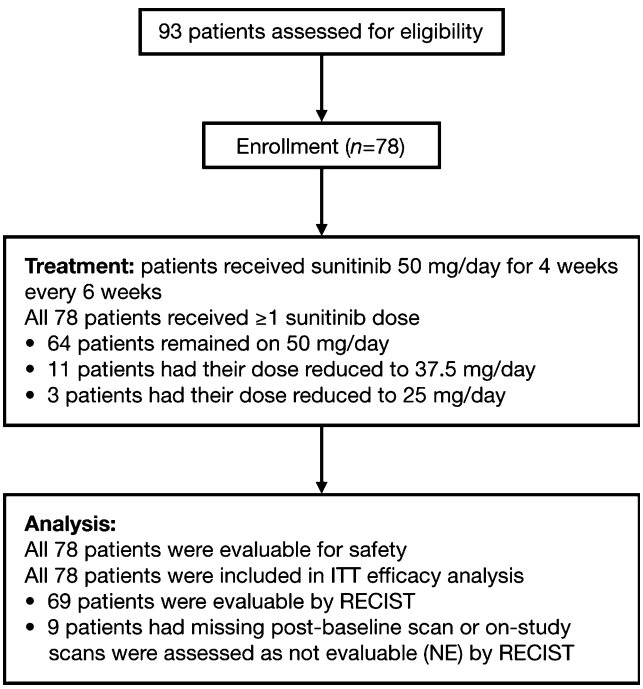

Fig. 1 Patient disposition. ITT, intention-to-treat. RECIST, Response Evaluation Criteria in Solid Tumors

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

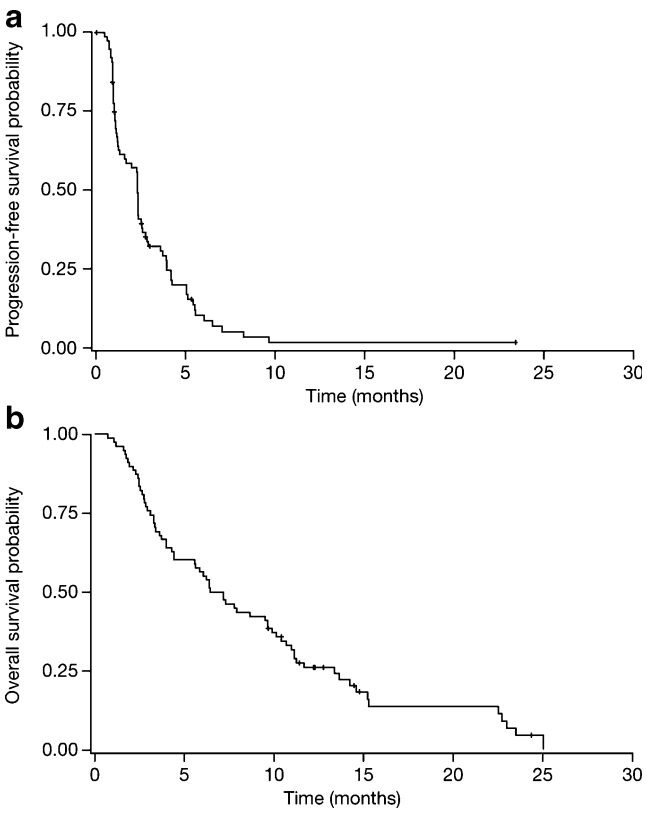

Fig. 2 Kaplan-Meier curve of a progression-free survival and **b** overall survival following treatment with sunitinib 50 mg/day on Schedule 4/2

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

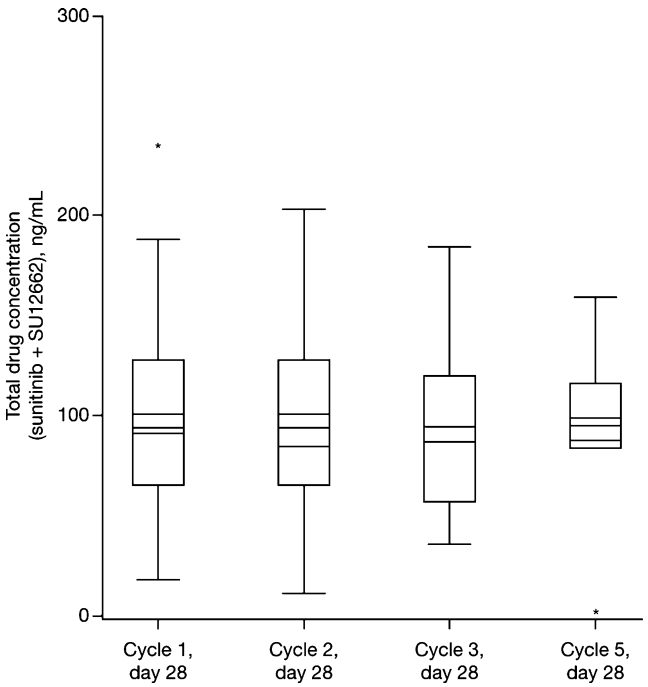

Fig. 3 Total drug (sunitinib + SU12662) dose-corrected (reference dose: 50 mg) plasma trough concentration versus cycle/day box plot. Box boundaries denote 25th and 75th percentiles; lines within the box show the median value and expected range of the median. Whiskers indicate the minimum and maximum 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.

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