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16.10. JCOG Data and Safety Monitoring Committee

During the trial period, the Data and Safety Monitoring Committee will oversee the adverse event reports, interim analysis reports, monitoring report reviews, and protocol revision reviews

(Refer to the homepage for a list of the committee members, http://www.jcog.jp/basic/org/committee/jury.html. However, the committee members of the study group conducting this trial will not be directly involved in reviews of this trial.

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16.11. JCOG Audit Committee

During the trial period, the site-visit audits will be conducted by the audit committee.

(Refer to the home page for a list of committee members, http://www.jcog.jp/basic/org/committee/audit.html)

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Protocol Preparation

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17. Research results presentation

The main article for publication will be submitted to an English-language journal.

When presenting the final analyses, other than the principal analysis stipulated in the protocol, approval must be obtained beforehand from the Data and Safety Monitoring Committee.

However, the research chairman or secretariat may announce publications introducing the trial at scientific meetings or articles (general remarks), but it may not include analytical results of the trial endpoints. After enrollment completion, scientific meetings/articles on safety data and distribution of patient background may be presented with the approval of the research group chairman and the JCOG Data Center director; however approval from the Data and Safety Monitoring Committee is not required.

As a general rule, the hierarchy for the authors of the main publication of the trial results will include the research secretariat at the top, followed by the research chairman, the statistical officer of the Data Center (one officer at the time of conducting analyses for publication), and the group chairman. Following the names of these individuals, depending on the limitations stipulated by the author contribution guidelines, co-authors will be selected by each institutional coordinator or principal investigator and will be listed in order of the highest enrollment number.

All co-authors will review the article content prior to submission, and only those who agree to present the content will be included. If agreement to the content is not obtained even after having discussed it, with the approval of the research chairman or group chairman, that researcher may not be included as a co-author.

Because there may be several conference presentations, the research secretariat, research chairman, principal investigator, and coordinators of facilities with high enrollments will take turns making the presentations. The presenter will be determined by the research chairman with the approval of the group chairman. However, in the event of conference presentations, the preparation and content of the presentation will be the responsibility of the research chairman, and, as a general rule, the research chairman will contact the Data Center. Presenters other than the research secretariat may receive the aggregated/analysis results directly from the Data Center, without approval of the research secretariat or the JCOG Data Center director.

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19.Appendix

- Explanatory document and consent form
- Body surface area chart
- Toxicity classification (CTCAE v4.0-JCOG)
- Full set of CRFs
- JCOG Biobank project protocol
- JCOG Biobank project explanatory document and consent form

VI　研究成果の刊行物・別刷

革新的がん医療実用化研究事業
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Invest New Drugs (2014) 32:261–270
DOI 10.1007/s10637-013-9948-5

PHASE I STUDIES

Phase I study of sunitinib plus S-1 and cisplatin in Japanese patients with advanced or metastatic gastric cancer

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Received: 28 November 2012 / Accepted: 1 March 2013 / Published online: 12 May 2013

Summary *Background* This phase I, dose-finding study evaluated the maximum tolerated dose (MTD), safety, pharmacokinetics, and antitumor activity of sunitinib plus S-1/cisplatin in Japanese patients with advanced/metastatic gastric cancer. *Patients and methods* Patients received oral sunitinib on a continuous daily dosing (CDD) or 2-weeks-on/2-weeks-off schedule (Schedule 2/2; 25 mg/day or 37.5 mg/day), plus S-1 (80–120 mg/day)/cisplatin 60 mg/m^2. *Results* Twenty-seven patients received treatment, including 26 patients treated per protocol (sunitinib 25 mg/day CDD schedule, n=4; sunitinib 25 mg/day Schedule 2/2, n=16 [dose-limiting toxicity (DLT) cohort, n=6 plus expansion cohort, n=10]; sunitinib 37.5 mg/day Schedule 2/2, n=6). One patient erroneously self-administered sunitinib 12.5 mg/day and was excluded from the analyses. The MTD was sunitinib 25 mg/day on Schedule 2/2. DLTs were reported for: 2/4 patients given sunitinib 25 mg/day on the CDD schedule; 1/6 patients administered sunitinib 25 mg/day on Schedule 2/2 (grade [G] 3 neutropenic infection, G4 thrombocytopenia, and S-1 dose interruption ≥5 days), and 3/6 patients given sunitinib 37.5 mg/day on Schedule 2/2. Results below are for the overall MTD cohort (n=16). The most frequently reported G3/4 adverse events were neutropenia (93.8 %) and leukopenia (75.0 %). The objective response rate was 37.5 %; six additional patients experienced no disease progression for ≥24 weeks. Median progression-free survival was 12.5 months. No pharmacokinetic drug–drug interactions were observed between sunitinib/S-1/cisplatin and S-1/cisplatin. *Conclusions* The MTD of sunitinib was 25 mg/day on Schedule 2/2 combined with cisplatin/S-1 in patients with advanced/metastatic gastric cancer. This regimen had a manageable safety profile and preliminary antitumor activity.

Keywords Sunitinib · Gastric cancer · Phase I · Dose-finding

Presented in part on the clinical trial registry located at ClinicalTrials.gov (identification No. NCT00553696) and at:

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Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide, with more than 730,000 deaths estimated to have occurred in 2008 [1]. Globally, the

5-year survival rate for gastric cancer is approximately 20 % [2], and most patients present with advanced, non-resectable disease [3–5].

Despite recent advances in the treatment for gastric cancer [6], a standard chemotherapy regimen has not been established for recurrent or unresectable advanced gastric cancer; combination chemotherapy is associated with significant survival and quality of life advantages, compared with best supportive care [7, 8]. The use of a 5-fluorouracil (5-FU)-based regimen in combination with a platinum analog is the most widely accepted first-line treatment regimen, although combination therapy does have a higher associated toxicity burden compared with single-agent chemotherapy [8].

Blockade of receptors such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) has been shown to inhibit tumor-related angiogenesis and tumor growth [9, 10]. Not only are these receptors expressed in gastric cancers but they are known to have direct effects on the growth and metastasis of this disease [9–14].

Sunitinib malate (SUTENT®; Pfizer Inc., New York, NY, USA) is an oral, multitargeted, tyrosine kinase inhibitor of VEGFRs 1–3, PDGFR-α and -β, and other receptors [15–17]. Sunitinib is approved multinationally for the treatment of unresectable and/or metastatic imatinib-resistant/-intolerant gastrointestinal stromal tumor, advanced/metastatic renal cell carcinoma, and unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors. Phase II study results in advanced gastric cancer have shown that sunitinib had activity as a single-agent; progression-free survival (PFS) was 2.3 months and overall survival was 6.8 months in the second-line setting [18].

In preclinical tumor models, sunitinib has been shown to enhance the antitumor activity of 5-FU and cisplatin, suggesting that sunitinib might enhance the effect of chemotherapy in cancer patients [19, 20]. In the First-Line Advanced Gastric Cancer Study (FLAGS), the combination of S-1, an oral derivative of 5-FU, and cisplatin was found to be effective when administered as a 3-week on/1-week off regimen (Schedule 3/1) [21]. Therefore, this phase I, dose-finding study was conducted to determine the maximum tolerated dose (MTD) and overall safety profile of sunitinib plus S-1 and cisplatin in Japanese patients with advanced/metastatic gastric cancer. Tolerability, pharmacokinetics (PK), and antitumor activity were also evaluated.

Materials and methods

Study population

Patients (male or female) eligible for inclusion in this study were aged ≥20 years, had an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and histologically or cytologically confirmed Stage IV gastric adenocarcinoma or gastroesophageal junction adenocarcinoma not amenable to surgery or radiation. Prior adjuvant therapy was permitted with a recurrence-free interval of >3 months after the completion of adjuvant therapy. Prior chemotherapy in the advanced/metastatic setting was not permitted; one regimen of chemotherapy, such as S-1 monotherapy, without progressive disease was allowed if the duration of treatment was less than 4 weeks.

Exclusion criteria included central nervous system (CNS) metastases, carcinomatous meningitis, or uncontrolled hypertension (blood pressure >150/100 mmHg). Patients with severe/unstable angina, myocardial infarction, coronary artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, including transient ischemic attack, or pulmonary embolism within 12 months prior to starting study treatment were also excluded.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the declaration of Helsinki, and applicable local regulatory requirements and laws. Approval from the institutional review board or independent ethics committee with the appropriate jurisdiction was required for each participating investigator/center. Written informed consent was obtained from all patients.

Study design

This was a phase I, open-label, dose-finding study of sunitinib in combination with S-1 and cisplatin in patients with advanced/metastatic gastric cancer (NCT00553696). Patients received open-label, oral S-1 at a starting dose of 80–120 mg/day (based on body surface area) on Schedule 3/1 and a cisplatin 60 mg/m^2 infusion on day 1 that was repeated every 28 days. Patients were allocated to different doses of oral sunitinib based on a 3+3 design. Initially, sunitinib was planned to be administered on a continuous daily dosing (CDD) schedule or on Schedule 3/1. After four patients received treatment in the CDD arm, the protocol was revised to use a 2-week-on/2-week-off schedule (Schedule 2/2), instead of Schedule 3/1, due to the pattern of adverse events (AEs). Patients received sunitinib 25 mg/day on a CDD schedule, or 25 mg/day or 37.5 mg/day on Schedule 2/2 in 4-week cycles (Fig. 1).

Initially, three patients were enrolled to receive sunitinib 25 mg/day on the CDD schedule in combination with S-1 and cisplatin 60 mg/m^2. If no patients experienced a dose-limiting toxicity (DLT) in cycle 1 then patients would be enrolled to the next highest dose level. If no more than one of the initial three patients experienced a DLT within cycle 1, then the cohort was expanded to a total of six patients. If no more than one of these six patients experienced a DLT,

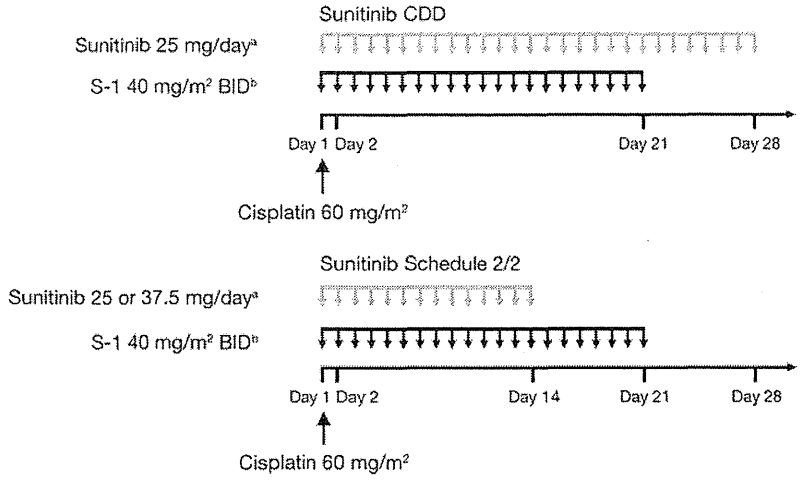

Fig. 1 Treatment schema. [a]Sunitinib dose withheld on cycle 1 day 1 to enable pharmacokinetic analysis of S-1 and cisplatin. [b]S-1 and cisplatin dose withheld on cycle 1 day 1 to enable pharmacokinetic analysis of sunitinib. *BID* twice daily; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

then patients would be enrolled at the next highest dose level.

The MTD was defined as the highest dose cohort where 0/3 or ≤1/6 patients experienced a DLT, with the next highest dose having at least 2/3 or 2/6 patients who experienced a DLT. DLTs are defined in Table 1. In this study, the MTD level was confirmed by expanding enrollment to include up to 10 additional patients with advanced/metastatic disease in order to obtain additional safety data for the combination treatment. It was anticipated that a total of approximately 30 patients would be enrolled in this study.

Dose modifications of sunitinib were not allowed until a DLT was reached. Once dose reduction occurred due to study drug-related toxicity, the dose was not re-escalated. Patients could undergo a maximum of two dose reductions of either S-1 and/or cisplatin. However, patients requiring more than two dose reductions of S-1 or sunitinib were withdrawn from the study. Additionally, patients with >1 missed cisplatin dose were withdrawn. Treatment was continued for 8 cycles or until disease progression, unacceptable toxicity, or withdrawal of patient consent.

The primary endpoint was the assessment of first-cycle DLTs for sunitinib plus S-1 and cisplatin. Secondary endpoints included overall safety, tumor response, PFS, and PK.

Assessments

Patients were evaluable for DLT assessment if they received all day 1 chemotherapy and ≥80 % of their sunitinib doses and S-1 doses. Those who could not receive ≥80 % of their doses for reasons other than a DLT were excluded from the DLT evaluation. Tumor assessment was performed at baseline, on day 22 of cycle 1, and every 4 weeks thereafter until radiographic-confirmed disease progression or end of treatment scan. Objective tumor response in patients with at least one target lesion was measured using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [22]

Table 1 Definition of DLT

Category	DLT criteria
Hematologic	Grade 4 neutropenia lasting ≥7 days
	Grade ≥3 febrile neutropenia
	Grade ≥3 neutropenic infection
	Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding
Non-hematologic[a]	Grade 3 toxicities lasting ≥7 days
	Grade 4 non-hematologic toxicity
	Grade 3/4 nausea, vomiting or diarrhea persisting despite maximum supportive therapy
Missed/delayed dose due to toxicity	Break from sunitinib dose ≥6/28 days on the CDD schedule or ≥3/14 days on Schedule 2/2
	Break from S-1 dose ≥5/21 days per cycle
	Delay of >3 weeks in starting the second treatment cycle

CDD continuous daily dosing; *DLT* dose-limiting toxicity; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

[a] Exceptions: hyperamylasemia or hyperlipasemia without other clinical evidence of pancreatitis and asymptomatic hyperuricemia; asymptomatic hypertension with adequately controlled blood pressure

and confirmed no sooner than 4 weeks after the initial documentation of response.

Safety was assessed at regular intervals (during cycle 1 on days 1, 2, 8, 15, and 22; during cycles 2–8 on days 1, 2, and 21; and during cycles ≥9 on days 1 and 21). AEs were monitored during the study and graded using the National Cancer Institute Common Terminology for Adverse Events version 3.0 clinical assessments, including laboratory testing for blood hematology and serum chemistry.

To investigate PK drug–drug interactions, full PK profiles of sunitinib, its active metabolite SU12662, S-1 (5-FU, tegafur) and cisplatin (total and free) were assessed in all cohorts comprising the 3+3 design, and in the MTD expansion cohort. Blood samples for analyses of cisplatin and S-1 were collected on cycle 1 days 1–2 (S-1 and cisplatin), before starting sunitinib dosing on day 2, and on cycle 2 days 1–2 (in combination with sunitinib) in the MTD cohort. In the expansion cohort, blood samples for the analyses of sunitinib and SU12662 were collected on cycle 1 days 1–2 (sunitinib alone), prior to administration of S-1 and cisplatin on day 2, and cycle 2 days 1–2 (in combination with S-1 and cisplatin). PK parameters were calculated using non-compartmental methods.

Trough plasma concentrations of sunitinib and SU12662 were obtained at steady state on cycles 1–3 days 21–22 for the CDD schedule, and cycles 1–3 days 14–15 for Schedule 2/2. Blood samples were obtained before the administration of sunitinib and S-1.

On the day of cisplatin PK sampling, blood was drawn pre-dose (before administration of cisplatin, S-1 or sunitinib) and at 0.5, 1, 2, 8, and 22 h after completing infusion. Samples for evaluation of sunitinib, SU12662, and S-1 PK were obtained pre-dose (before administration of either S-1 or sunitinib) and at 1, 2, 4, 6, 8, and 10 h post-dose (before dosing of S-1). For sunitinib and SU12662, a sample was also obtained 24 h post-dose.

Plasma samples were analyzed for sunitinib and SU12662 concentrations by Bioanalytical Systems Inc. (USA) using a validated high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) method. Tegafur and 5-FU plasma concentrations were also determined using a validated HPLC-MS/MS method by Tandem Labs (USA). Cisplatin concentrations were determined in both plasma and plasma ultra filtrate samples by Covance Laboratories Inc. (USA) using a validated Inductively Coupled Plasma–Mass Spectrometric (ICP/MS) method.

Statistical analysis

The sample size was determined on an empirical rather than statistical basis. Assessment of 3–6 patients for each cohort was considered adequate to characterize the safety of a treatment regimen prior to investigation in phase II clinical trials. It was anticipated that up to 30 patients would be enrolled in this study.

Efficacy analyses included all patients who received at least one protocol-specified dose of sunitinib. Descriptive statistics were used to summarize all patient characteristics, treatment administration/compliance, antitumor activity, and safety; PFS was summarized using the Kaplan–Meier method. In an unplanned exploratory analysis, clinical benefit rate (CBR; percentage of patients with a complete response, partial response, and stable disease ≥24 weeks) and PFS were calculated in patients with scirrhous-type disease of primary tumors.

Results

Patient characteristics

In total, 27 patients received treatment, including 26 patients treated per protocol (sunitinib 25 mg/day on the CDD schedule, 4; sunitinib 25 mg/day on Schedule 2/2, 16 [DLT cohort, 6 plus expansion cohort, 10]; sunitinib 37.5 mg/day on Schedule 2/2, 6), and one patient who was assigned to sunitinib 25 mg/day on Schedule 2/2 and erroneously self-administered sunitinib 12.5 mg/day throughout the study. The latter patient was excluded from the efficacy analyses. One patient remained on study as of April 2012. Demographic and baseline disease characteristics are shown in Table 2. Overall, eight patients had scirrhous-type disease (seven patients in the MTD cohort).

Safety and drug exposure

Twenty-seven patients were evaluable for safety. The MTD was determined to be sunitinib 25 mg/day on Schedule 2/2 plus cisplatin and S-1, and a further 10 patients were allocated to this cohort. Of the four patients who received sunitinib 25 mg/day on the CDD schedule, two DLTs were reported: grade 4 thrombocytopenia (n=1), and grade 4 thrombocytopenia plus grade 3 febrile neutropenia (n=1). Subsequently, the treatment frequency was reduced to sunitinib 25 mg/day on Schedule 2/2. In the second cohort, one of six patients reported a DLT: grade 3 neutropenic infection plus grade 4 thrombocytopenia and S-1 dose interruption of ≥5 days. As defined in the protocol, the sunitinib dose was then increased to 37.5 mg/day on Schedule 2/2, where three of six patients experienced a DLT: grade 3 febrile neutropenia plus S-1 dose interruption of ≥5 days (n=1), grade 4 thrombocytopenia (n=1), and grade 4 neutropenia of ≥7 days (n=1).

All patients experienced at least one AE. No grade 5 AEs occurred. Serious AEs (SAEs) were reported in 13

Table 2 Baseline patient characteristics

	CDD schedule sunitinib 25 mg/day	Schedule 2/2 sunitinib 25 mg/day		Schedule 2/2 sunitinib 37.5 mg/day
	All patients (n=4)[a]	All patients (n=16)[b,c]	Patients with scirrhous-type disease (n=7)	All patients (n=6)[d]
Gender, male, n (%)	2 (50.0)	13 (81.3)	6 (85.7)	4 (66.7)
Age, years				
Median	63.0	60.0	57.0	60.5
Range	44–73	31–71	31–67	28–71
ECOG performance status, n (%)				
0	1 (25.0)	7 (43.8)	2 (28.6)	3 (50.0)
1	3 (75.0)	9 (56.3)	5 (71.4)	3 (50.0)
Measurable disease, n (%)	3 (75.0)	11 (68.8)	5 (71.4)	4 (66.7)
Histology, n (%)				
Diffuse	2 (50.0)	9 (56.2)	6 (85.7)	2 (33.3)
Intestinal	2 (50.0)	7 (43.8)	1 (14.3)	3 (50.0)
Other	0 (0)	0 (0)	0 (0)	1[e] (16.7)
Prior surgery, n (%)	1 (25.0)	5 (31.3)	1 (14.3)	2 (33.3)
Prior systemic therapy, n (%)				
0	2 (50.0)	16 (100.0)	7 (100.0)	5 (83.3)
1	2 (50.0)	0 (0)	0 (0)	1 (16.7)
≥2	0 (0)	0 (0)	0 (0)	0 (0)

CDD continuous daily dosing; *ECOG* Eastern Cooperative Oncology Group; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

[a] Includes one patient with scirrhous-type disease

[b] Includes 10 patients from the expansion cohort

[c] The subject assigned to sunitinib 25 mg/day on Schedule 2/2 who mistakenly received sunitinib 12.5 mg/day was excluded from the efficacy analyses. At baseline, this patient had an ECOG performance status of 0, stage IV measurable intestinal disease, with 2 involved tumor sites (liver and lymph node) and no prior surgery or systemic therapy

[d] No patients had scirrhous-type disease in this cohort

[e] This patient had mucinous histology

patients overall (48.1 %). Dose reductions due to AEs occurred for all three drugs: sunitinib: n=8; S-1: n=7; cisplatin: n=8. At the MTD, the median relative dose intensity (% actual/intended dose intensity) was 80.6 % (range, 32.4–100.0) for sunitinib (25 mg/day, Schedule 2/2), 68.2 % (35.7–85.7) for S-1, and 73.8 % (27.1–98.9) for cisplatin. Overall, seven patients discontinued the study treatment due to AEs, including four patients in the MTD cohort.

In the MTD cohort (sunitinib 25 mg/day, Schedule 2/2; n=16), the frequencies of common AEs of any grade are presented in Table 3. Neutropenia was the most frequently reported grade 3 or 4 AE, occurring in 15 patients (93.8 %). In total, 75.0 % of patients in the MTD cohort experienced grade 3 or 4 leukopenia. Fatigue, decreased appetite, nausea, constipation, thrombocytopenia, and stomatitis were the most common grade 1 or 2 AEs reported. In this cohort, SAEs occurred in eight patients (50.0 %); the most frequent SAEs were febrile neutropenia (n=3, 18.8 %) and platelet count decreased (n=2, 12.5 %).

Pharmacokinetics

The MTD combination of sunitinib (25 mg/day, Schedule 2/2) with S-1 plus cisplatin demonstrated no changes in the PK of sunitinib or its active metabolite (SU12662). In addition, combination treatment had no impact on the PK of cisplatin, tegafur, 5-FU, or S-1, compared with S-1 plus cisplatin alone (Table 4).

The mean trough plasma concentrations (C_{trough}) of sunitinib, SU12662, and total drug were 33.5 ng/mL, 13.9 ng/mL, and 47.5 ng/mL, respectively, for sunitinib 25 mg/day, and 69.9 ng/mL, 24.0 ng/mL, and 93.4 ng/mL, respectively, for sunitinib 37.5 mg/day. These C_{trough} values suggested that plasma concentrations of sunitinib increased in a dose-dependent manner.

Antitumor activity

All patients were evaluable for efficacy. In the MTD group (sunitinib 25 mg/day, Schedule 2/2), 11/16 patients had

Table 3 Treatment-emergent (all-causality) adverse events in ≥30 % of patients in the maximum tolerated dose cohort (sunitinib 25 mg/day on Schedule 2/2+cisplatin+S-1; n=16)

Adverse event, n (%)	Grade 1/2	Grade 3/4	All grades
Leukopenia	4 (25.0)	12 (75.0)	16 (100.0)
Neutropenia	1 (6.3)	15 (93.8)	16 (100.0)
Anemia	6 (37.5)	9 (56.3)	15 (93.8)
Decreased appetite	14 (87.5)	1 (6.3)	15 (93.8)
Thrombocytopenia	9 (56.3)	6 (37.5)	15 (93.8)
Fatigue	14 (87.5)	0	14 (87.5)
Nausea	14 (87.5)	0	14 (87.5)
Constipation	12 (75.0)	0	12 (75.0)
Stomatitis	9 (56.3)	0	9 (56.3)
Diarrhea	7 (43.8)	1 (6.3)	8 (50.0)
Dysgeusia	7 (43.8)	0	7 (43.8)
Pyrexia	7 (43.8)	0	7 (43.8)
Hiccups	6 (37.5)	0	6 (37.5)
Rash	5 (31.3)	0	5 (31.3)
Vomiting	5 (31.3)	0	5 (31.3)

Schedule 2/2 2 weeks on treatment followed by 2 weeks off treatment

measurable disease. No patients had a complete response, and partial responses occurred in 6/11 patients (54.5 %) with measurable disease, resulting in an overall objective response rate (ORR) of 37.5 % (95 % confidence interval [CI], 15.2–64.6) in 16 evaluable patients. A further six patients experienced no disease progression for ≥24 weeks, producing a CBR of 75.0 % (95 % CI, 47.6–92.7) among the 16 patients. Maximum percentage reduction in target lesion size in the 11 patients with measurable disease is shown in Fig. 2. The CBR for patients treated at the MTD with scirrhous-type disease was 57.1 % (95 % CI, 18.4–90.1; 4/7 patients). Tumor response in one patient with scirrhous-type disease is shown in Fig. 3. At the MTD, median PFS was 12.5 months (95 % CI, 6.4–16.5) and 6-month survival was 78.3 % (95 % CI, 56.5–100.0; Table 5; Fig. 4). Among the seven patients with scirrhous-type disease, four of five patients who had measurable lesion had a partial response, and median PFS was 12.5 months (95 % CI, 10.1–13.3).

Discussion

In this study, the MTD of sunitinib in combination with S-1 (80–120 mg) plus cisplatin 60 mg/m^2 was established as 25 mg/day on Schedule 2/2 in patients with advanced or metastatic gastric cancer for whom curative therapy was not an option. Other tested combinations included sunitinib 25 mg/day on a CDD schedule and a dose-increment from the MTD cohort to 37.5 mg; both cohorts were discontinued after DLTs were experienced. An additional 10 patients were then enrolled in the MTD cohort and followed for safety, antitumor activity, and PK parameters.

The MTD combination regimen demonstrated a manageable safety profile, with neutropenia and leukopenia as the most frequently reported grade 3 or 4 AEs: 93.8 % and 75.0 %, respectively. This safety profile was also consistent with a similar phase I dose-escalation study conducted in Western patients with advanced gastric cancer [23]. In general, the type of AEs was consistent with those previously reported when 5-FU and cisplatin were administered in patients with gastric cancer [24], although the frequency of events, particularly hematologic AEs, was greater than expected from previous studies of sunitinib in other tumor types [18, 25–28]. Previously reported mild skin reactions associated with sunitinib, such as yellowing skin/discoloration [29], were not observed in this study. There were no grade 3 or 4 non-

Table 4 Pharmacokinetics in the maximum tolerated dose cohort (sunitinib 25 mg/day on Schedule 2/2+cisplatin+S-1)

Treatment	Analyte	n	Mean C_{max} ng/mL (CV%)		Mean AUC_{last} ng·h/mL (CV%)	
			Sunitinib alone or SP	Combined	Sunitinib alone or SP	Combined
Sunitinib	Sunitinib	7	15.8 (32.2)	16.2 (44.6)	234 (25.3)	244 (38.6)
	SU12662	7	2.9 (43.6)	2.8 (49.3)	46.0 (34.2)	50.5 (50.7)
	Total drug	7	18.5 (33.0)	19.0 (42.3)	280 (25.0)	294 (37.2)
S-1	Tegafur	5	1,500 (9.8)	1,688 (26.9)	8,290 (10.5)	9,163 (12.7)
	5-FU	5	144 (23.5)	114 (16.5)	582 (19.3)	522 (28.0)
Cisplatin	Total	5	1,794 (7.8)	1,984 (3.6)	27,478 (7.1)	31,574 (5.4)
	Free	5	178 (68.3)	187 (74.6)	790 (25.8)	973 (28.3)

AUC_{last} area under the plasma concentration–time curve from time zero until last quantifiable observation; *C_{max}* maximum concentration; *CV* coefficient of variation; *5-FU* 5-fluorouracil; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment; *SP* cisplatin 60 mg/m^2 every 28 days+S-1 40 mg/m^2 twice daily every 3/1 weeks; *SU12662* sunitinib active metabolite

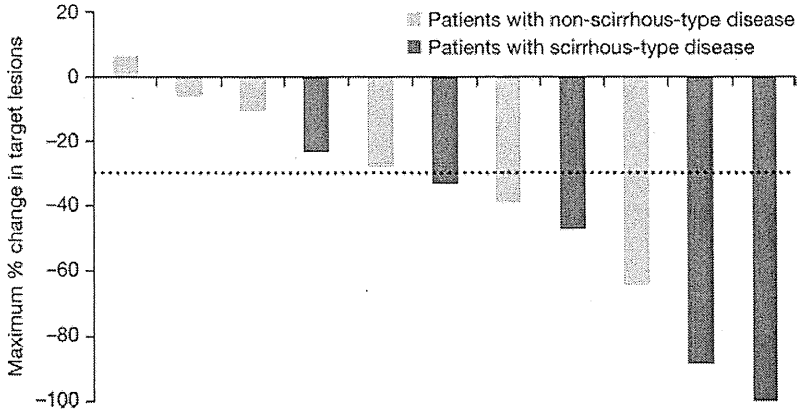

Fig. 2 Maximum percentage change in target lesion size in the maximum tolerated dose (MTD) cohort (sunitinib 25 mg/day on Schedule 2/2+cisplatin+S-1).[a] *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment. [a]Five of 16 patients receiving the MTD did not have measurable disease

hematologic events reported in ≥30 % of patients within the MTD cohort. No new safety signals were observed for sunitinib.

Although tumor evaluation was not the primary objective of this study, the ORR for the MTD cohort was 37.5 % (95 % CI, 15.2–64.6) and included responses in patients with scirrhous-type disease. Since five of 16 patients treated at the MTD did not have measurable disease and were assessed as non-responders in the ORR calculation, tumor response rates may be underestimated in our study. The ORR at the MTD among the 11 patients with measurable disease was 54.5 %. Median PFS was 12.5 months (95 % CI, 6.4–16.5) in the overall MTD cohort. These results demonstrate promising preliminary antitumor activity, compared with that observed for sunitinib as a single-agent modality in advanced gastric cancer, [18] and with the median PFS of 6 months reported for S-1 plus cisplatin [30]. However, our results must be interpreted with caution given the limited sample size studied.

A multitargeted tyrosine kinase inhibitor like sunitinib may be a promising drug for scirrhous gastric cancer. Our preliminary results suggest that sunitinib in combination

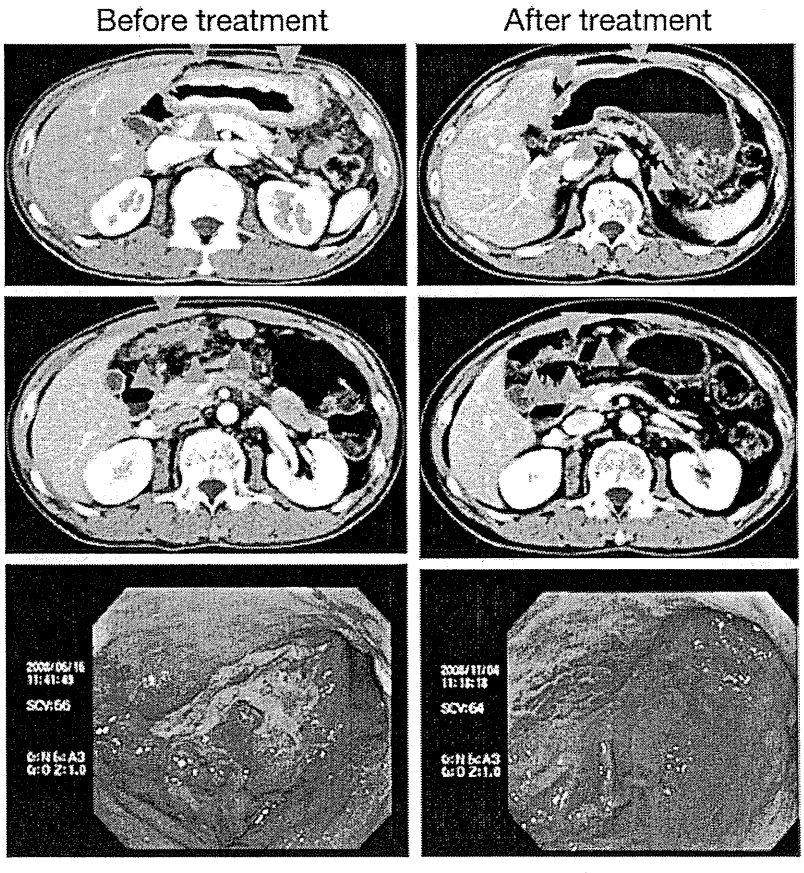

Fig. 3 Tumor response in a patient with scirrhous gastric cancer who received the maximum tolerated dose of sunitinib (25 mg/day on Schedule 2/2) combined with cisplatin and S-1. Blue arrowheads: primary lesion; orange arrowheads: peritoneal metastasis; green arrowheads: lymph node metastasis; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

Table 5 Summary of progression-free survival

	CDD schedule	Schedule 2/2	
	Sunitinib 25 mg/day (n=4)	Sunitinib 25 mg/day (n=16)[a]	Sunitinib 37.5 mg/day (n=6)
Patients with events, n (%)	2 (50.0)	9 (56.3)	4 (66.7)
Progression-free survival, months[b]			
Median	7.1	12.5	5.8
95 % CI	6.7–7.5	6.4–16.5	4.4–7.9
Probability of being event-free at month 6[c]			
Percentage	100.0	78.3	50.0
95 % CI[d]	100.0–100.0	56.5–100.0	1.0–99.0
Exploratory analysis: scirrhous-type disease			
		Schedule 2/2	
		Sunitinib 25 mg/day (n=7)[a]	
Patients with events, n (%)		4 (57.1)	
Progression-free survival, months[b]			
Median		12.5	
95 % CI		10.1–13.3	

CDD continuous daily dosing; *CI* confidence interval; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

[a] Maximum tolerated dose

[b] Based on the Brookmeyer and Crowley Method

[c] Estimated from the Kaplan–Meier curve

[d] Calculated from the product-limit method

with S-1 and cisplatin might have antitumor activity in patients with this disease type. However, as only seven of 16 patients at the MTD had scirrhous-type disease, caution should be used when interpreting these results. Despite this caveat, these data are encouraging, as scirrhous gastric cancer carries a worse prognosis than the non-scirrhous-type [31, 32], as it is characterized by rapid cancer cell infiltration and proliferation accompanied by extensive stromal fibrosis [32]. The proliferative and invasive ability of scirrhous gastric cancer cells have been shown to be closely associated with the growth factors produced by organ-specific fibroblasts and other stromal cells [32]. Therefore, targeting this cancer–stroma interaction using a multitargeted tyrosine kinase inhibitor such as sunitinib could be a reasonable treatment option for patients with scirrhous gastric cancer. However, large randomized studies would be required to confirm this hypothesis.

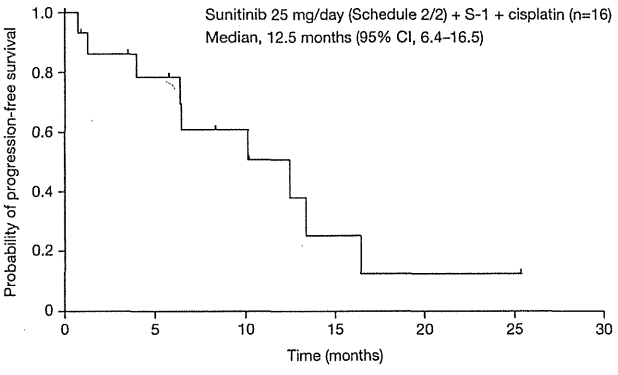

Fig. 4 Kaplan-Meier estimate of progression-free survival in the maximum tolerated dose cohort (sunitinib 25 mg/day on Schedule 2/2+ cisplatin+S-1). *CI* confidence interval; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

The combination of sunitinib with cisplatin plus S-1 demonstrated no PK drug–drug interactions, consistent with the different pathways of metabolism and elimination for these drugs. These findings are consistent with those from the phase I study with cisplatin plus 5-FU in Western patients [23]. The mean observed C_{trough} plasma concentration of 47.5 ng/mL, for total drug (sunitinib plus SU12662) at steady-state with sunitinib 25 mg/day dosing, in the present study suggests that optimal sunitinib exposure was almost achieved, in terms of the required concentration for target inhibition of ≥50 ng/mL [16].

In summary, the MTD of sunitinib was 25 mg/day on Schedule 2/2 in combination with cisplatin and S-1 when administered as a first-line therapy in patients with advanced or metastatic gastric cancer. This combination had a manageable safety profile and showed preliminary evidence of antitumor activity.

Acknowledgments We thank the participating patients and their families, as well as the investigators, research nurses, study coordinators, and operations staff. Medical writing support was provided by

Nicola Crofts and Molly Heitz (ACUMED®, Tytherington, UK) with funding from Pfizer Inc.

Conflict of interest Narikazu Boku, Nozomu Machida, Kei Muro, and Yoshinori Miyata have nothing to disclose.

Mariajose Lechuga and Nobuyuki Kimura are Pfizer Inc. employees and hold Pfizer Inc. stock.

Satoshi Hashigaki and Mie Suzuki are Pfizer Inc. employees.

Funding source This study was sponsored by Pfizer Inc.

Quantity of supporting information None

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Gastric Cancer (2014) 17:383–386
DOI 10.1007/s10120-013-0264-8

SHORT COMMUNICATION

Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer

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Received: 4 December 2012 / Accepted: 21 April 2013 / Published online: 30 May 2013

Abstract
Background We previously reported that S-1 plus cisplatin was feasible as adjuvant chemotherapy for stage III gastric cancer after D2 gastrectomy. Herein we evaluate the recurrence-free survival and overall survival rates as secondary endpoints based on updated follow-up data.
Methods Patients with stage III gastric cancer who underwent D2 gastrectomy were enrolled. Treatment consisted of 3 cycles of S-1 (40 mg/m^2 PO) twice daily on days 1–21 and cisplatin (60 mg/m^2 IV) on day 8, and S-1 was given on days 1–28 every 6 weeks until 1 year after surgery.
Results From August 2007 to September 2009, 63 patients were accrued. Overall, 34 and 25 patients had stage IIIA and IIIB disease, respectively. After a median follow-up of 3.9 years, 16 patients experienced recurrence and 11 patients died. The 3-year recurrence-free survival rate was 74.1 % (95 % CI: 60.8–83.5 %, IIIA 81.8 %, IIIB 64.0 %). The 3-year overall survival rate was 84.5 % (95 % CI: 72.3–91.6 %, IIIA 87.9 %, IIIB 80.0 %).

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Recurrence sites included the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$).
Conclusion The present results indicate that adjuvant therapy with S-1 plus 3 cycles of cisplatin may provide a survival benefit to patients with stage III gastric cancer.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

In 2007, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated the efficacy of S-1 for stage II–III Gastric Cancer (GC) patients who underwent curative resection with D2 gastrectomy [1, 2]. The addition of S-1 improved the overall survival (OS) rate, with a low incidence of adverse events and good compliance. According to this result, in Japan, the currently recommended adjuvant treatment after D2 gastrectomy is S-1 for 1 year. However, the 5-year OS rates in stage III patients receiving S-1 have been less satisfactory: 67.1 and 50.2 % for stage IIIA and IIIB, respectively. Therefore, identification of more effective treatments for stage III GC is urgently needed. So firstly we evaluated the feasibility of S-1 plus cisplatin, that is now considered to be one of the standard regimens for metastatic or recurrent GC [3] as adjuvant chemotherapy for Stage III GC after D2 gastrectomy.

As results, treatment completion rates after 3 cycles of S-1 plus cisplatin were 72 % (42/58; 95 % CI: 60–84 %; 57 % [12/21] before and 81 % [30/37] after the protocol amendment). Grade 3/4 toxicities included neutropenia (40 %), anorexia (28 %), and febrile neutropenia (4 %) before the protocol amendment, and neutropenia (37 %), anorexia (8 %), and febrile neutropenia (3 %) after the amendment implementation. Therefore, we concluded that the amended S-1 plus cisplatin regimen is feasible as adjuvant chemotherapy [4].

In this report, we evaluate the recurrence-free survival (RFS) and OS as secondary endpoints based on updated follow-up data.

Methods

Patients eligible for this trial had either stage IIIA (T2,N2; T3,N1; T4,N0) or stage IIIB (T3,N2; T4,N1) [5] gastric adenocarcinoma and had undergone D2 gastrectomy with R0 surgical resection. Additional details were described as previously [4]. The protocol was approved by the institutional review board at each participating center. Treatment according to the original protocol was initiated 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin (SP) followed by S-1 for up to 1 year. In the SP step, each cycle consisted of 40 mg/m^2 S-1 taken orally twice-daily for 21 days plus a 2-hour infusion of 60 mg/m^2 cisplatin on day 8. Each cycle was administered at 5-week intervals. In the S-1 step, 40 mg/m^2 S-1 was taken for 28 days at 6-week intervals. During enrollment, some toxicity was reported during the first cycle of SP, particularly neutropenia and anorexia. To minimize patient's risk, we elected to amend the protocol. Treatment according to the amended protocol was initiated 4–6 weeks after surgery and consisted of the following: the first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 was administered for up to 1 year. Tumor assessments with ultrasonography, computed tomography, and GI endoscopy and radiography were performed every 6 months for first 2 years after surgery, and annually thereafter (maximum follow-up 5 years). RFS was defined as the time from enrollment to the recurrence or death, whichever occurred first. OS was defined as the time from enrollment to death from any cause.

Results

From August 2007 to July 2009, 63 patients (25 patients in the original protocol, 38 patients in the amended protocol) were accrued from five Japanese institutions. Overall, 34 patients (54 %) had stage IIIA disease and 25 (40 %) had stage IIIB disease. The patient clinical characteristics have been reported previously [4]. After enrollment, 5 patients were deemed ineligible due to confirmed stage II disease ($n = 2$), stage Ib disease ($n = 1$), stage IV disease ($n = 1$), and cancer other than GC ($n = 1$).

OS and RFS were analyzed in 58 eligible patients. At the time of data cut-off on July 31, 2012, 11 patients had died, 5 patients were alive with recurrence, and the remaining 42 patients were alive without recurrence. The median follow-up period was 46 months. All patients could be followed-up for at least 3 years from the date of surgery. Kaplan–Meier estimates are shown that the 3-year OS rate was 84.5 % (95 % CI: 72.3–91.6 %) (Fig. 1a), and the 3-year RFS rate was 74.1 % (95 % CI: 60.8–83.5 %) (Fig. 1b). According to disease stage, the 3-year OS rate of patients with stage IIIA disease was 87.9 % (95 % CI: 70.9–95.3 %) (Fig. 2a), and the 3-year RFS rate was 81.8 % (95 % CI: 63.9–91.4 %) (Fig. 2b). The 3-year OS rate of patients with stage IIIB disease was 80.0 % (95 % CI: 58.4–91.1 %) (Fig. 2a). The 3-year RFS rate was 64.0 % (95 % CI: 42.2–79.4 %) (Fig. 2b).

In addition, there was no significant difference in survival between the original protocol and the amended

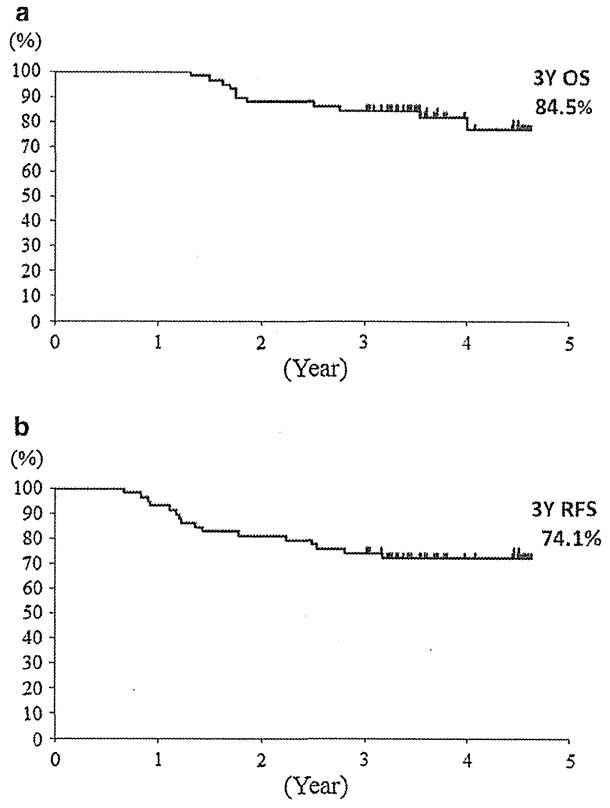

Fig. 1 Kaplan–Meier estimates of **a** overall survival and **b** relapse-free survival for all eligible patients

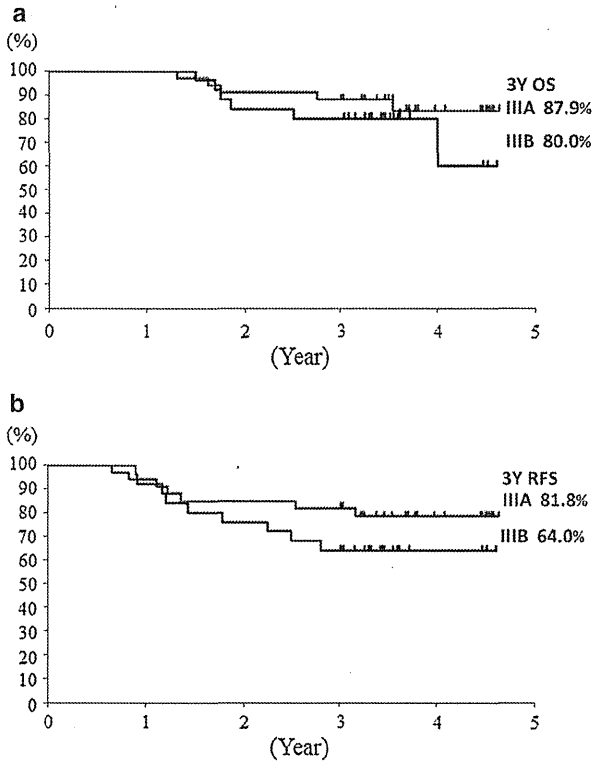

Fig. 2 Kaplan–Meier estimates of **a** overall survival and **b** relapse-free survival for patients with stage IIIA and IIIB gastric cancer

protocol. The 3-year OS rate of patients with stage IIIA disease in the original protocol ($n = 16$) and the amended ($n = 17$) was 87.5 and 88.2 %, respectively, and the 3-year RFS rate was 75.0 and 82.4 %, respectively. The 3-year OS rate of patients with stage IIIB disease was 80.0 % in the original protocol ($n = 5$) and the amended protocol ($n = 20$), and the 3-year RFS rate was 60.0 and 65.0 %, respectively.

The most common sites of relapse were the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$). Two patients experienced relapses simultaneously in the liver and the lymph nodes. No local relapse was observed. After relapse, the median survival time was estimated to be 351 days. Subsequent therapies were taxanes ($n = 7$), SP ($n = 4$), S-1 ($n = 3$), and CPT-11 ($n = 1$), and 1 case underwent surgery (oophorectomy) followed by paclitaxcel.

Discussion

In this study, postoperative S-1 plus 3 cycles of cisplatin demonstrated promising efficacy with respect to 3-year RFS and OS for stage III GC.

Recently, the results of the CLASSIC trial indicated that adjuvant capecitabine and oxaliplatin improved 3-year disease-free survival (DFS) compared with surgery alone in GC patients [6]. The subgroup analysis suggested that combined capecitabine and oxaliplatin were beneficial not only for stage II patients but also for stage IIIA and stage IIIB patients (the hazard rates compared to surgery alone were 0.57 and 0.57, respectively). This result suggests that combination therapy with fluoropyrimidine and a platinum agent may be more beneficial than fluoropyrimidine alone in patients with stage III disease after D2 gastrectomy.

Although small-sample comparisons should be made with caution, there was no significant difference in survival between the original protocol and the amended protocol. It is suggested that delay of cisplatin administration in our amended protocol didn't sacrifice the efficacy in terms of survival. Consequently, we believe that completion of 3 cycles of cisplatin is important, even though we changed the first cycle to S-1 monotherapy and delayed additional cisplatin until cycles 2, 3, and 4. Moreover, our amended protocol was beneficial in the reduction of grade 3/4 anorexia and nausea, even though we did not use NK-1 receptor antagonists, because they were not approved in Japan at that time. Now we could manage the