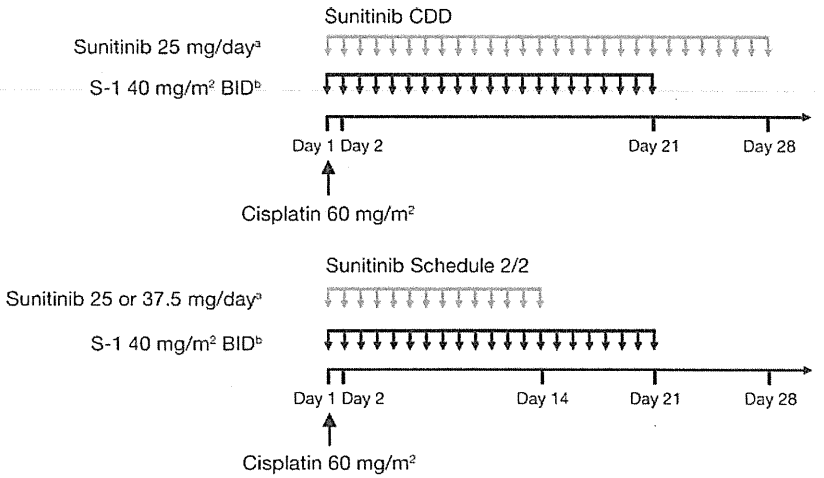


**Fig. 1** Treatment schema. [a]Sunitinib dose withheld on cycle 1 day 1 to enable pharmacokinetic analysis of S-1 and cisplatin. [b]S-1 and cisplatin dose withheld on cycle 1 day 1 to enable pharmacokinetic analysis of sunitinib. *BID* twice daily; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks 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 However, patients requiring more than two dose reductions of S-1 or sunitinib were withdrawn from the study.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1 missed cisplatin dose were withdrawn.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

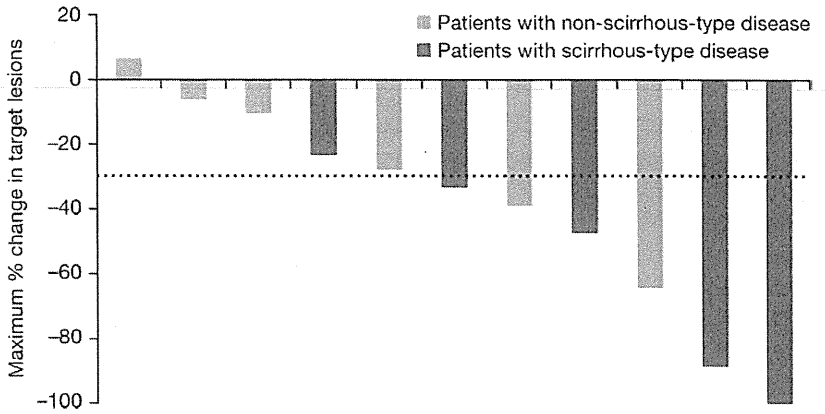


**Fig. 2** Maximum percentage change in target lesion size in the maximum tolerated dose (MTD) cohort (sunitinib 25 mg/day on Schedule 2/2+cisplatin+S-1).[a] *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment. [a]Five of 16 patients receiving the MTD did not have measurable disease

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

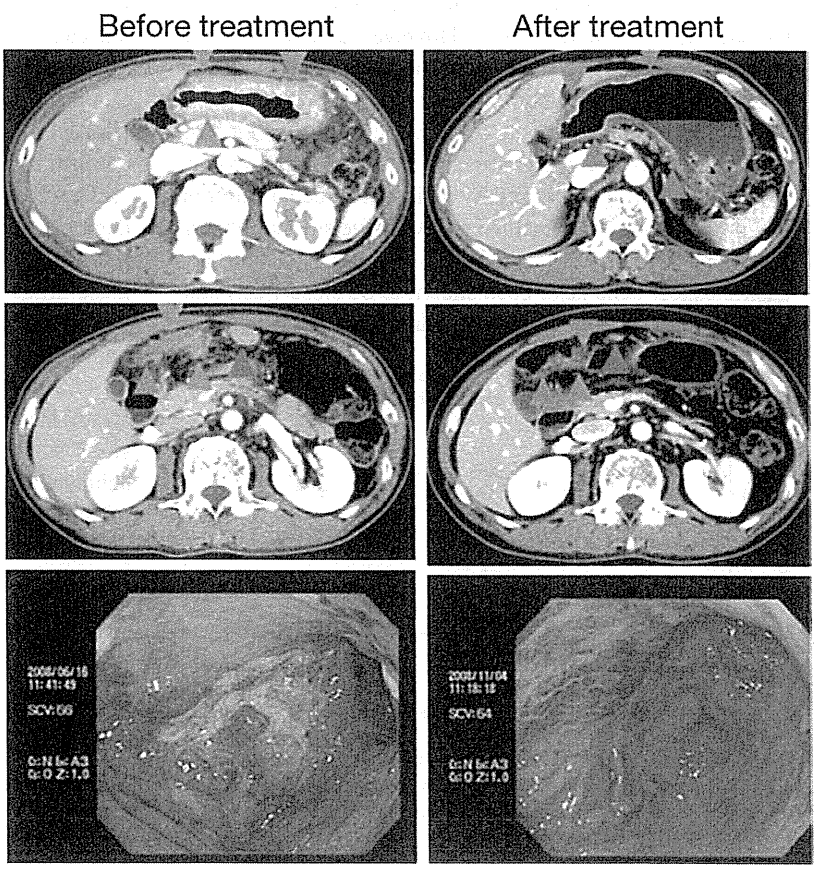


**Fig. 3** Tumor response in a patient with scirrhous gastric cancer who received the maximum tolerated dose of sunitinib (25 mg/day on Schedule 2/2) combined with cisplatin and S-1. Blue arrowheads: primary lesion; orange arrowheads: peritoneal metastasis; green arrowheads: lymph node metastasis; *Schedule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

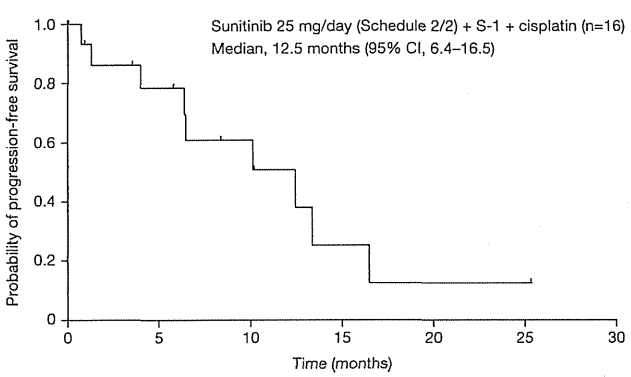


**Fig. 4** Kaplan-Meier estimate of progression-free survival in the maximum tolerated dose cohort (sunitinib 25 mg/day on Schedule 2/2+ cisplatin+S-1). *CI* confidence interval; *Schedule 2/2* 2 weeks on treatment followed by 2 weeks off treatment

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.

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**Quantity of supporting information** None



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ORIGINAL ARTICLE

# Correlation between overall survival and other endpoints in clinical trials of second-line chemotherapy for patients with advanced gastric cancer

**Kohei Shitara · Keitaro Matsuo · Kei Muro · Toshihiko Doi · Atsushi Ohtsu**

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**Abstract**
*Background* The correlation between progression-free survival (PFS) or time to progression (TTP) and overall survival (OS) has been evaluated in patients with advanced gastric cancer (AGC) who received first-line chemotherapy. No corresponding analysis has been done in patients who have undergone second-line chemotherapy.
*Methods* We evaluated the correlation between PFS, TTP, objective response rate (ORR), disease control rate (DCR), and OS in patients with AGC who underwent second-line chemotherapy. Correlations were evaluated by Spearman rank correlation coefficient ($\rho$).
*Results* Sixty-four trials, including 10 randomized studies, were selected for analysis. Median PFS/TTP moderately correlated with OS ($\rho = 0.56$). The correlation tended to be stronger in non-Asian trials ($\rho = 0.74$) than in Asian trials ($\rho = 0.37$). ORR and DCR did not strongly correlate with OS ($\rho = 0.38$ for ORR; $\rho = 0.54$ for DCR). The hazard ratio of PFS and OS in each of the arms of the 10 randomized studies also showed a low correlation ($\rho = 0.36$).
*Conclusions* PFS/TTP, ORR, and DCR did not correlate sufficiently with OS to be used as surrogate endpoints in patients with AGC who have undergone second-line chemotherapy. Further research is needed based on individual patient data from ongoing randomized trials.

**Keywords** Chemotherapy · Gastric cancer · Second-line chemotherapy · Surrogate endpoint · Progression-free survival · Time-to-progression

## Introduction

Gastric cancer remains one of the most common malignancies and leading causes of cancer death worldwide [1]. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor, with median overall survival (OS) of only 1 year with commonly used first-line combination chemotherapy regimens (fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines) [2–7]. Trastuzumab, a humanized monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2), has recently been shown to improve the prognosis of HER2-positive AGC [7], although these cases account for fewer than 20 % of all AGCs. Because median progression-free survival (PFS) associated with these first-line chemotherapies is around 6 months and most patients ultimately experience disease progression, development of effective second-line chemotherapy is critical. Several phase II studies of second-line chemotherapy have suggested that taxanes (paclitaxel or docetaxel) or irinotecan can be effective, with corresponding objective response rates (ORRs) of approximately 10–20 %. Recently, a small

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K. Shitara · T. Doi · A. Ohtsu
Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan

K. Shitara (✉) · K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: kouheis0824@yahoo.co.jp

K. Matsuo
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

randomized study suggested that irinotecan improved outcomes in patients with pretreated AGC [8]. Another randomized study that compared docetaxel or irinotecan and best supportive care for AGC patients with one or two previous lines of chemotherapy also showed the survival benefit of salvage chemotherapy (OS, 5.8 vs. 3.8 months) [9].

Correlations between PFS or other endpoints and OS have been analyzed in an effort to identify surrogate endpoints of OS [10–15]. A validated shorter-term surrogate endpoint would likely both reduce drug development costs and facilitate the assessment of efficacy [16]. Previously, a literature-based analysis and an individual patient data meta-analysis evaluated PFS as surrogate endpoint for OS in patients with AGC who underwent first-line chemotherapy [14, 15]. However, no corresponding analysis had been done in patients who underwent second-line chemotherapy for AGC. Thus, the goal of the present study was to conduct a comprehensive analysis of the correlation between PFS or other endpoints and OS in patients with AGC who underwent second-line chemotherapy.

## Materials and methods

### Search for studies

We conducted a literature search for trials through computer-based searches of the Medline database (January 2002 and January 2013) and of abstracts from conference proceedings of the American Society of Clinical Oncology (2002–2012), Gastrointestinal Cancer Symposium (2002–2013), and European Cancer Conference and European Society for Medical Oncology (2002–2012). To avoid publication bias, both published and unpublished trials were identified. Data were gathered as possible from presentations in meeting as well as abstracts.

Search keywords included "gastric cancer" and "second-line chemotherapy." The search was also guided by a thorough examination of reference lists of original and review articles. No limitation based on language was defined. We included unpublished data if sufficient information on study design, characteristics of participants, interventions, and outcomes was available from an abstract or meeting presentation.

### Procedures

The data were abstracted in accordance with the Quality of Reporting of Meta-analyses (QUORUM) guidelines [17]. Prospective trials (single-arm or randomized trials) of chemotherapy for chemotherapy-pretreated adenocarcinoma (metastatic disease or unresectable locally advanced disease or recurrent) of the stomach or gastroesophageal junction were included in the analysis. Because some trials included patients who received experimental treatments as second-line or third-line chemotherapy, these studies were also included. However, we excluded studies in which all patients received experimental treatments as third-line chemotherapy. Trials that compared chemotherapy with best supportive care were also included, as were those that included patients with adenocarcinoma of the distal esophagus. Eligibility was limited to trials that reported data on OS with either or both PFS and TTP. Exclusion criteria included trials designed to assess combined modality treatments, including radiotherapy and surgery (neoadjuvant or adjuvant chemotherapy).

For each trial, the following information was extracted: first author's name; year of publication or report; trial design; trial region; number of enrolled patients; treatment regimens. The following data were also extracted if reported: previous treatment regimens, and proportion of patients with measurable lesions. For trials with more than two treatment arms, we constructed multiple pairs of each investigational arm and the reference arm.

### Statistical methods

For each trial, median PFS, TTP, ORR, disease control rate (DCR; proportion of patients who achieved complete or partial response or stable disease), and OS were abstracted. In the case of randomized studies, hazard ratio (HR) with 95 % confidence intervals (CI) for clinical outcome (PFS/TTP and OS) was also abstracted. If the HR was not provided, we estimated HR and 95 % CI as relevant effect measures directly or indirectly from the given data [18]. The nonparametric Spearman rank correlation coefficient ($\rho$) was used as a measure of correlation between the median PFS/TTP and OS and of correlation between HR of PFS/TTP and HR of OS. As the number of subject studies was limited, we applied bootstrap resampling [19] using 10,000 bootstrap samples to estimate 95 % CI for correlation coefficients.

To investigate possible reasons for heterogeneity of correlation, subgroup analyses were conducted according to trial region (Asian vs. non-Asian), reported data (old trials; before 2009 vs. recent trials; 2009 or later), status of publication (published vs. presentation only), endpoint for progression (PFS vs. TTP), previous chemotherapy regimens [fluoropyrimidine plus platinum (FP) mandatory vs. not defined], treatment line (second-line only vs. second-line and third-line) and treatment regimens (taxane-based vs. irinotecan-based). In the case of global trials, data were classified as both Asian and non-Asian unless suitable subset analysis results were provided. Median values of each endpoint were calculated, and differences in subsets

were evaluated using the Mann–Whitney test. Statistical analyses were performed using STATA ver. 10 (Stata Corp., College Station, TX, USA). All tests were two sided, and $p$ values less than 0.05 were considered statistically significant.

## Results

### Selection of studies

A total of 640 potentially relevant reports were identified, of which 472 were initially excluded by title view (Fig. 1). After review of the remaining studies, 64 trials were identified as eligible for this meta-analysis, including a total of 75 treatment arms and 4,286 patients (Supplement 1). Forty-four trials were published, and another 20 trials were presentations or abstracts only. Table 1 shows the characteristics of the 64 trials. Only 10 trials were randomized trials (5 phase II and 5 phase III), and 54 were single-arm phase II studies. By region, 39 were conducted in Asia, 23 were conducted in non-Asia regions, and 2 were global studies that included Asia. Sixteen trials included only patients who received a previous regimen that included FP as first-line chemotherapy. Forty-nine trials included only patients with measurable lesions. Forty-one studies described disease progression with previous chemotherapy as inclusion criteria. The most common primary endpoint was ORR ($n = 39$), followed by OS ($n = 10$). Only 16 studies assessed tumor response by independent review. Most commonly used regimes were taxanes followed by irinotecan or platinum-based therapy. As a time to event for progression, more studies reported PFS ($n = 41$) than TTP ($n = 23$), whereas no trial reported both PFS and TTP. Subset analysis according to region (Asia and non-Asia) was reported in one global phase II trial, and these subset data were accordingly included in analyses that focused on comparing Asian and non-Asian trials.

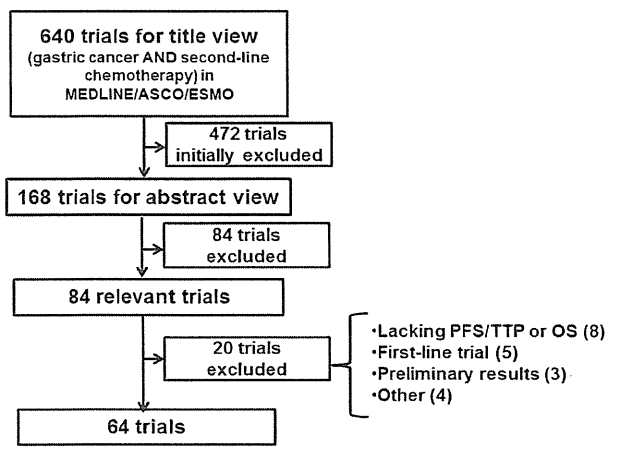


**Fig. 1** Selection process for trials. *PFS/TTP* progression-free survival/time to progression; *OS* overall survival

### Results of each endpoint according to subsets

Median value of reported OS among the 64 trials was 7.6 months, and median PFS or TTP was 3.0 months (Table 2). Median OS tended to be longer in Asian trials than in non-Asian trials (8.1 vs. 6.0 months; $p < 0.001$). In contrast, median PFS or TTP were not significantly different when comparing Asian and non-Asian trials (3.0 vs. 3.1 months; $p = 0.19$). Unpublished trials were associated with longer OS than published trials (8.1 vs. 6.7 months; $p = 0.02$). No other subset analysis showed significant

**Table 1** Characteristics of the 60 clinical trials analyzed in the present study

| Characteristic | *n* | % |
|---|---|---|
| Reported year | | |
| Before 2009 | 28 | 44 |
| 2009–2012 | 36 | 56 |
| Trial setting | | |
| Single-arm phase II | 54 | 84 |
| Randomized phase II | 5 | 8 |
| Phase III | 5 | 8 |
| Trial area | | |
| Asia | 39 | 61 |
| Non-Asia | 22 | 34 |
| Global, including Asia | 3 | 5 |
| Previous chemotherapy | | |
| Fluoropyrimidine and platinum agents mandatory | 16 | 25 |
| Various | 48 | 75 |
| Inclusion criteria | | |
| Measurable lesion mandatory | 49 | 77 |
| Primary endpoint | | |
| Objective response rate | 39 | 61 |
| Overall survival | 10 | 16 |
| Progression-free survival or time to progression | 5 | 8 |
| Disease control rate | 2 | 3 |
| Not reported or not available | 8 | 13 |
| Treatment line | | |
| Second-line only | 49 | 77 |
| Second- and third-line | 15 | 23 |
| Investigated agents[a] | | |
| Taxanes | 32 | 50 |
| Irinotecan | 26 | 41 |
| Fluoropyrimidine | 21 | 33 |
| Platinum agents | 18 | 28 |
| Others | 25 | 39 |

[a] Among 75 treatment arms, some overlapped

**Table 2** Results of each endpoint according to subsets

| Subset | Number of arms | Median OS (months) | *p* value | Median PFS/TTP (months) | *p* value | ORR (%) | *p* value | DCR (%) | *p* value |
|---|---|---|---|---|---|---|---|---|---|
| All | 75 | 7.6 | | 3.0 | | 17.9 | | 53.8 | |
| Trial area[a] | | | | | | | | | |
| Asia | 47 | 8.1 | <0.001 | 3.0 | 0.19 | 20.2 | 0.25 | 55.4 | 0.21 |
| Non-Asia | 23 | 6.0 | | 3.1 | | 15.5 | | 50.0 | |
| Reported year | | | | | | | | | |
| Before 2009 | 37 | 7.2 | 0.08 | 3.5 | 0.26 | 19.2 | 0.15 | 53.1 | 0.72 |
| 2009 or later | 38 | 7.8 | | 2.9 | | 16.1 | | 54.6 | |
| Publication | | | | | | | | | |
| Published | 46 | 6.7 | 0.02 | 3.1 | 0.86 | 18.9 | 0.11 | 55.0 | 0.98 |
| Presentation only | 29 | 8.1 | | 3.0 | | 20.0 | | 52.2 | |
| Endpoint | | | | | | | | | |
| PFS | 51 | 7.7 | 0.08 | 3.0 | 0.50 | 17.0 | 0.08 | 52.2 | 0.42 |
| TTP | 24 | 7.0 | | 3.6 | | 20.6 | | 55.0 | |
| Measurable lesion | | | | | | | | | |
| Mandatory | 52 | 7.0 | 0.07 | 3.0 | 0.63 | 18.2 | 0.36 | 55.0 | 0.35 |
| Not mandatory | 23 | 8.2 | | 3.0 | | 17.0 | | 46.2 | |
| Previous chemotherapy | | | | | | | | | |
| FP mandatory | 19 | 6.6 | 0.13 | 2.9 | 0.22 | 14.8 | 0.29 | 50.5 | 0.48 |
| Not defined or other | 56 | 7.7 | | 3.1 | | 18.3 | | 54.8 | |
| Treatment line | | | | | | | | | |
| Second-line only | 59 | 7.6 | 0.41 | 3.3 | 0.11 | 18.4 | 0.30 | 55.0 | 0.09 |
| Second- and third-line | 16 | 6.6 | | 2.6 | | 17.0 | | 48.0 | |
| Regimen[b] | | | | | | | | | |
| Taxane-based | 31 | 8 | 0.31 | 3.6 | 0.78 | 17.5 | 0.41 | 58.0 | 0.34 |
| Irinotecan-based | 26 | 7.6 | | 3.4 | | 18.5 | | 53.0 | |

*OS* overall survival, *PFS* progression-free survival, *TTP* time to progression, *ORR* objective response rate, *DCR* disease control rate

Statistical analyses were performed using the Mann–Whitney test, with the level of significance set at $p < 0.05$ (italicized)

[a] Excluded two global trials

[b] Excluded arm of taxane plus irinotecan or other regimens

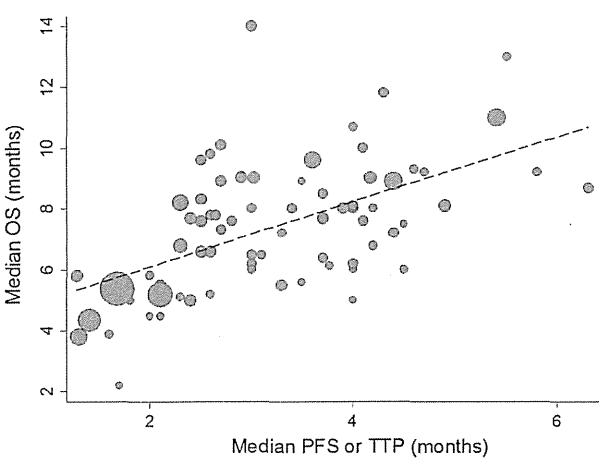


**Fig. 2** Correlation between median progression-free survival/time to progression (PFS/TTP) and overall survival (OS). Size of *gray* markers (*circles*) corresponds to the number of randomized patients in the trial in this analysis. Median PFS or TTP and OS were moderately correlated ($r = 0.51$, 95 % CI 0.31–0.71)

differences in OS or PFS/TTP. Median reported ORR and DCR were 17.9 % and 53.8 %, respectively. DCR tend to be higher in trials of second-line only therapy when compared with trials of second- and third-line therapy ($p = 0.09$), although no other subset showed significant differences in DCR.

## Correlation between PFS or TTP and OS

Median PFS or TTP and OS were moderately correlated ($\rho = 0.56$, 95 % CI 0.34–0.74; Fig. 2; Table 3). The correlation tended to be stronger with PFS ($\rho = 0.65$) than with TTP ($\rho = 0.28$), stronger in non-Asian trials ($\rho = 0.74$) than in Asian trials ($\rho = 0.37$; Fig. 3; Table 3), and stronger in trials with second-line and third-line chemotherapy ($\rho = 0.47$) than in trials of second-line therapy only ($\rho = 0.77$). The correlation was almost similar when comparing published trials vs. presentation only ($\rho = 0.52$, $\rho = 0.60$).

**Table 3** Correlation between PFS/TTP, ORR, DCR, and OS

| Subset | PFS/TTP and OS | | ORR and OS | | DCR and OS | |
|---|---|---|---|---|---|---|
| | $\rho$ | 95 % CI | $\rho$ | 95 % CI | $\rho$ | 95 % CI |
| All | 0.56 | 0.37 to 0.74 | 0.38 | 0.16 to 0.61 | 0.54 | 0.33 to 0.75 |
| Trial area[a] | | | | | | |
| Asia | 0.37 | 0.10 to 0.63 | 0.27 | −0.01 to 0.55 | 0.43 | 0.12 to 0.74 |
| Non-Asia | 0.74 | 0.50 to 0.98 | 0.35 | −0.10 to 0.80 | 0.66 | 0.35 to 0.97 |
| Reported year | | | | | | |
| Before 2009 | 0.47 | 0.16 to 0.77 | 0.13 | −0.22 to 0.47 | 0.49 | 0.13 to 0.76 |
| 2009 or later | 0.64 | 0.43 to 0.86 | 0.59 | 0.32 to 0.86 | 0.63 | 0.33 to 0.92 |
| Publication | | | | | | |
| Published | 0.52 | 0.29 to 0.75 | 0.31 | 0.02 to 0.61 | 0.55 | 0.30 to 0.79 |
| Presentation only | 0.60 | 0.38 to 0.93 | 0.75 | 0.55 to 0.96 | 0.47 | 0.02 to 0.93 |
| Endpoint | | | | | | |
| PFS | 0.65 | 0.46 to 0.83 | 0.56 | 0.33 to 0.80 | 0.63 | 0.41 to 0.84 |
| TTP | 0.28 | −0.17 to 0.73 | 0.07 | −0.39 to 0.54 | 0.23 | −0.28 to 0.73 |
| Measurable lesion | | | | | | |
| Mandatory | 0.51 | 0.28 to 0.74 | 0.31 | 0.03 to 0.59 | 0.51 | 0.27 to 0.75 |
| Not mandatory | 0.59 | 0.27 to 0.92 | 0.69 | 0.35 to 1.00 | 0.78 | 0.36 to 1.00 |
| Previous chemotherapy | | | | | | |
| FP only | 0.55 | 0.20 to 0.91 | 0.42 | 0.02 to 0.83 | 0.37 | −0.09 to 0.82 |
| Not defined or others | 0.55 | 0.33 to 0.77 | 0.36 | 0.08 to 0.63 | 0.61 | 0.38 to 0.84 |
| Treatment line | | | | | | |
| Second-line only | 0.47 | 0.24 to 0.70 | 0.39 | 0.16 to 0.63 | 0.39 | 0.12 to 0.66 |
| Second- and third-line | 0.77 | 0.49 to 1.00 | 0.23 | −0.37 to 0.84 | 0.89 | 0.72 to 1.00 |
| Regimen[b] | | | | | | |
| Taxane-based | 0.35 | −0.01 to 0.71 | 0.39 | 0.05 to 0.73 | 0.27 | −0.20 to 0.75 |
| Irinotecan-based | 0.46 | 0.10 to 0.81 | 0.09 | −0.28 to 0.46 | 0.56 | 0.20 to 0.92 |

*OS* overall survival, *PFS* progression-free survival, *TTP* time to progression, *ORR* objective response rate, *FP* fluoropyrimidine and platinum agents

[a] Excluded one global trial

[b] Excluded arm of taxane plus irinotecan or other regimens

### Correlation between ORR, DCR, and OS

The ORR and DCR was not strongly correlated with OS ($\rho = 0.38$ for ORR, 95 % CI 0.16–0.61; $\rho = 0.54$ for DCR, 95 % CI 0.33–0.75; Fig. 4), although DCR was more strongly correlated with OS when compared with ORR vs. OS in the whole cohort or any subset (Table 3).

### Correlation between HR for PFS/TTP and OS in randomized trials

A total of 11 pairs of HRs for PFS/TTP and OS between treatment arms were available from the 10 randomized trials (reported in 9 trials and estimated in 1 trial). The HR of PFS/TTP and OS in each arm showed a low correlation ($\rho = 0.36$, 95 % CI −0.30 to 1.00; Fig. 5). Wide 95 % CI indicated that the sample sizes were too small for this type of analysis.

## Discussion

This is the first study to evaluate the correlation between PFS, TTP, or other endpoints and OS in patients with AGC who underwent second-line chemotherapy for AGC. Our results suggests that PFS/TTP, ORR, and DCR did not correlate sufficiently with OS to be used as surrogate endpoints for OS in patients with AGC who underwent second-line chemotherapy. We should interpret our results cautiously because this study is of exploratory nature and has the following several limitations. (1) Our analysis is based on literature-based data without individual patient data. (2) Most of the included studies were single-arm studies, and only ten of the studies were randomized trials. (3) Little information was available about subsequent treatment including crossover treatment, which may weaken the surrogacy. Against these limitations, we consider that our work could convey important aspects with

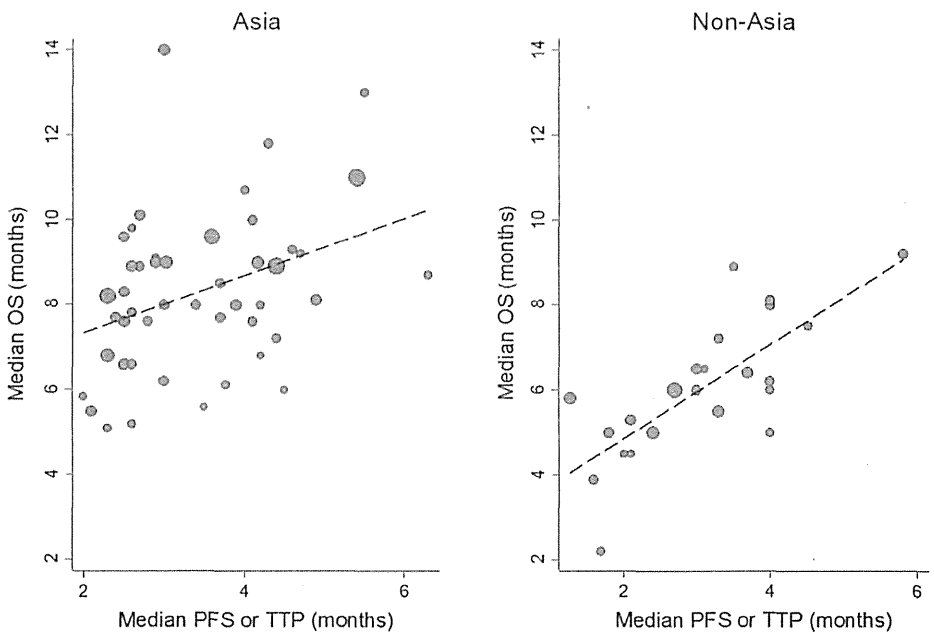


**Fig. 3** Correlation between median PFS/TTP and OS according to trial area. The correlation tended to be stronger in non-Asian trials ($\rho = 0.74$) than in Asian trials ($\rho = 0.37$)

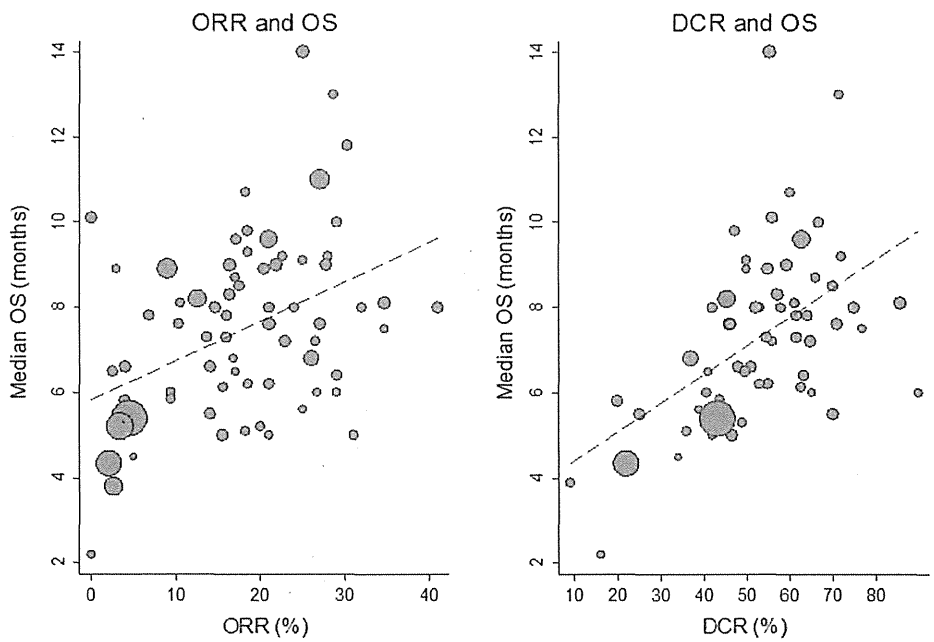


**Fig. 4** Correlation between objective response rate (ORR) or disease control rate (DCR) and OS. ORR and DCR were not strongly correlated with OS ($\rho = 0.38$ for ORR, 95 % CI 0.16–0.61; $\rho = 0.54$ for DCR, 95 % CI 0.33–0.75)

regard to the trial conduct and data collection for the future trials of second-line therapy for advanced gastric cancers.

Previously, two meta-analyses studied whether PFS could be a surrogate endpoint for OS in patients with AGC who underwent first-line chemotherapy [14, 15]. According to a literature-based analysis of 36 randomized trials [14], median PFS or TTP moderately correlated with median OS ($\rho = 0.70$). The correlation coefficient between HR of PFS or TTP and OS was 0.80. Another meta-analysis called the GASTRIC project (Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration) analyzed data from 4,102 AGC patients included in 20 randomized trials [15]. The correlation between treatment effects on PFS and OS in each trial was only moderate (trial-level decision coefficient $R^2$ adjusted for estimation errors was 0.61), which is the same strength of relationship seen in the literature-based analysis [14]. Correlations between PFS and PS were lower for AGC than for those in patients with advanced colorectal cancer [10] or for those seen in studies of adjuvant treatment for colorectal cancer

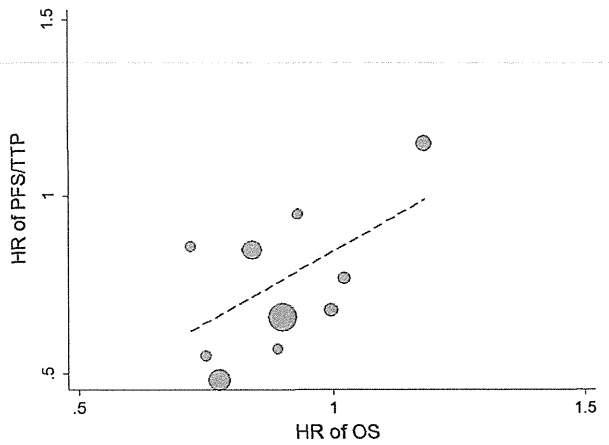


**Fig. 5** Hazard ratio (HR) of PFS/TTP and OS in ten randomized studies. The HR/TTP of PFS was moderately correlated with OS in each arm ($\rho = 0.36$, 95 % CI −0.30 to 1.00)

or gastric cancer [20, 21]. These results suggest that PFS is not a good surrogate for OS in patients undergoing first-line chemotherapy for AGC.

Recently, it has been suggested that second-line chemotherapy prolonged the OS of patients with AGC, according to two randomized studies [8, 9]. Therefore, we conducted a literature-based analysis of endpoint of clinical trials patients who underwent second-line chemotherapy for ACG. The present analysis showed that there was an insufficient correlation between OS and other endpoints, which is similar to data observed in the first-line setting. There are several possible reasons for these results. First, heterogeneity of treatment, especially in terms of subsequent chemotherapy, may affect the results. In this analysis, median PFS was almost the same when comparing Asian trials and non-Asian trials, whereas OS was significantly longer in Asian trials when compared with non-Asian trials. One possible reason for this difference in survival after progression is the effect of subsequent treatment, as already suggested in the first-line setting [22]. Indeed, the proportion of patients who receive subsequent chemotherapy is higher in Asian trials than in Western trials [22, 23]; in the AVAGAST (a study of bevacizumab in combination with capecitabine and cisplatin as first-line therapy in patients with AGC) study, 66 % of Asian patients received second-line chemotherapy compared with 31 % of patients in Europe and 21 % in America [23]. Although the proportion of patients who can receive subsequent therapy is expected to be lower in second-line trials than in first-line trials, 40 % of patients in Korean randomized studies received subsequent therapy after second- and third-line chemotherapy [9]. Also, in the West Japan Oncology Group (WJOG) 4407 study, which compared irinotecan and weekly paclitaxel as second-line chemotherapy, more than 70 % of patients received third-line chemotherapy in both arms [24]. Therefore, subsequent therapy may contribute to the difference in OS according to trial area and confound the correlation in the current analysis, similar to the phenomenon seen in a previous analysis [14].

Another possible reason of moderate correlation of PFS and OS may be heterogeneity in inclusion criteria and patient characteristics. Types of prior chemotherapy before enrollment or investigational agents were quite variable in this population. Also, the definition of failure of prior chemotherapy varied between source studies. Although subset analysis according to prior treatment or treatment regimens did not show a strong correlation between each endpoint, these heterogeneities may contribute to the weak correlation between each endpoint in our analysis. Further, although most studies included patients with measurable lesions, the Japan Clinical Oncology Group (JCOG) 0407 study included patients with peritoneal metastasis, which is associated with a low frequency of measurable lesions [25]. By contrast, the WJOG4007 study excluded patients with apparent peritoneal metastasis [24]. These variations in inclusion criteria might affect the results of correlation.

Although this study showed that there was an insufficient correlation between OS and all endpoints examined, the correlation between ORR and OS was much weaker than that between PFS, TTP or DCR, and OS. These results suggest that a single-arm phase II study with a primary endpoint of ORR may not be adequate to evaluate the efficacy of second-line chemotherapy for AGC. Randomised phase II studies that compare standard treatments and investigational treatments may be better methods of screening for effective treatments to include within phase III trials [26].

This study has several methodological limitations. First, as already described, most of the component studies were single-arm studies, and only ten of the studies were randomized trials. Although there is no consensus in terms of what defines a valid surrogate endpoint, any candidate endpoint must correlate with the true endpoint, and effects on the surrogate endpoint must correlate with those on the true endpoint [27, 28]. However, the effect of each treatments on the surrogate endpoints may be difficult to analyze in this case, as there were relatively few randomized trials available. Second, the present study was not based on an analysis of data from individual patients, which is a confirmatory method of evaluating individual-level measures of agreement between the two endpoints (PFS/TTP and OS) [29]. Additional individual data analysis, especially using ongoing randomized studies, might therefore be necessary to characterize the surrogacy of endpoints. Finally, most trials analyzed in this study provided little information on disease progression after prior chemotherapy, and only a few studies evaluated patient responses by external review. Also, interval to evaluation imaging is also

varied. Therefore, it is impossible to confirm whether the evaluation of disease progression was consistent among the trial arms.

In conclusion, our exploratory analysis suggests that PFS/TTP, ORR, and DCR do not correlate sufficiently with OS to be used as surrogate endpoints in patients with AGC who have undergone second-line chemotherapy. Further research is needed based on individual patient data from ongoing randomized trials to evaluate an optimal surrogate endpoint.

**Conflict of interest** None of the authors has financial or personal conflicts of interest to disclose.

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REVIEW ARTICLE

# Surgical resection of hepatic metastasis from gastric cancer: a review and new recommendation in the Japanese gastric cancer treatment guidelines

**Yasuhiro Kodera · Kazumasa Fujitani · Norimasa Fukushima · Seiji Ito · Kei Muro · Norifumi Ohashi · Takaki Yoshikawa · Daisuke Kobayashi · Chie Tanaka · Michitaka Fujiwara**

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**Abstract** Liver metastases from gastric cancer are rarely indicated for surgery because they are often diagnosed as multiple nodules occupying both lobes and coexist with extrahepatic disease. A literature search identified no clinical trials on hepatectomy for this disease; only retrospective studies of a relatively small number of cases collected over more than a decade, mostly from a single institution, were found. Five-year survival rates from these reports ranged from 0 % to 37 %, and long-term survivors were observed among carefully selected case series. The most commonly reported prognostic factor was the number of metastatic nodules, and patients with a solitary metastasis tended to have superior outcome. Patients diagnosed to have a small number of metastatic nodules by modern imaging tools could be indicated for surgery. Because both intrahepatic and extrahepatic recurrences are common, patients are likely to benefit from perioperative adjuvant chemotherapy, although it is not possible at this time to specify which regimen is the most appropriate.

**Keywords** Liver metastasis · Hepatectomy · Stage IV gastric cancer · Treatment guidelines

Y. Kodera (✉) · D. Kobayashi · C. Tanaka · M. Fujiwara
Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan
e-mail: ykodera@med.nagoya-u.ac.jp

K. Fujitani
Department of Surgery, Osaka General Medical Center, Osaka, Japan

N. Fukushima
Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan

S. Ito
Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Aichi, Japan

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, Japan

N. Ohashi
Department of Gastroenterological Surgery, Aichi Medical University, Aichi, Japan

T. Yoshikawa
Department of Gastroenterological Surgery, Kanagawa Cancer Center, Kanagawa, Japan

## Introduction

Hepatectomy for liver metastases should only be attempted when cure is the goal because hepatectomy usually does not relieve symptoms. Colorectal liver metastases are widely considered as targets of surgery with intent to cure, because they often present as a liver-only disease [1], which is not always the case with other types of cancer. A prognostic model based on several prognostic factors effectively stratified cancers of various origins into three groups in a comprehensive analysis of various noncolorectal nonendocrine liver metastases treated by hepatectomy in 41 French centers [2]. Gastric cancer metastasis in that report was classified into the intermediate-risk group in which 5-year survival rate was in the range of 15–30 %, with hepatic metastasis from pancreatic cancer, melanoma, and duodenal cancer. The low-risk group with a 5-year survival rate >30 % consisted of metastases from adrenal cancer, ovarian cancer, breast cancer, and renal cancer among others, and a high-risk group with 5-year survival

<15 % consisted of metastases from cancer of the lung, esophagus, head and neck, and gastroesophageal junction.

Gastric cancer is known to be heterogeneous in nature, consisting of cancer cells with varying biological characteristics. Gastric cancer can metastasize through the lymphatic pathway, the hematogenous pathway, and by direct dissemination into the peritoneal cavity from the serosal surface. Moreover, the fate of cancer cells that enter the portal circulation could vary. Hematogenous metastases can occur according to both the seed-and-soil hypothesis and the anatomical/mechanical hypothesis, neither of which needs to be mutually exclusive, and the extent to which either mechanism is operational depends on the tumor under investigation [3]. When gastric cancer cells spread through the hematogenous pathway, its first site of metastasis according to the anatomical/mechanical hypothesis would be the liver, followed by the lung. In addition, several gastric cancers spread along the seed-and-soil route, resulting in various distant metastases in the absence of hepatic metastases [4]. This result is in contrast with colorectal cancer in which the anatomical/mechanical hypothesis would seem more often applicable. The aggressive characteristics and unpredictable nature of gastric cancer cells are the reason that surgical resection of hepatic metastases has not been seriously considered.

However, some might not agree that gastric cancer even with solitary liver metastasis should always be considered as a contraindication for surgical treatment. The Japanese Gastric Cancer Treatment Guidelines recommend only chemotherapy, radiation, palliative surgery, and best supportive care for treatment of Stage IV or metastatic gastric cancer [5]. Recently, the guidelines committee of the Japan Gastric Cancer Association decided to revisit the treatment of potentially resectable M1 disease. A working group was organized to discuss whether any tentative comments could be added to the next version of the guidelines regarding surgical treatment with curative intent of (1) patients with resectable hepatic metastasis, (2) patients who are positive for cytological examination of peritoneal washes, and (3) patients with swollen nodes in the paraaortic region. This article is a summary of the literature search and discussion on gastric cancer hepatic metastasis by the members of the working group for this task.

## Literature search

A search for relevant literature was conducted in March 2013 using PubMed and Scopus. Key search terms used included "gastric cancer," "liver metastasis," "hepatectomy," and "surgery" to find articles on hepatectomy for gastric cancer metastasis to the liver that were published in English after 2000. Sixty-eight articles were identified, of which the following were excluded: 15 articles that included either other types of distant metastases or hepatic metastasis from other cancer types with no independent outcome data for gastric cancer metastases, 15 articles with emphasis on treatment modalities other than hepatectomy, 6 articles with fewer than 15 cases, 5 articles on prediction and diagnosis of hepatic metastasis, 4 review articles, 3 articles on irrelevant subjects, and 1 article describing only hepatic metastasis from pT1 stage cancer. Three articles analyzed patients from the same institution, and the most recent report by Takemura et al. [6] was selected and added to a total of 17 articles to be analyzed in the current review [2, 6–21]. Most of the papers were retrospective single-institution analyses of consecutive patients who underwent hepatectomy during a given period, with two exceptions in which patients were recruited from multiple institutions [5, 7]. Wang et al. [8] analyzed only patients with synchronous liver metastases, but all other papers discussed both synchronous and metachronous metastases. Two papers analyzed all patients with hepatic metastasis who underwent gastrectomy, regardless of whether the patients underwent hepatectomy [9, 10]. Data of the patients who went on to receive hepatectomy could be retrieved from these reports for subsequent analyses. A paper by Adam et al. was a comprehensive analysis of noncolorectal nonendocrine liver metastases [2], from which patients with gastric cancer metastases could be retrieved for some of the analyses in this review.

## Results and discussion

The median number of patients analyzed among the 17 series was 25 (range, 15–73), spanning a median period of 15 years (range, 5–36). Details such as the indication for surgery, diagnostic modalities used, type of surgery performed, and adjuvant treatments given were diverse and, in addition, could have changed substantially in each institution during the periods studied. Synopses of findings in the 17 papers are summarized in Table 1.

The type of hepatectomy performed was diverse. A greater proportion of patients underwent wedge or nonanatomic resection of the metastatic nodules, and major hepatectomy such as hemihepatectomy was reserved for 23.4 % of the patients (79 of 337). The selection was presumably based on the number, size, and location of the tumors rather than the surgeons' intent to perform anatomic resection for additional resection margin. In cases of colorectal liver metastasis, the preservation of hepatic parenchyma is considered to be of increasing importance in the setting of chemotherapy-associated steatohepatitis and the growing number of patients undergoing repeated metastectomy [22]. Even in gastric cancer metastasis, the most

**Table 1** Outcome of the patients with gastric cancer liver metastasis

| References | No. of cases | Enrolled | Age (years) | Synchronous | metachronous | No. with solitary metastasis | Operative death | Mortality (%) | Morbidity (%) | 1-year survival rate (%) | 3-year survival rate (%) | 5-year survival rate (%) | No. of 5-year survivors | MST (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Takemura et al. [6] | 64 | 1993–2011 | 65 | 34 | 30 | 37 | 0 | 0 | 23 | 84 | 50 | 37 | 27 | 34 |
| Wang et al. [8] | 30 | 2003–2008 | 60 | 30 | 0 | 22 | 0 | 0 | | 43.3 | 16.7 | 16.7 | 5 | 11 |
| Schildberg et al. [20] | 31 | 1972–2008 | 65 | 17 | 14 | | 2 | 6 | 29 | 75 | 25 | 13 | 4 | 14 |
| Garancini et al. [19] | 21 | 1998–2007 | 64 | 12 | 9 | 12 | 0 | 0 | 19 | 68 | 31 | 19 | 3 | 11 |
| Miki et al. [18] | 25 | 1995–2009 | 72 | 16 | 9 | | | | | 73.9 | 42.8 | 36.7 | 9 | 33.4 |
| Makino et al. [10] | 16 | 1992–2007 | 65.8 | 9 | 7 | 9 | 0 | 0 | | 82.3 | 46.4 | 37.1 | 4 | 38.3 |
| Tsujimoto et al. [17] | 17 | 1980–2007 | 66.3 | 8 | 8 | 13 | 0 | 0 | | 75 | 37.5 | 31.5 | 5 | 34 |
| Cheon et al. [9][a] | 41 | 1995–2005 | 61 | 30 | 11 | 28 | 1 | 3 | | 75.3 | 31.7 | 20.8 | 3 | 17 |
| Thelen et al. [16] | 24 | 1988–2002 | 64 | 15 | 9 | 13 | 1 | 4.2 | 21 | 53 | 22 | 15 | 2 | 10 |
| Morise et al. [15] | 18 | 1989–2004 | 64 | 11 | 7 | 14 | 0 | 0 | | 56.3 | 27.3 | 27.3 | 3 | 13 |
| Sakamoto et al. [14] | 37 | 1990–2005 | | 16 | 21 | 21 | 0 | 0 | 24 | | | 11 | 2 | 31 |
| Adam et al. [2] | 64 | 1983–2004 | | | | | | | | | | 27 | 17 | 15 |
| Shirabe et al. [7] | 36 | 1979–2001 | 66 | 16 | 20 | | 0 | 0 | | 64 | 26 | 26 | 4 | |
| Zacherl et al. [13] | 15 | 1980–1999 | | 10 | 5 | 8 | 1 | 67 | 47 | 35.7 | 14.3 | 0 | 0 | 8.8 |
| Okano et al. [12] | 19 | 1986–1999 | 69 | 13 | 6 | 10 | 0 | 0 | | 77 | 34 | 34 | 3 | |
| Ambiru et al. [11] | 40 | 1975–1999 | | | | | 0 | 0 | | | | 18 | 6 | 12 |
| Imamura et al. [21] | 17 | 1990–1997 | | 7 | 10 | 8 | 0 | 0 | | 47 | 22 | 0 | 0 | |
| Total | 515 | | | | | 195 (61.1 %) | 5 | 1.1 | | | | 18.8 | 97 | |

*MST* median survival time

[a] Data include nine patients who were treated by radiofrequency ablation (RFA)