

Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum

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BACKGROUND: Docetaxel is widely used as a chemotherapeutic agent for gastric cancer treatment. A combined regimen with sunitinib demonstrated a synergistic antitumour effect in a preclinical model. The aim of this study was to evaluate the efficacy and safety of this combination in patients with unresectable or metastatic advanced gastric cancer following failure of treatment with a fluoropyrimidine and platinum combination.

METHODS: This open-label, phase II, randomised trial enrolled patients with unresectable or metastatic gastric cancer. Patients were assigned to either a docetaxel monotherapy arm (D only arm: 60 mg m⁻², every 3 weeks) or a combination arm (DS arm: docetaxel + sunitinib 37.5 mg every day). The primary end point of the study was time to progression and the secondary end points were overall response rate, disease control rate, overall survival, and toxicity profile. A pharmacokinetic study was also performed. **RESULTS:** A total of 107 patients were entered into the study. The TTP was not significantly prolonged in the DS arm when compared with the D only arm (DS vs D only arm: 3.9 months (95% confidence interval (CI) 2.9–4.9) vs 2.6 months (95% CI 1.8–3.5) ($P = 0.206$). The hazard ratio for TTP was 0.77 (95% CI 0.52–1.16). However, the objective response rate was significantly higher in the DS arm (41.1% vs 14.3%, $P = 0.002$). Patients in the DS arm experienced stomatitis, diarrhoea, and hand-foot syndrome more frequently.

CONCLUSION: The addition of sunitinib to docetaxel did not significantly prolong TTP, although it significantly increased response.

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Gastric cancer is the fourth most common cancer worldwide, with nearly one million new cases diagnosed every year (Jemal *et al*, 2011). It is also one of the leading causes of cancer-related mortality in Asia (Jung *et al*, 2011; Tanaka *et al*, 2011). For patients with recurrent or metastatic disease, chemotherapy can improve survival and can also possibly provide significant palliation of symptoms (Pyrhonen *et al*, 1995; Glimelius *et al*, 1997). In terms of first-line regimens, a combination of fluoropyrimidine and platinum is regarded as a standard option as this combination has shown superior clinical outcomes in phase III trials when compared with fluoropyrimidine monotherapy and other combinations (Wagner *et al*, 2006). However, less than half of the patients achieve an objective response and the duration, even in these responders, is as short as a few months (Van Cutsem *et al*, 2002).

Recently, we have conducted a randomised phase III trial to compare best supportive care vs best supportive care plus chemotherapy (irinotecan or docetaxel) following the failure of fluoropyrimidine/platinum-based chemotherapy for the treatment

of gastric cancer. In this phase III trial, 193 gastric cancer patients were randomly assigned to second-line chemotherapy ($n = 128$) or best supportive care ($n = 65$). A significant prolongation in survival was observed for the second-line chemotherapy arm when compared with best supportive care (hazard ratio, 0.63; 95% CI, 0.47–0.86; $P = 0.004$) (Park *et al*, 2011). Thus, second-line chemotherapy should be considered in selected patients with gastric cancer.

Docetaxel is one of the most widely used chemotherapeutic agents for the second-line treatment of gastric cancer. Docetaxel exerts its antitumour activity by stabilising microtubules. It also inhibits the anti-apoptotic gene *Bcl2* and promotes the expression of p27, a cell-cycle inhibitor, as well as other pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) (Nishiyama and Wada, 2009). As a monotherapy, this agent has shown an overall response rate of around 15% and time to progression (TTP) of 2.5–3 months (Bang *et al*, 2002; Giuliani *et al*, 2003; Lee *et al*, 2008). Combination of docetaxel with other agents, such as platinum as a treatment for gastric cancer, has failed to demonstrate any significant improvement in efficacy in most studies, when compared with docetaxel alone (Park *et al*, 2004; Nguyen *et al*, 2006; Barone *et al*, 2007; Zhong *et al*, 2008; Kim *et al*, 2011). Although one study has shown that the addition of docetaxel was associated with improved clinical outcomes

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(Van Cutsem *et al*, 2006), docetaxel is not widely recommended as a standard treatment option because of its high rate of toxicity, including neutropenia and neurotoxicity, and also the need for subsequent discontinuation of the treatment (Ilson, 2007).

Sunitinib is an oral inhibitor of multiple receptor tyrosine kinases that are involved in tumour proliferation and angiogenesis, specifically platelet-derived growth factor receptor, VEGF receptor, KIT, Flt-3, and RET (Abrams *et al*, 2003a; Mendel *et al*, 2003; O'Farrell *et al*, 2003). This agent has shown efficacy against many solid cancers, including metastatic clear cell renal cell carcinoma (Motzer *et al*, 2009), imatinib-refractory gastrointestinal stromal tumour (Demetri *et al*, 2006), and pancreatic neuroendocrine tumour (Raymond *et al*, 2011). In preclinical studies, docetaxel and sunitinib demonstrated additive antitumour activity in mouse xenograft models of non-small-cell lung cancer and breast cancer (Abrams *et al*, 2003b; Christensen JG, 2008). Recently, in a multicentre, phase II trial, single-agent sunitinib given in a second-line setting demonstrated an overall response rate of 2.6% with 32.1% of stable disease lasting more than 6 weeks and manageable toxicity in patients with advanced gastric cancer (AGC) (Bang *et al*, 2010). In the present study, we conducted a randomised, phase II trial of docetaxel singly or in combination with sunitinib in patients who had experienced failure of fluoropyrimidine and platinum therapy. This study is registered at clinicaltrials.gov as #NCT01238055.

MATERIALS AND METHODS

Study design

This was an open-label, phase II, two arm, randomised, single centre study conducted at Samsung Medical Center, Seoul, Korea. The protocol was approved by the institutional review board at Samsung Medical Center and the trial was conducted in accordance with the Declaration of Helsinki. All patients were required to give written informed consent before enrolment. Pfizer (Seoul, Korea) provided sunitinib *gratis*, but was not involved in the accrual or analysis of the data or in the preparation of the manuscript.

Patients

Patients aged ≥ 18 years with unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction, whose cancer had progressed after a first-line fluoropyrimidine and platinum combination regimen, were eligible to enter the study. Other eligibility criteria were as follows: measurable or evaluable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1; performance status 0–2 by Eastern Cooperative Oncology Group scale; adequate organ function including bone marrow (absolute neutrophil count $\geq 1500 \mu\text{l}^{-1}$, platelet $\geq 100\,000 \mu\text{l}^{-1}$), liver (AST/ALT $\leq 2.5 \times \text{ULN}$, $5.0 \times \text{ULN}$ if liver involvement, total serum bilirubin $\leq 2.0 \text{ mg dl}^{-1}$) and kidney (serum creatinine $\leq 1.5 \times \text{ULN}$); life expectancy of more than 3 months; and written informed consent. Patients with severe comorbid illness and/or active infections, grade 3 or higher haemorrhage according to CTCAE v3.0 (US National Cancer Institute) within prior 4 weeks, pregnant or lactating women, or active CNS metastases not controllable with radiotherapy or corticosteroids were excluded from the study.

Treatment

Patients were randomised in 1:1 ratio either to a docetaxel plus sunitinib (DS arm) arm or to a docetaxel single arm (D only arm) using a random permuted block design. Random assignment was stratified by ECOG performance status (0, 1 vs 2). Docetaxel was administered at the dose of 60 mg m^{-2} on day 1 of each 3-week

cycle and sunitinib was administered orally at the starting dose of 37.5 mg daily, on a continuous daily dosing schedule. Tumour evaluation was performed every two cycles and response to chemotherapy was assessed in accordance with the RECIST criteria v1.1. Clinical laboratory evaluations (biochemistry, haematology, and urinalysis) were carried out on day 1 of every cycle. Toxicity assessment adhered to CTCAE v3.0. Treatment was discontinued in case of tumour progression, unacceptable toxicity, or consent withdrawal. No crossover to the DS arm was allowed for patients in the D only arm after progression.

For patients receiving docetaxel administration, if grade 4 neutropenia, febrile neutropenia, skin/nail changes, or grade 2 peripheral neuropathy developed, dose was reduced to 45 mg m^{-2} . If a patient continued to experience these toxicities (other than neuropathy) at 45 mg m^{-2} , treatment was discontinued. In terms of peripheral neuropathy, treatment was discontinued if grade 3 or 4 toxicity was developed. For patients receiving sunitinib administration, if grade 3 toxicity developed, sunitinib was withheld until the toxicity was resolved to $< \text{grade } 2$, then treatment was reduced to 25 mg . If a second occurrence of $> \text{grade } 1$ toxicity occurred, sunitinib was further reduced to 12.5 mg . At a third occurrence of $> \text{grade } 1$ toxicity, sunitinib was discontinued.

Pharmacokinetic analysis

Average steady-state plasma concentrations ($C_{\text{ss,av}}$) for sunitinib and its active metabolite SU12662 were measured on the last day of cycles 2, 4, and 6, before drug administration of the next cycle. All the samples were centrifuged at 2092 g for 10 min immediately after collection, and stored frozen at -70°C until assayed. Plasma concentrations of sunitinib and SU12662 were determined by high performance liquid chromatography coupled with tandem mass spectrometry. The lower limit of quantification was 0.25 ng ml^{-1} for sunitinib and SU12662.

Data analysis was performed on the intent-to-treat population using the last observation carried forward method for missing data. Dose-normalised $C_{\text{ss,av}}$ of sunitinib and SU12662 at each cycle was analysed by repeated-measures ANOVA (SAS, version 9.1; SAS Institute Inc., Cary, NC, USA).

Statistics

The primary end point of the current study was TTP, which was defined as the interval between the date of first study treatment and the date of documented disease progression. The secondary end points were objective response rate (ORR), disease control rate (DCR), and overall survival (OS), which was calculated from the date of first study treatment to the date of death and toxicity profile. TTP and OS were calculated by the Kaplan–Meier product–limit method.

For sample size calculation, we initially assumed 12 months of accrual period and 6 months of follow-up period. The current study was designed with two-sided, $\alpha = 0.05$, 90% power to detect a null median TTP of 2 months and experimental median TTP of 4 months ($N = 108$). Assuming a 10% dropout rate, total target accrual number was 116 ($108 + 10\%$). The sample size was recalculated on February 2011 owing to a longer patient accrual period (> 24 months) than originally planned (12 months). The revised sample size calculation was designed with two-sided, $\alpha = 0.05$, 90% power to detect a null median TTP of 2 months and experimental median TTP of 4 months ($N = 108$) after a 36-month accrual period and 18-month follow-up ($N = 92$). We amended the protocol to accrue 102 patients. The laboratory data and prognostic factors obtained from demographic data on the baseline were evaluated by Pearson's Chi-square test for patient homogeneity on the baseline between the two arms and the associations among the prognostic factors. The efficacy and toxicity of the two arms were evaluated by comparing response rate, DCR, and incidence of toxicity using Pearson's chi-square

tests, while TTP and OS were compared by log-rank tests. For pharmacokinetic study, the protocol was amended (at the time of 80 patient accrual) to enrol patients for pharmacokinetic blood sampling. Those patients who had consented for pharmacokinetic sampling, which was not mandatory, were enrolled.

RESULTS

Patient characteristics

Between December 2008 and February 2011, 107 patients were entered into the study. As 2 patients withdrew their consent before treatment, clinical outcomes and toxicities were evaluated in 105 patients. The median age of the patients was 53 years (20–72) and male:female ratio was 73 (69.5%):32 (30.5%). The ECOG performance scale indicated a grade of 0–1 for 96 (91.4%) patients. After randomisation, 56 patients (53.3%) were allocated to the DS arm and 49 patients (46.7%) to the docetaxel arm (D only arm). Demographics of the two arms, including median age, sex ratio, ECOG performance scale, laboratory findings (except serum alkaline phosphatase level), and sites of metastatic lesions, were not significantly different. These details are provided in Table 1.

Pharmacokinetic analysis

A total of 66 plasma concentrations (33 for sunitinib, 33 for SU12662) from 13 patients were analysed. No differences were noted in the dose-normalised $C_{ss,av}$ of sunitinib and SU12662 over the cycle using repeated-measures ANOVA (Table 2 and Figure 1).

Treatment response and survival

A total of 423 cycles were administered, with a median of three cycles given per patient (range 1–18). No significant difference was noted between the DS and D only arms in terms of the median number of treatment cycles ($P=0.283$). At the time of analysis, 97 cases (92.3%) of progression had occurred, including 52 cases (92.9%) in the DS arm and 45 cases (91.8%) in the D only arm. The TTP was not significantly prolonged in the DS arm when compared with the D only arm (DS vs D only arm: 3.9 months (95% confidence interval (CI) 2.9–4.9) vs 2.6 months (95% CI 1.8–3.5), $P=0.206$) (Figure 2). The hazard ratio for TTP was 0.77 (95% CI 0.52–1.16). The response rate was significantly higher for the DS arm than for the D only arm (DS vs D only arm: 41.1% (95% CI 28.1–55.0) vs 14.3% (95% CI 6.0–27.2), $P=0.002$) (Table 3). Notably, one patient with multiple liver metastases achieved complete remission after 4 cycles of docetaxel and sunitinib. The patient is still maintaining complete remission after completion of 4 cycles of docetaxel and sunitinib (that is, for more than 2 years) at the time of this writing (Figure 3). The DS arm had 1 CR, 29 PRs, 37 SDs, and 38 PDs, by RECIST 1.1. All treatment responses were centrally reviewed while blinded to the treatment arm. A similar tendency was observed for the DCR, which was 75.0% (42/56, 95% CI 61.6–85.6) in the DS arm and 51.0% (25/49, 95% CI 36.3–65.6) in the D only arm ($P=0.011$, Table 3).

The DS regimen did not significantly improve survival when compared with the D only regimen (DS vs D only arm: 8.0 (95% CI 5.4–10.6) vs 6.6 (95% CI 3.6–9.7), $P=0.802$) (Figure 4). The hazard ratio for OS was 0.94 (95% CI 0.60–1.49).

Adverse events

Among the 105 patients whose toxicity profile was assessed, 64 patients (61.0%) experienced grade at least one grade 3–4 adverse event (AE). The most common grade 3–4 AE was neutropenia, which occurred in 18 patients (32.1%) in the DS arm and 10 patients (20.4%) in the D only arm. Overall, the incidence of grade 3–4 AEs was not significantly different between the two arms

Table 1 Patients' characteristics

	DS arm (n = 56)	D arm (n = 49)	P-value
Age, median (range)	54.0 (20–72)	52 (36–70)	0.356
Sex (N (%))			
Male	40 (71.4)	33 (67.3)	0.650
Female	16 (28.6)	16 (32.7)	
ECOG (N (%))			
0	2 (3.6)	3 (6.1)	0.603
1	28 (85.7)	43 (87.8)	
2	6 (10.7)	3 (6.1)	
Laboratory findings (median, range)			
WBC	6135 (2910–17270)	5900 (3110–12170)	0.352
Haemoglobin	10.9 (8.0–17.1)	11.1 (8.4–15.5)	0.529
Platelet	201 000 (75 000–495 000)	187 000 (89000–497 000)	0.094
ANC	3470 (1080–13700)	3500 (1390–9630)	0.571
Calcium	9.0 (7.1–11.1)	9.0 (7.7–10.5)	0.138
Creatinine	0.8 (0.4–3.3)	0.8 (0.6–6.4)	0.312
Total protein	6.5 (3.9–7.8)	6.6 (4.6–8.0)	0.108
Albumin	4.0 (1.9–4.8)	4.1 (2.4–4.9)	0.484
ALP	80 (43–975)	93 (45–1418)	0.029
AST	19 (11–66)	24 (10–58)	0.980
ALT	14 (5–38)	15 (5–49)	0.804
Total bilirubin	0.5 (0.2–2.3)	0.5 (0.2–1.6)	0.063
Site of metastases (N, (%))			
Liver			0.081
Yes	24 (42.9)	13 (26.5)	
No	32 (57.1)	36 (73.5)	
Lung			0.251
Yes	5 (8.9)	8 (16.3)	
No	51 (91.1)	41 (83.7)	
Abdominal lymph nodes			0.530
Yes	32 (57.1)	25 (51.0)	
No	24 (42.9)	24 (49.0)	
Neck lymph nodes			0.892
Yes	2 (3.6)	2 (4.1)	
No	54 (96.4)	47 (95.9)	
Peritoneal seeding			0.124
Yes	17 (30.4)	22 (44.9)	
No	39 (69.6)	27 (55.1)	
Bone			0.565
Yes	3 (5.4)	4 (8.2)	
No	53 (94.6)	45 (91.8)	
Number of metastatic sites (N (%))			
0	9 (16.1)	2 (4.1)	
1	23 (41.1)	26 (53.1)	
2	18 (32.1)	15 (30.6)	
3	6 (10.7)	6 (12.2)	
Prior chemotherapy (N (%))			
Capecitabine + cisplatin		74 (70.5%)	
TS-1 + cisplatin		18 (17.1%)	
Epirubicin + capecitabine + cisplatin		6 (5.7%)	
FOLFOX		5 (4.8%)	
TS-1 + oxaliplatin		2 (1.9%)	

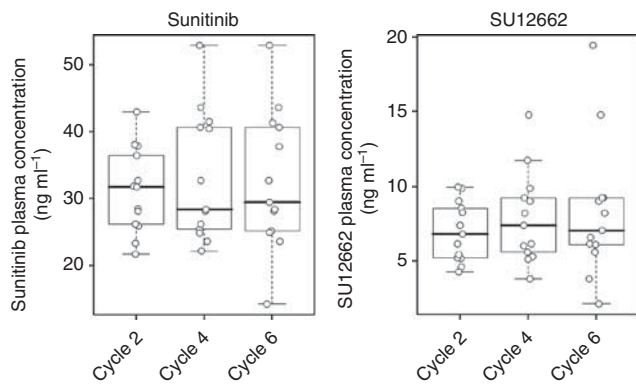
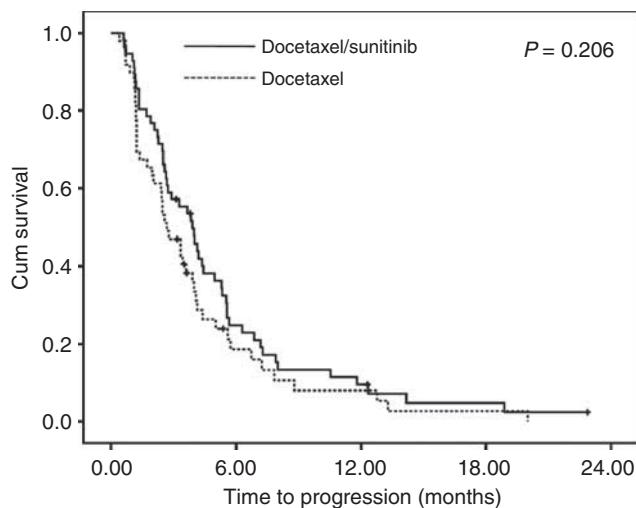
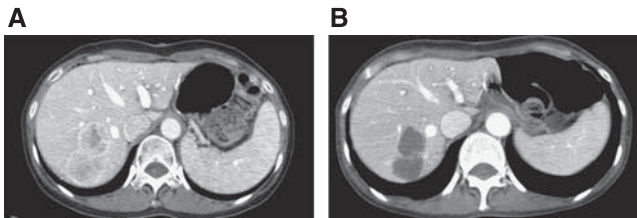
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; D = docetaxel monotherapy; DS = docetaxel + sunitinib; ECOG = Eastern Cooperative Oncology Group; FOLFOX = oxaliplatin, 5-fluorouracil, leucovorin; WBC = white blood corpuscles.

(46.4% (26/56) in the DS arm, 30.6% (15/49) in the D only arm, $P=0.112$). In addition, no statistical difference was observed between the two groups in terms of haematological toxicity (including anaemia, leukopenia, neutropenia, thrombocytopenia, and febrile neutropenia), nausea, vomiting, neuropathy, and myalgia. However, patients who received docetaxel and sunitinib

Table 2 Sunitinib and SU12662 pharmacokinetic variables at each cycle

	Cycle 2	Cycle 4	Cycle 6	P-value ^a
Dose-normalised sunitinib $C_{ss,av}$	31.2 ± 6.33	33.1 ± 9.63	32.5 ± 10.33	0.8514
Dose-normalised SU12662 $C_{ss,av}$	6.97 ± 2.00	7.85 ± 3.06	8.24 ± 4.54	0.6157

Abbreviations: ANOVA = analysis of variance; $C_{ss,av}$ = average steady-state plasma concentrations. ^aRepeated-measures ANOVA. Concentration values are shown as mean ± s.d.

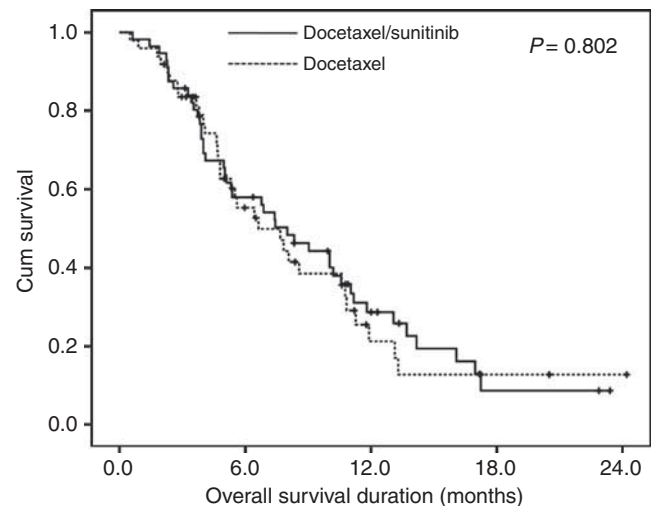
**Figure 1** Dose-normalised $C_{ss,av}$ of sunitinib and SU12662 at each cycle.**Figure 2** Time to progression curve of the patients.**Figure 3** A case of complete response of docetaxel/sunitinib combination. (A) Baseline image. (B) After four cycles of treatment.

had a greater chance of experiencing stomatitis, diarrhoea, and hand-foot syndrome (HFS) than did those who received docetaxel only. These details are described in Table 4.

Table 3 Tumour response according to the treatment group

	DS arm (n = 56)	D arm (n = 49)	Total (n = 105)
Best response (N, %)			
Complete response	1 (1.8)	0 (0.0)	1 (1.0)
Partial response	22 (39.3)	7 (14.3)	29 (27.6)
Stable disease	19 (33.9)	18 (36.7)	37 (35.2)
Progressive disease	14 (25.0)	24 (49.0)	38 (36.2)
Overall response rate (%)	23/56 (41.1)	7/49 (14.3)	P = 0.002
Disease control rate (%)	42/56 (75.0)	25/49 (51.0)	P = 0.011

Abbreviations: D = docetaxel monotherapy; DS = docetaxel + sunitinib.

**Figure 4** Overall survival curve of the patients.**Table 4** Adverse events (N, %)

	DS arm		D arm		P-value
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Anaemia	45 (80.4)	6 (10.7)	41 (83.7)	5 (10.2)	0.856
Leukopenia	13 (23.2)	12 (21.4)	5 (10.2)	7 (14.3)	0.084
Neutropenia	8 (14.3)	18 (32.1)	4 (8.2)	10 (20.4)	0.169
Thrombocytopenia	26 (46.4)	2 (3.6)	13 (26.5)	2 (4.1)	0.107
Febrile neutropenia	N/A	15 (26.8)	N/A	8 (16.3)	0.196
Nausea	19 (33.9)	none	13 (26.5)	none	0.411
Vomiting	9 (16.1)	none	6 (12.2)	none	0.576
Stomatitis	29 (51.8)	none	7 (14.3)	none	<0.001
Diarrhoea	14 (25.0)	6 (10.7)	6 (12.2)	1 (2.0)	0.033
Hand-foot syndrome	27 (48.2)	3 (5.4)	10 (20.4)	none	0.002
Neuropathy	37 (66.1)	none	28 (57.1)	none	0.347
Myalgia	8 (14.3)	none	11 (22.4)	1 (2.0)	0.295

Abbreviations: D = docetaxel monotherapy; DS = docetaxel + sunitinib.

The occurrence of these AEs led to at least one cycle of dose reduction in 46 (43.8%) patients and treatment delay in 57 (54.3%) patients. The DS arm showed 39 and 50 cases of dose reduction and treatment delay, respectively, out of 230 cycles of treatment. The D only arm showed 23 and 44 cases of dose reduction and treatment delay, respectively, out of 193 cycles. Occurrences of dose reduction (29/56, 51.8% in arm A, 17/49, 34.7% in arm B, $P = 0.078$) and treatment delay (32/56, 57.1% in arm A, 25/49, 51% in arm B, $P = 0.530$) were not significantly different between the two groups. The dose intensity was 65% of the planned dose for docetaxel and 60% of the planned dose for sunitinib.

DISCUSSION

In this phase II randomised study, we analysed the efficacy and toxicity of 3-weekly administration of docetaxel 60 mg m⁻² combined with daily administration of sunitinib 37.5 mg in patients with AGC who had failed to respond to first-line fluoropyrimidine and platinum. The current study showed the following findings: (1) combination of docetaxel and sunitinib demonstrated a median TTP of 3.9 months (95% CI 2.9–4.9), while docetaxel monotherapy demonstrated a median TTP of 2.6 months (95% CI 1.8–3.5) ($P=0.206$). Importantly, patients who had received the combined treatment showed significantly higher ORR (DS vs D only arm: 41.1% vs 14.3%, $P=0.002$). However, patients in the DS arm experienced stomatitis, diarrhoea, and HFS more frequently than did patients in the D only arm.

In the current study, 56 patients received docetaxel combined with sunitinib. Importantly, one patient who had multiple liver metastases from gastric cancer, and who had failed to respond to previous TS-1/cisplatin chemotherapy, achieved complete remission after docetaxel/sunitinib and has maintained remission for >2 years (Figure 3). The high response rate with the docetaxel and sunitinib combination in gastric cancer suggests that this regimen might be feasible in a neoadjuvant setting where response rate is important. Although the DS regimen did not prolong TTP in all GC patients, the regimen substantially increased response rate and thus may be important as a preoperative regimen in gastric cancer patients with limited metastases. In addition, the docetaxel and sunitinib combination may be tested in the first-line setting for gastric cancer. Based on our phase III trial which compared docetaxel, irinotecan and supportive care in salvage setting for gastric cancer, irinotecan monotherapy seemed better than docetaxel alone (Park *et al*, 2011). However, at the time of the study design, the phase III trial was ongoing and there was lack of preclinical data for irinotecan and sunitinib combination. There are few phase I dose-finding studies for the combination of sunitinib and docetaxel (Robert *et al*, 2010; de Jonge *et al*, 2011). The recommended dose for the combination was docetaxel 75 mg m⁻² q 3 weeks and sunitinib 37.5 mg daily. Initially, we had planned to administer the above regimen. However, the first two patients had grade 4 neutropenia with febrile episode. After internal discussion with the internal safety monitoring board, we had decided to lower the dose to docetaxel 60 mg m⁻² and sunitinib 37.5 mg daily every 3 weeks.

The PK results of sunitinib and SU12662 obtained at steady-state were similar to those from single-agent trials in patients with advanced solid malignancies (Britten *et al*, 2008). As mentioned earlier, no difference was observed for the dose-normalised $C_{ss,av}$ of sunitinib and SU12662 over the cycle. Therefore, the conclusion may be made that autoinduction or autoinhibition of sunitinib or SU12662 metabolism has not been observed with prolonged dosing.

Identification of predictive biomarkers that could identify the subset of gastric cancer patients who might dramatically respond to docetaxel and sunitinib will be clinically important. Although our study failed to demonstrate improved TTP in the docetaxel and sunitinib combination arm, it did indicate that some gastric cancer patients may respond dramatically to a combined docetaxel and sunitinib treatment. Identification of key biomarkers that might predict treatment response to sunitinib will aid clinicians in designing future enriched clinical trials on sunitinib as a treatment for metastatic gastric cancer. Currently, no specific biomarker has been identified that can predict treatment response to sunitinib.

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The German Arbeitsgemeinschaft Internistische Onkologie (AIO) study investigated the associations between serum VEGF-C concentrations and treatment outcome in a phase II sunitinib monotherapy trial for gastric cancer (Moehler *et al*, 2011). However, owing to limited tissue availability, the biomarker study in the AIO study was not conclusive. Recent pharmacogenetic analysis has revealed that patients harbouring certain single-nucleotide polymorphisms (SNPs) are predisposed to experience more frequent toxicities or lower response (van Erp *et al*, 2009; Garcia-Donas *et al*, 2011) when treated with sunitinib. We have collected serial blood samples as well as paraffin-embedded tissues for further correlative analyses and soon will report the predictive and prognostic role of those SNPs in sunitinib treatment.

Grade 3–4 neutropenia, which is a serious toxicity of the docetaxel and sunitinib combination, occurred in 18 patients (32.1%) in the DS arm and 10 patients in the D arm ($P=0.169$). Overall, the incidences of other haematological toxicities including anaemia, leukopenia, or thrombocytopenia were not significantly different between the two groups. The incidence of febrile neutropenia was not significantly different in the two arms ($P=0.196$) and no subsequent mortality was observed. Although this could be the result of the small number of the recruited patients, we authors do not consider this AE to be a major problem for the docetaxel and sunitinib combination treatment.

However, in the DS arm, the incidences of any grade of stomatitis, diarrhoea, and HFS were more frequent than in the D arm, with statistical significance (any grade stomatitis: 51.8% vs 14.3% ($P<0.001$); any grade diarrhea: 35.7% vs 14.2% ($P=0.033$); any grade HFS: 53.6% vs 20.4% ($P=0.002$)). Because of these AEs, a substantial number of patients needed treatment modifications. Patients who had received the DS treatment showed a tendency to experience more frequent dose reductions, but the difference was not statistically significant (29/56, 51.8% in arm DS, 17/49, 34.7% in arm D, $P=0.078$). Therefore, we might conclude that future clinical trials will combine sunitinib and conventional chemotherapeutic agents safely, by providing appropriate management of the AEs.

In conclusion, although the primary end point has not been met in this randomised phase II trial, the study has demonstrated that the addition of sunitinib can substantially improve response rate in metastatic gastric cancer in a second-line setting. Compared with docetaxel monotherapy, the addition of sunitinib was not associated with additional toxicity except stomatitis, diarrhoea, and HFS, and was not associated with more frequent treatment modification. The observation of some long-term responders indicates that the clinical development of sunitinib should still be pursued for treatment of gastric cancer. Especially with the advent of the personalised medicine, we should focus on exploring biomarkers that could identify those few gastric cancer patients who would dramatically respond to sunitinib.

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Conflict of interest

The authors declare no conflict of interest.

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