Cancer Chemother Pharmacol (2008) 63:1–8
DOI 10.1007/s00280-008-0701-2

ORIGINAL ARTICLE

A phase II study of irinotecan and docetaxel combination chemotherapy for patients with previously treated metastatic or recurrent advanced gastric cancer

Sun Jin Sym · Heung Moon Chang · Hye Jin Kang · Sung Sook Lee · Min-Hee Ryu · Jae-Lyun Lee · Tae-Won Kim · Jeong Hwan Yook · Sung Tae Oh · Byung Sik Kim · Yoon-Koo Kang

Received: 6 December 2007 / Accepted: 5 February 2008 / Published online: 21 February 2008

Abstract
Purpose Irinotecan (I) and docetaxel (D), each of which has a unique mechanism of action, were recently introduced in the treatment of patients with advanced gastric cancer (AGC). We have evaluated the efficacy and safety of the ID combination for AGC patients after failure of fluoropyrimidine- or platinum-based chemotherapy.
Materials and methods Patients with relapsed or progressive AGC after prior fluoropyrimidine- or platinum-based chemotherapy were treated with I (160 mg/m^2, 90 min) followed by D (65 mg/m^2, 1 h) every 3 weeks. Because of the unacceptable toxicity among the first ten patients, the doses were reduced for I (120 mg/m^2) and D (50 mg/m^2) every 3 weeks.
Results Forty-nine patients, of median age 53 years (range, 27–68 years), were treated with 170 cycles of chemotherapy (median, 2 cycles; range, 1–12 cycles). Three patients achieved complete response and seven achieved partial response, resulting in an overall response rate (ORR) of 20.4% [95% confidence interval (CI), 9.1–31.7%], with a median duration of 7.1 months (range: 2.1–69.1 months). ORR was 60% (95% CI, 29.6–90.3%) for the higher dose and 10.3% (95% CI, 0.7–19.8%) for the lower dose. Median time to progression for all patients was 2.7 months (95% CI, 1.7–3.8 months) and the median overall survival was 8.9 months (95% CI, 6.6–11.3 months). Grade 3/4 toxicities included neutropenia (90%), febrile neutropenia (50%), asthenia (40%), and diarrhea (10%) with the higher dose and neutropenia (71%), febrile neutropenia (11%), diarrhea (24%), and asthenia (24%) with the lower dose. There were two possible treatment-related deaths.
Conclusion The combination of irinotecan and docetaxel, once every three weeks shows anti-tumor activity but is not feasible as a second-line treatment for AGC patients after failure of fluoropyrimidine- or platinum-based chemotherapy due to the high rate of toxicities.

Keywords Gastric cancer · Docetaxel · Irinotecan · Chemotherapy

S. J. Sym and H. M. Chang have contributed equally to this article.

S. J. Sym · H. M. Chang · S. S. Lee · M.-H. Ryu · J.-L. Lee · T.-W. Kim · Y.-K. Kang (✉)
Division of Oncology, Departments of Medicine,
Asan Medical Center, University of Ulsan College of Medicine,
388-1 Pungnap-2 Dong, Songpa Gu, Seoul 138-736, South Korea
e-mail: ykkang@amc.seoul.kr

J. H. Yook · S. T. Oh · B. S. Kim
Department of Surgery, Asan Medical Center,
University of Ulsan College of Medicine,
388-1 Pungnap-2 Dong, Songpa Gu, Seoul 138-736, South Korea

H. J. Kang
Division of Oncology, Department of Medicine,
Korea Institute of Radiological and Medical Sciences,
215-4 Goneung-Dong, Seoul, South Korea

Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related deaths worldwide [1]. In Korean, gastric cancer is the most common cancer (24%) and the second leading cause of cancer-related deaths (19%) [2]. Many patients present initially with locally advanced or distant metastasis. Even after complete resection, local and distant relapse rates are still high. For these patients, palliative chemotherapy has been found to improve the quality of life and overall survival when compared with best supportive care alone [3–5]. First

line chemotherapy usually consists of different combination of 5-fluorouracil (5-FU) and cisplatin, including FP (5-FU and cisplatin) and ECF (epirubicin, cisplatin, and 5-FU) regimens. Several randomized phase III trials have shown that the FP regimen improved response rates and progression-free survival when compared with 5-FU alone or with other combination regimens including 5-FU [6, 7]. In addition, a phase III trial has shown that ECF results in a superior overall response rate and improved median survival when compared with other combinations [8]. More recently, the oral 5-FU pro-drugs, capecitabine [9] and S-1 [10], have been used to overcome the inconveniences associated with intravenous infusion of 5-FU and improve safety. Two phase III trials have shown that intravenous infusion of 5-FU could be replaced by oral fluoropyrimidines without impairment of efficacy [11, 12].

Although many patients with metastatic or recurrent gastric cancer initially respond to chemotherapy, they eventually show disease progression. Second-line treatments used to date, however, have been unsatisfactory, indicating an urgent need to develop active chemotherapy regimens, including new active compounds, for patients with metastatic or recurrent gastric cancer.

Docetaxel is a semisynthetic taxoid prepared from the noncytotoxic precursor 10-deacetyl baccatin III, which is extracted from the needles of the European yew, *Taxus baccata*. It promotes tubulin assembly into microtubules and inhibits depolymerization to free tubulin, thus blocking cells in the M-phase of the cell cycle [13, 14].

Phase II trials have shown that docetaxel monotherapy has appreciable activity in gastric cancer. Single-agent docetaxel achieved response rates of 17–24% in previously untreated patients [15, 16], and 17–20% as second-line treatment [17–19].

CPT-11 (irinotecan) is a semi-synthetic, water-soluble derivative of the plant alkaloid camptothecin. CPT-11 is enzymatically converted to its active metabolite, SN-38, which inhibits the eukaryotic enzyme DNA-topoisomerase I, thus blocking cells in the S-phase of the cell cycle [20].

Single-agent irinotecan achieved response rate of 16–20% in the advanced gastric cancer patients who had received prior chemotherapy [21, 22].

Sequential administration of docetaxel and CPT-11 in vitro resulted in synergistic cytotoxicity for human lung cancer cell lines, with the order of administration being unimportant [23].

In a phase I trial of irinotecan and docetaxel in patients with advanced solid tumors, the combination showed antitumor activity and no evidence of a clinically significant interaction between these two agents. The recommended dose was irinotecan 160 mg/m^2 and docetaxel 65 mg/m^2 every 3 weeks, with the most common dose-limiting toxicity being myelosuppression [24].

Due to their different mechanisms of action at different phases of the cell cycles and the single-agent activity of docetaxel and irinotecan in patients with advanced gastric cancer, we designed a phase II trial to examine the activity and feasibility of this combination in previously treated patients with metastatic or recurrent advanced gastric cancer.

Materials and methods

Patient selection

The patients were required to be 18–70 years of age, with histologically proven metastatic or recurrent gastric adenocarcinoma and at least one unidimensionally measurable lesion, and a performance status of 0–2 on the eastern cooperative oncology group (ECOG) scale. In addition, patients were required to have previous adjuvant or palliative chemotherapy containing fluoropyrimidine (F)- or platinum (P) completed at least 4 weeks prior to enrollment in this study. Patients could not have previous exposure to topoisomerase I inhibitors or taxanes.

Other inclusion criteria included adequate bone marrow [absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l], renal function (serum creatinine <1.5 mg/dl), and hepatic function [bilirubin $\leq$1.5 mg/dl, hepatic transaminase $\leq$3 upper limit of normal range (ULN) and prothormbine time <1.25 ULN; in the presence of hepatic metastasis, hepatic transaminase <5 ULN].

Patient whose tumors had progressed more than 12 months after the last adjuvant chemotherapy were excluded. Patients were also excluded if they had brain meastases, significant gastrointestinal bleeding or obstruction, serious comorbid conditions, another active malignancy, or lacked the ability to comply with the requirements of the protocol.

The protocol was approved by the Institutional Review Board of Asan Medical Center, and written informed consent was obtained from all patients before enrollment.

Treatment schedule

Initially, irinotecan was administered as an intravenous infusion at 160 mg/m^2 for 90 min, followed immediately by an intravenous infusion of docetaxel at 65 mg/m^2 for 60 min once every three weeks, which was established by a phase I study [24]. Because of unacceptable rates of severe toxicity after the treatment of ten patients (see "Results"), we decided to amend this regimen by reducing both the agents by 25% (irinotecan 120 mg/m^2 and docetaxel 50 mg/m^2).

Oral dexamethasone (8 mg twice daily for six doses, starting 24 h before decetaxel) and parenteral pheniramine

maleate were administered to prevent docetaxel-induced hypersensitivity. All patients received 5-HT3 inhibitors and dexamethasone 10 mg i.v. as antiemetics. Patients with acute cholinergic symptoms were administered 0.25 mg of atropine subcutaneously. All patients were counseled about the importance of early recognition and treatment of diarrhea with loperamide. Prophylactic administration of granulocyte-colony stimulation factor (G-CSF) was not allowed.

The next chemotherapy cycle was delayed if ANC was $<1.5 \times 10^9$/l or platelet count was $<100 \times 10^9$/l on the day of infusion. Non-hematological toxicities, excluding alopecia, were required to be grade 1 or better, prior to initiation of each cycle. Doses of irinotecan and docetaxel were reduced by 25% in subsequent cycles if patients experienced grade 4 neutropenia for more than 7 days, grade 3 or 4 neutropenia with fever, or grade 4 thrombocytopenia. Doses of docetaxel alone were reduced by 25% in subsequent cycles if patients experienced grade 2 neuropathy; patients who experienced grade 3 or 4 neuropathy were withdrawn from the study. Doses of irinotecan alone were reduced by 25% in subsequent cycles if patients experienced grade 3 diarrhea; patients who experienced grade 4 diarreha were withdrawn. Doses of irinotecan and docetaxel were also reduced by 25% if patients experienced any other grade $\geq$3 non-hematologic toxicity, except for alopecia, nausea, and vomiting. Once a dose reduction was instituted, it was maintained through subsequent chemotherapy cycles, unless a further dose reduction was required. If chemotherapy dose was reduced three times or if toxicities persisted for more than 3 weeks following the time of planned treatment, patients were withdrawn from the study. Chemotherapy was continued until disease progression or unacceptable toxicity developed.

Study assessments

As screening assessment, including a medical history, physical examination, ECG, chest X-ray, and tumor assessment by computed tomography (CT) scan, was performed within 3 weeks before starting the treatment. Within 3 days of starting treatment, and on day 1 of each treatment cycle, patients were assessed for vital sign and an ECOG performance status, and laboratory tests (complete blood counts, blood chemistry) were performed. Response was evaluated by CT scan every two cycles until the tumor progressed, with each assessment using the same imaging technique as at baseline. Tumor responses were classified according to the response evaluation criteria in solid tumor (RECIST) guidelines. Patients with complete response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later. Patients with no confirmed tumor response were not regarded as responders. Adverse events were graded according to the "NCI-CTCAE" scale, version 2.0.

Statistical analysis

The primary end point was the objective response rate (ORR). Simon's optimal two-stage design was used to test the null hypothesis $P_0 \leq 0.05$ versus the alternative hypothesis $P_1 \geq 0.2$. The first stage required at least two confirmed responses of 21 patients enrolled with $\alpha = 0.05$ and $\beta = 0.1$ before the second stage commenced. The second stage included an additional 20 assessable patients; if 5 or more achieved a confirmed response, the primary end point would be met.

The duration of response (DR), time to progression (TTP), and overall survival (OS) were estimated using the Kaplan–Meier method and the difference between curves were analyzed using the log-rank test. The DR was defined as the interval from the onset of CR or PR until evidence of PD. TTP was calculated from the initiation of chemotherapy until disease progression, and OS was measured from the initiation of chemotherapy to the date of last follow-up or death. TTP and OS have been updated to 30 May 2007. Statistical comparisons were made using an SPSS software package version 12.0. (SPSS Inc., Chicago, IL USA).

Results

Patient characteristics

Between June 2001 and May 2003, 49 patients were enrolled in the study, their demographic and clinical characteristic are summarized in Table 1. Median patient age was 53 years (range, 27–68 years), and 47 (96%) had a good performance status (ECOG PS 0 or 1). Thirty patients (61%) had recurrent disease after curative resection. Twenty-nine patients (59%) had received adjuvant chemotherapy and ten (20%) had received palliative chemotherapy after recurrence. In 20 patients who received the ID regimen as a salvage treatment after adjuvant chemotherapy, the median interval from the last adjuvant chemotherapy to disease progression was 5.1 months (range, 1.1–9.5 months).

Drug administration

The median number of chemotherapy cycles per patients was two (range, 1–12 cycles; total 170 cycles). The initial chemotherapy regimen, administered to the first ten patients, consisted of irinotecan 160 mg/m^2 and docetaxel 65 mg/m^2 on day 1 every 3 weeks. These ten patients required dose reductions, since nine experienced grade 3 or 4

Table 1 Patient characteristics

Characteristic	No.	%
Total	49	100
Age (years)		
Median	53	
Range	27–68	
Sex		
Male	40	82
Female	9	18
ECOG performance status		
0	4	8
1	43	88
2	2	4
Histology		
Well/moderately differentiated	18	37
Poorly differentiated or signet-ring cell type	26	53
Unknown	5	10
Metastasis sites		
Liver	20	41
Abdominal lymph node	33	67
Peritoneum	11	22
Cervical lymph node	6	12
No. of metastatic sites		
1	26	53
≥2	23	47
Disease status		
Recurrent	30	61
Initially metastatic	19	39
Previous chemotherapy		
Adjuvant chemotherapy[a]	29	59
Fluoropyrimidine + platinum containing regimen	14	
Fluoropyrimidine ± etoposide	7	
5-FU + adriamycin + methotrexate	8	
Palliative chemotherapy	29	59
Fluoropyrimidine + platinum containing regimen	27	
Fluoropyrimidine ± etoposide	2	
Progression after the last previous chemotherapy		
<6 months	29	59
≥ 6 months	20	41

[a] Five patients also received mitomycin C

neutropenia and five experienced neutropenic fever. The reduced dose, administered to the remainder of the cohort, consisted of irinotecan 120 mg/m^2 and docetaxel 50 mg/m^2 on day 1 every 3 weeks.

Efficacy and survival

A total of 43 patients were evaluable for response. Response was not assessable in six patients: three were lost to follow-up, two after the first cycle and one after the second cycle; two died after the first cycle; and one refused treatment. We found that three patients achieved CR and seven achieved PR, resulting in an ORR of 20.4% [95% confidence interval (CI), 9.1–31.7%] in the intention-to-treat analysis. Another 17 patients had stable disease, making the overall tumor control rate 55.1%. Of the ten patients who achieved CR or PR, six had been treated with the high dose and four with the reduced dose regimen, making the ORR in the latter group significantly lower ($P = 0.002$) (Table 2).

Table 2 Tumor response

	Dose level		
	High ($n = 10$)	Low ($n = 39$)	Total ($n = 49$)
Complete response	2 (20%)	1 (2.6%)	3 (6.1%)
Partial response	4 (40%)	3 (7.7%)	7 (14.3%)
Stable disease	1 (10%)	16 (41.0%)	17 (34.7%)
Progressive disease	2 (20%)	14 (35.9%)	16 (32.7%)
Not evaluable	1 (10%)	5 (12.8%)	6 (12.2%)
Overall response rate	60%	10.3%	20.4%

The ORR in patients whose tumors had progressed more than 6 months after the last previous chemotherapy (late progression group) was higher than that in patients whose tumor progressed within 6 months of completing previous chemotherapy (early progression group) (30 vs. 13.8%), although the difference did not reach statistical significance ($P = 0.279$).

The median RD in the ten responding patients was 7.1 months (range 2.1–69.1 months). At the time of analysis, only one patient who had achieved CR was alive. The median TTP of all patients was 2.7 months (95% CI, 1.7–3.8 months) and the median OS was 8.9 months (95% CI, 6.6–11.3 months), with a 1-year survival rate of 38.8% (Fig. 1). When we compared the outcomes of the high and low dose groups, we found that the former had significantly prolonged TTP (4.0 vs. 2.4 months, $P = 0.037$), but not OS (9.5 vs. 8.8 months, $P = 0.225$). When compared with the early progression group, the late progression group tended toward more prolonged TTP (1.6 vs. 3.4 months) and OS (7.7 vs. 12.3 months), but the differences did not reach statistical significance.

Adverse events

The 49 patients received a total of 170 treatment cycles. No data were available for four cycles because three patients were lost to follow-up and one died after the first treatment cycle. As noted, dose reductions were instituted after enrollment of the first ten patients. The frequencies of

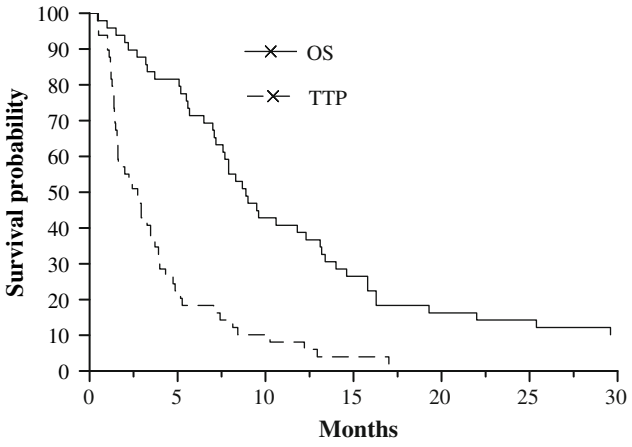

Fig. 1 Time to progression (*TTP*) and overall survival (*OS*) for all eligible patients

treatment-related hematological and nonhematological toxicities at each dose are listed in Table 3.

At the high-dose level, the most common treatment-related hematological toxicity was neuropenia, which occurred at grade 3/4 intensity in nine patients (90%), with five (50%) patients who experienced febrile neutropenia requiring hospitalization. However, there were no treatment-related deaths in this dose level. Grade 3 asthenia was observed in four (40%) patients. Subsequent to dose reduction, 26 of 38 patients (71%) experienced grade 3/4 neutropenia and 4 (11%) experienced febrile neutropenia (Table 3). There were two deaths (4%) that may have been associated with treatment; one patient died at home of unknown causes 14 days after the first treatment cycle, and the second died at another hospital of aspiration pneumonia during a treatment delay due to grade 3 neutropenia.

Treatment interruption or dose reduction was required in 46 cycles (27.1%). Docetaxel dose reductions were required in 36 cycles (21.2%), because of hematological toxicities in 31 (86%) and poor tolerability in 5 cycles (14%). Irinotecan dose reductions were required in 41 cycles (24.1%), due to hematological toxicities in 28 (68%), diarrhea in seven cycles (17%), poor tolerability in five cycles (12%), and stomatitis in one cycle (2%).

The mean relative dose intensity for the first six treatment cycles at the high dose level was 0.87 (range 0.57–1.0) for docetaxel and 0.83 (range 0.56–1.0) for irinotecan. At the reduced dose level, the mean relative dose intensity for the first six treatment cycles was 0.97 (range 0.66–1.20) for docetaxel and 0.95 (range 0.75–1.0) for irinotecan (Fig. 2).

Discussion

The results presented here indicate that, in patients with recurrent or metastatic gastric cancer who failed fluoropyrimidine- or platinum-based chemotherapy, the combination of irinotecan and docetaxel every 3 weeks was active but intolerable at doses of 160 and 65 mg/m^2, respectively, and tolerable but not active at doses of 120 and 50 mg/m^2, respectively.

This 3 weekly regimen as recommended phase I trial [24] showed promising efficacy, with a tumor response rate

Table 3 Adverse events at each dose level (n = 48)

	High (n = 10)				Low (n = 38)			
	Grade (% of patients)				Grade (% of patients)			
	1	2	3	4	1	2	3	4
Hematological								
Anemia	40	40	20	0	45	45	10	0
Leukopenia	0	20	50	30	18	40	24	16
Neutropenia	0	10	10	80	8	16	32	39
Febrile neutropenia	–	–	30	20	–	–	8	3
Thrombocytopenia	40	0	0	0	39	5	3	0
Nonhematological								
Nausea	30	40	0	0	63	16	0	0
Vomiting	10	10	0	0	18	18	0	0
Stomatitis	40	10	0	0	16	32	0	0
Diarrhea	30	40	10	0	34	18	21	3
Asthenia	20	40	40	0	37	31	24	0
Neuropathy	50	10	0	0	58	5	0	0
Myalgia	10	20	10	0	13	13	13	0
Edema	10	0	0	0	5	5	0	0
Elevated transaminase	10	10	0	0	16	0	0	0

There were two deaths (4%), probably associated with treatment, at the lower dose level

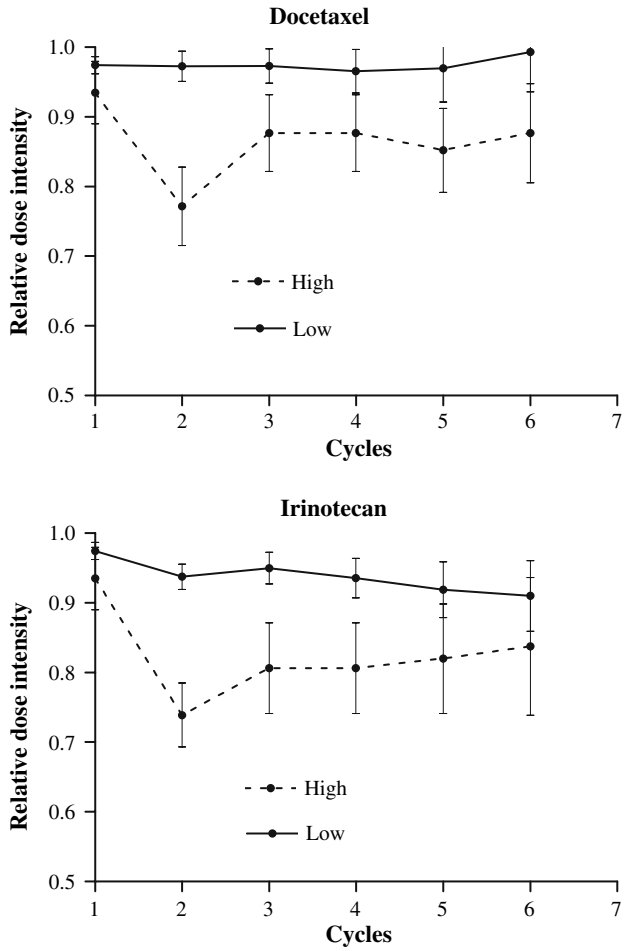

Fig. 2 Relative dose intensity of *docetaxel* and *irinotecan* at each dose level during the first six *cycles*

of 60%, a median TTP of 4.0 months, and a median overall survival of 9.5 months. However, we found that at this recommended doses, nine of ten patients experienced grade 3/4 neutropenia, five of ten required hospitalization for febrile neutropenia, and four of ten patients experienced grade 3 asthenia. This unacceptable degree of toxicity necessitated a dose reduction, which resulted in a decreased incidence and severity of toxicity. These toxicities, while tolerable, were not mild, with 71% of patients experiencing grade 3/4 neutropenia, 11% febrile neutropenia, and 24% grade 3 asthenia. In addition, of the remaining 39 patients, only four (10.3%) responded to this reduced dose regimen.

In the current study, we used the combination of irinotecan plus docetaxel administered once every 3 weeks, which was established by a phase I study that enrolled patients with incurable cancer had undergone at least one prior treatment using chemotherapy or radiotherapy. The dose-limiting toxicity consisting of prolonged grade 4 neutropenia occurred in three of the six patients at irinotecan doses of 200 mg/m^2 and docetaxel doses of 65 mg/m^2. Therefore, the recommend phase II dose was irinotecan 160 mg/m^2 and docetaxel 65 mg/m^2. No dose-limiting toxicities occurred at this dose [24]. However, in contrast to the data from the phase I study, several phase II studies using this regimen resulted in a high incidence of severe toxicity. A phase II study with irinotecan (130 mg/m^2) followed by docetaxel (50 mg/m^2) every 3 weeks as first-line treatment in patients with metastatic adenocarcinoma of the lower esophagus and gastric cardia resulted in grade 4 neutropenia and fever in eight patients (61.5%), necessitating dose reductions [25]. Another phase II study in esophageal cancer patients previously treated with cisplatin found that all patients treated with irinotecan 160 mg/m^2 plus doectaxel 65 mg/m^2 every 3 weeks required hospitalization due to febrile neutropenia, requiring amendment of this regimen [26]. Of interest, an additional phase I study recommended that patients be administered a higher dose regimen, consisting of docetaxel 75 mg/m^2 followed by irinotecan 250 mg/m^2 [27]. However a phase II study of these dosages as first-line treatment in patients with AGC resulted in a very high rates of grade 3/4 toxicities, including 85.4% for grade 4 neutropenia, 41.4% for febrile neutropenia/infection with neutropenia, and 42.9% for grade 3 diarrhea [28].

The reasons for these disparities between phase I and phase II studies are not evident. There have been no evidences suggesting ethnic differences in incidence of toxicities, indicating that these disparities are not due to ethnic differences in UDP-glucuronosyltransferase 1A1 genotype, which can predict severe toxicity of irinotecan [29]. Patient populations, however, may have differed in performance status, tumor type, and extent of prior therapy.

Owing to the high incidence of toxicities and treatment interruptions using this regimen, we decided to reduce both the agents by 25% which was the usual dose modification used in phase II trials. Although administration of lower doses decreased the rate of hematological toxicities, the response (10.3%) rates was not superior to those observed in single-agent docetaxel and irinotecan trials. In second-line settings in AGC patients, single-agent docetaxel has achieved overall response rates of 17–20% [17–19] and single-agent irinotecan has achieved overall response rates of 16–20% [21, 22]. Because there was no evidence of significant pharmacokinetic interactions between these two agents [24, 27], the reason for the absence of additive activities at low dose levels with still considerable toxicities, compared with each single agent alone as a second-line treatment, is unclear. These patients were neither elderly nor in a poor prognostic group.

In our study, no prophylactic G-CSF was allowed. Because myelosuppression is the major dose limiting toxicity of both of these agents, the use of prophylactic G-CSF may allow higher doses of both agents to be given in combination without risks of significant myelosuppression, especially neutropenia [30, 31]. To date, however, the role

of second-line treatment for AGC patients after initial treatment with a fluoropyrimidine- or platinum-based regimen remains largely undefined in terms of survival, quality of life, and cost-effectiveness. Therefore, in this setting, palliation of symptoms and improvement in the quality of life is one of the major roles of palliative chemotherapy. Although hematologic toxicity in the present study could, theoretically, be improved by growth factor support, the combination regimen of irinotecan and docetaxel administered every 3 weeks is not an appropriate second-line treatment for AGC patients, considering the high frequency of non-hematologic toxicity.

Another approach to improve tolerability of this combination may be weekly administration of both the agents. First-line treatment with docetaxel (30 mg/m^2) plus irinotecan (70 mg/m^2) on days 1 and 8 every 3 weeks of patients with AGC resulted in more favorable hematological toxicity profiles, with a 57.4% rate of grade 3/4 neutropenia, 23.4% of febrile neutropenia, and 19.1% of grade 3/4 diarrhea [32]. In general, however, the tolerability is better as first-line than as second-line treatment, making it difficult to compare weekly and every 3 weeks regimens. Therefore, further investigations are needed to obtain a precise estimate of the degree of toxicity of weekly administration of both the agents as second-line treatment for AGC patients.

In conclusion, we have shown that the combination regimen of irinotecan and docetaxel administered every 3 weeks is active but not feasible as second-line treatment for patients with AGC after failure of fluoropyrimidine- or platinum-based chemotherapy.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Shin HR, Jung KW, Won YJ, Park JG (2004) 2002 annual report of the Korea central cancer registry: based on registered data from 139 hospitals. Cancer Res Treat 36:103–114
3. Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoden PO (1994) Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 5:189–190
4. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M (1993) Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 72:37–41
5. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M (1995) Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:587–591
6. Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC, Kang YK, Shin DB, Kim HT, Kim HJ et al (1993) A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer 71:3813–3818
7. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S (2003) Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 21:54–59
8. Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, Joffe JK, Mackean M, Mansi J, Leahy M, Hill A, Oates J, Rao S, Nicolson M, Hickish T (1999) Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 80:269–272
9. Kim TW, Kang YK, Ahn JH, Chang HM, Yook JH, Oh ST, Kim BS, Lee JS (2002) Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced gastric cancer. Ann Oncol 13:1893–1898
10. Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsumura Y, Gotoh M (2003) Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 89:2207–2212
11. Sumpter K, Harper-Wynne C, Cunningham D, Rao S, Tebbutt N, Norman AR, Ward C, Iveson T, Nicolson M, Hickish T, Hill M, Oates J (2005) Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 92:1976–1983
12. Kang Y, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Salas MP, Suarez T, Santamaria J (2006) Randomized phase III trial of capecitiabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients with advanced gastric cancer (AGC): efficacy and safety results Proc Am Soc Clin Oncol 24:183S
13. Gueritte-Voegelein F, Guenard D, Lavelle F, Le Goff MT, Mangatal L, Potier P (1991) Relationships between the structure of taxol analogues and their antimitotic activity. J Med Chem 34:992–998
14. Ringel I, Horwitz SB (1991) Studies with RP 56976 (taxotere): a semisynthetic analogue of taxol. J Natl Cancer Inst 83:288–291
15. Sulkes A, Smyth J, Sessa C, Dirix LY, Vermorken JB, Kaye S, Wanders J, Franklin H, LeBail N, Verweij J (1994) Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC early clinical trials group. Br J Cancer 70:380–383
16. Einzig AI, Neuberg D, Remick SC, Karp DD, O'Dwyer PJ, Stewart JA, Benson AB 3rd (1996) Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: the eastern cooperative oncology group (ECOG) results of protocol E1293. Med Oncol 13:87–93
17. Vanhoefer U, Wilke H, Harstrick A, Achterrath W, Preusser P, Stahl M, Clemens M, Thiel E, Flasshove M, Fink U, Trenn G, Seeber S (1999) Phase II study of docetaxel as second line chemotherapy in metastatic gastric cancer. Proc Am Soc Clin Oncol 18:303
18. Giuliani F, Gebbia V, De Vita F, Maiello E, Di Bisceglie M, Catalano G, Gebbia N, Colucci G (2003) Docetaxel as salvage therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico Italia Meridionale (G.O.I.M.). Anticancer Res 23:4219–4222
19. Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, Kim BS, Kim M, Chun YJ, Lee JS, Kang YK (2008) A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. Cancer Chemother Pharmacol 61(4):631–637
20. Tanizawa A, Fujimori A, Fujimori Y, Pommier Y (1994) Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. J Natl Cancer Inst 86:836–842
21. Chun JH, Kim HK, Lee JS, Choi JY, Lee HG, Yoon SM, Choi IJ, Ryu KW, Kim YW, Bae JM (2004) Weekly irinotecan in patients

with metastatic gastric cancer failing cisplatin-based chemotherapy. Jpn J Clin Oncol 34:8–13
22. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, Yoshino M, Taguchi T, Ogawa N (1994) [Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group]. Gan To Kagaku Ryoho 21:1033–1038
23. Okishio K, Kudoh S, Hirata K (1995) Schedule dependent additive effect of docetaxel and irinotecan in vitro. Proc Jpn J Cancer Res 86:619
24. Adjei AA, Klein CE, Kastrissios H, Goldberg RM, Alberts SR, Pitot HC, Sloan JA, Reid JM, Hanson LJ, Atherton P, Rubin J, Erlichman C (2000) Phase I and pharmacokinetic study of irinotecan and docetaxel in patients with advanced solid tumors: preliminary evidence of clinical activity. J Clin Oncol 18:1116–1123
25. Jatoi A, Tirona MT, Cha SS, Alberts SR, Rowland KM, Morton RF, Nair S, Kardinal CG, Stella PJ, Mailliard JA, Sargen D, Goldberg RM (2002) A phase II trial of docetaxel and CPT-11 in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction, and gastric cardia. Int J Gastrointest Cancer 32:115–123
26. Lordick F, von Schilling C, Bernhard H, Hennig M, Bredenkamp R, Peschel C (2003) Phase II trial of irinotecan plus docetaxel in cisplatin-pretreated relapsed or refractory oesophageal cancer. Br J Cancer 89:630–633
27. Couteau C, Risse ML, Ducreux M, Lefresne-Soulas F, Riva A, Lebecq A, Ruffie P, Rougier P, Lokiec F, Bruno R, Armand JP (2000) Phase I and pharmacokinetic study of docetaxel and irinotecan in patients with advanced solid tumors. J Clin Oncol 18:3545–3552
28. Hawkins R, Cunningham D, Soerbye H, Adenis A, Canon J-L, Lopez-Vicanco G, Jacques C, Stenger P, Zuber E, Misset J-L (2003) Randomized phase II trial of docetaxel plus irinotecan versus docetaxel plus 5-fluorouracil (5FU) in patients with untreated advanced gastric adenocarcinoma (AGAC). Proc Am Soc Clin Oncol 22:257
29. Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ (2004) Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 22:1382–1388
30. Kurtz JE, Negrier S, Husseini F, Limacher JM, Borel C, Wagner JP, Prevot G, Bergerat JP, Dufour P (2003) A phase II study of docetaxel-irinotecan combination in advanced pancreatic cancer. Hepatogastroenterology 50:567–570
31. Polyzos A, Kosmas C, Toufexi H, Malamos N, Lagadas A, Kosmidis C, Ginopoulos P, Ziras N, Kandilis K, Georgoulias V (2005) Docetaxel in combination with irinotecan (CPT-11) in platinum-resistant paclitaxel-pretreated ovarian cancer. Anticancer Res 25:3559–3564
32. Park SR, Chun JH, Yu MS, Lee JH, Ryu KW, Choi IJ, Kim CG, Lee JS, Kim YW, Bae JM, Kim HK (2006) Phase II study of docetaxel and irinotecan combination chemotherapy in metastatic gastric carcinoma. Br J Cancer 94:1402–1406