Phase I/II study of irinotecan (CPT-11) and S-1 in the treatment of advanced gastric cancer

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A phase I/II study to determine the recommended dose for combination therapy with CPT-11 (irinotecan hydrochloride) and S-1 (tegafur, gimestat and otastat potassium) for advanced or recurrent gastric cancer, and to assess the safety and efficacy of this therapy. In the phase I portion of the study, S-1 was administered from day 1 to 14 at a fixed dose approved in Japan (80 mg/m^2/day), and CPT-11 was administered on days 1 and 8, with its dose being escalated to 100 from 80 mg/m^2. This regimen was repeated at 3-week intervals. The phase II portion of the study assessed the efficacy and safety of this regimen at the recommended dose determined in the phase I portion of the study. Seven patients were enrolled in the phase I portion of the study. The dose-limiting toxicity was the delay of administration owing to adverse reactions (leucopenia and diarrhea). The maximum tolerated dose of CPT-11 was 100 mg/m^2 and the recommended dose was determined to be 80 mg/m^2. In the phase II portion of the study, 10 patients with no prior chemotherapy regimen were enrolled. The median number of treatment cycles given was 4.5, the response rate was 20.0% (2/10) in all patients, the tumor control rate stable disease or better response was 60% (6/10) and the mean survival time was 311 days. Major adverse reactions included a decreased hemoglobin level, diarrhea, nausea and anorexia of grade 3 or worse (each occurred in 10% of the patients). Other adverse reactions were slight and well tolerated. The present combination therapy with CPT-11 and S-1 produced a low response rate but a high tumor control rate (stable disease or better response) and slight prolongation of survival time. This is a well-tolerated ambulatory regimen for advanced gastric cancer. *Anti-Cancer Drugs* 18:605–610 © 2007 Lippincott Williams & Wilkins.

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Introduction

In 2001, 49 958 patients died from gastric cancer in Japan, making gastric cancer the second deadliest cancer, surpassed only by lung cancer. Deaths from gastric cancer account for 16.6% of all cancer deaths. In a comparison of age-adjusted mortality rate from gastric cancer in 28 countries, Japan led all other nations for both men and women, indicating that the number of gastric cancer patients is greater in Japan than in any other country [1].

It has been reported that, among treatments for advanced or recurrent gastric cancer, chemotherapy significantly prolongs survival time compared with best supportive care [2–4], but chemotherapy that could be regarded as standard treatment has not been well established. In Japan, advanced or recurrent gastric cancer has been treated by chemotherapy mainly with 5-fluorouracil (5-FU). In 1992, the Japan Clinical Oncology Group conducted a study to compare monotherapy with 5-FU with 5-FU + cisplatin (CDDP) (FP) or UFT + mitomycin C (UFTM). Neither FP treatment nor UFTM treatment produced better therapeutic results than monotherapy with 5-FU [5]. This finding suggests limitations in exploring standard treatment mainly with 5-FU and thus the advent of a new antitumor agent is awaited.

Irinotecan hydrochloride (CPT-11) is an antitumor agent developed in Japan. Its mechanism of action involves the inhibition of topoisomerase I (Topo I) [6] and it has been reported to be effective against advanced gastrointestinal cancer [7]. The response rate to monotherapy with CPT-11 was 18.4% in eligible patients with advanced or recurrent gastric cancer. About half of the patients

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developed leucopenia, which was reversible. Clinical studies of combination therapy with CPT-11 and other chemotherapeutic agents are also promising [8]. The response rate after combination chemotherapy with CPT-11 and CDDP has been reported to be 42–59% [9–11], and the median survival time (MST) to be 365 days [11]. Combination therapy with CDDP, however, is highly toxic and is reported to involve a high incidence of adverse events [9–11]. Yano *et al.* [12] stated that CDDP should only be used by specialists who were familiar with treatment with antitumor agents.

S-1 (capsule containing tegafur, gimestat and otastat potassium) is an oral 5-FU derivative developed in Japan. It was designed to enhance the antitumor effect owing to an increase of blood 5-FU concentration, and to reduce gastrointestinal toxicity by combining tegafur (prodrug of 5-FU) with gimeracil and otastat potassium [13,14]. In addition, S-1 is a convenient oral agent. As the response rate to monotherapy with this drug is as high as 49–53.6% in patients with gastric cancer, it is now becoming the de-facto standard treatment for advanced or recurrent gastric cancer [15,16]. The effects and therapeutic results of chemotherapy based on 5-FU, including S-1, are related to thymidylate synthase (TS) expression [17]. Ichikawa *et al.* [18] showed that monotherapy with S-1 produced poor therapeutic effect in patients with high TS expression and that use of S-1 in combination with CPT-11 was effective for such patients with high TS expression. For this reason, clinical studies of combination therapy with CPT-11 and S-1 have been conducted in patients with advanced gastric cancer [19–22], but the dosage regimen has not been established.

Thus, we performed combination therapy with CPT-11 and S-1 (multi-center phase I/II study), in which CPT-11 was administered on days 1 and 8, whereas S-1 was administered from day 1 to 14, and a washout period of 1 week was provided (one course lasted 3 weeks).

Patients and methods

Eligibility criteria

Patients with unresectable advanced or recurrent gastric cancer were enrolled. The patients were required to satisfy the following eligibility criteria: histologically confirmed diagnosis of gastric cancer; age of 20–75 years; Eastern Cooperative Oncology Group performance status of 0–1; no prior chemotherapy regimen (among patients who had received adjuvant therapy with an oral 5-FU antitumor agent, those who had recurrence 6 months or more after the completion of this therapy were allowed to be enrolled); leukocyte count of 4000–12 000/μl and platelet count of $\geq$ 100 000/μl; total bilirubin level of $\leq$ 1.5 mg/dl, and aspartate aminotransferase and alanine aminotransferase levels of 100 IU/l; creatinine level of $\leq$ 1.2 mg/dl, and an estimated survival of at least 3 months. Before enrolment, all participants provided a written informed consent to participate in the study. Patients with any of the following conditions were excluded: severe coexisting medical illness (intestinal paresis or ileus, interstitial pneumonia, pulmonary fibrosis, poorly controlled diabetes mellitus), active multiple cancers and severe psychiatric disturbances. This study was conducted after being approved by the ethics committee of each participating institution.

Treatment schedule

In the phase I portion of the study, CPT-11 was initially given at a dose of 80 mg/m^2 over 90 min by intravenous infusion on days 1 and 8. The CPT-11 dose was then escalated in 20-mg/m^2 increments to confirm the safety of the treatment (Table 1). S-1 was administered orally according to the approved dosage regimen (80 mg/m^2/day) twice daily, i.e. after breakfast and after supper. This treatment was repeated every 3 weeks until disease progression, refusal by the patient or unacceptable adverse reactions.

Before chemotherapy, patients received antiemetics of 5-HT$_3$ receptor antagonist and steroids. Episodes of diarrhea were treated with loperamide hydrochloride as required.

The following dose adjustments were permitted. When grade 4 hematologic toxicity or grade 2 nonhematologic toxicity occurred, only the dose of CPT-11 was reduced to 60 mg/m^2 and the treatment was continued. When the serum creatinine level was 1.2–1.5 mg/dl, only the dose of S-1 was reduced by 20% and the treatment was continued.

Maximum tolerated dose and recommended dose

In the phase I portion of the study, dose-limiting toxicity during the first cycle of therapy was defined as any of the following: grade 4 hematologic toxicity, grade 3 nonhematologic toxicity (excluding nausea, anorexia, fatigue, loss of hair and vomiting), or when the second administration of CPT-11 or the start of the next course was postponed for 1 week or more. Three patients were assigned to each dose level. If any patient experienced dose-limiting toxicity, three more patients were assigned to receive the same dose. If three or more of the six patients experienced dose-limiting toxicity, the dose level was defined as the maximum-tolerated dose (MTD). The recommended dose of CPT-11 for the phase II study was defined as the dose one level lower than the MTD.

Evaluation

The tumor response was evaluated based on changes in the size of measurable lesions and assessment of evaluable lesions. Measurable lesions and evaluable lesions were defined and efficacy evaluated in accordance

with the Japanese criteria for evaluating the efficacy of chemotherapy and radiation therapy in the treatment of gastric cancer [23]. In brief, complete response was defined as the disappearance of all evidence of the tumor for at least 4 weeks. Partial response was defined as 50% or greater reduction in the sum of the products of the perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions or the progression of any existing lesions. Stable disease (SD) was defined as less than 50% reduction or less than 25% increase in the sum of the products of the perpendicular diameters of all lesions for at least 4 weeks without any evidence of new lesions or the progression of any existing lesions. Progressive disease was defined as a more than 25% increase of one or more lesions or the appearance of new lesions. Tumor measurements were performed every 4 weeks using computed tomography, plain chest radiographic films, upper gastrointestinal endoscopy and ultrasonography. Primary tumors were classified into the following three categories on the basis of radiographic and endoscopic findings: measurable, not measurable but evaluable and diffuse infiltration.

National Cancer Institute Common Toxicity Criteria version 2.0 (Nishiogu, Arakawa-ku, Tokyo, Japan) was applied to evaluate adverse events. An independent review committee reviewed the eligibility and suitability for assessment of the participants and response to treatment.

Results

Phase I study

Patient characteristics

A total of seven patients (six men, one woman) were enrolled in the phase I study between April 2003 and November 2003. The clinical characteristics of the patients are shown in Table 2. The median age was 62 years (range, 27–74). The performance status was 0 in 16 patients. Histologically, one patient had tubular adenocarcinoma, two patients had poorly differentiated adenocarcinoma and four had signet-ring cell carcinoma. Safety was evaluable in all seven patients. Three patients were initially assigned to receive dose level 1, and four patients were assigned to receive dose level 2. Dose-limiting toxicity occurred at dose level 2 and patients were added to this dose cohort. Table 1 summarizes the number of patients in each dose cohort.

Table 1 Dose-escalation schedule[a] and number of patients in phase I study

Dose level	Dose (mg/m^2)		No. of patients
	CPT-11	S-1	
1	80	80	3
2	100	80	4

[a]CPT-11 on days 1 and 8; S-1 on days 1–14.

Table 2 Clinical characteristics of patients in phase I and phase II studies

	Phase I ($n=7$)		Phase II ($n=10$)[a]	
Characteristic	No.	%	No.	%
Age (years)				
Median	62		63	
Range	(27–74)		(27–71)	
Sex				
Men	6	85.7	10	100.0
Women	1	14.3	0	–
Performance status (ECOG)[b]				
0	7	100.0	10	100.0
Histology				
Papillary adenocarcinoma	0	–	1	10.0
Tubular adenocarcinoma	1	14.3	4	40.0
Poorly differentiated adenocarcinoma	2	28.6	4	40.0
Signet-ring cell carcinoma	4	57.1	1	10.0
Site of metastasis				
Liver	1	22.2	4	40.0
Lymph nodes	6	38.9	8	80.0

[a]Included three cases of recommended dose in phase I.
[b]ECOG, Eastern Cooperative Oncology Group.

Dose-limiting toxicity and recommended dose for phase II study

Three of four patients in dose level 2 (CPT-11 100 mg/m^2 on days 1 and 8 + S-1 80 mg/m^2 on day 1–14) experienced dose-limiting toxicity. One patient was not able to receive the second dose of CPT-11 by day 15 because of grade 1 diarrhea. Another patient was not able to start the next course by day 29 because of grade 3 leucopenia, diarrhea and stomatitis. Still another patient was not able to receive the second dose of CPT-11 by day 15 because of grade 2 diarrhea and leucopenia (Table 3). Thus, 100 mg/m^2 was the maximum-tolerated CPT-11 dose, and a combination of CPT-11 80 mg/m^2 given on days 1 and 8 and S-1 80 mg/m^2 on days 1–14, in a 21-day cycle, was recommended for use in the phase II study.

Phase II study

Patient characteristics

Ten patients were enrolled in the phase II study between December 2003 and April 2005. Clinical characteristics of the patients are shown in Table 2. All patients met the entry criteria and were included in the analysis. The patients consisted of 10 men. All patients had not received prior chemotherapy. The median age of the patients was 63 years (range, 27–71). Histologically, one patient had papillary adenocarcinoma, four patients had tubular adenocarcinoma, four patients had poorly differentiated adenocarcinoma and one had signet-ring cell carcinoma. Performance status was 0 in 10 patients.

Tumor response and survival

Among the 10 patients with evaluable lesions, two (20.0%) exhibited a partial response. The tumor response rate (SD or better response) was 60% (6/10). The response rate according to site was 20.0% (1/8) at primary sites, 25.0% (2/8) for abdominal lymph node metastases

(Table 4). The median survival was 311 days in the 10 patients (Fig. 1). The median number of treatment cycles given was 4.5 (range, 1.5–12). The median of the total CPT-11 dose was 720 mg/m^2 (range, 240–1920).

Patients were taken off the study because of worsening of the primary disease (four patients), refusal by the patient (one patient), personal reason of the patient (one patient), unacceptable adverse reactions (one patient), completion of treatment (one patient) and continuation of treatment (two patients).

Safety

Hematologic toxicities of grade 3 or higher observed were decreased hemoglobin level in 10.0%. No other hematologic toxicities of grade 3 or higher were observed (Table 5). The nonhematologic toxicities of grade 3 or higher were diarrhea (10.0%), nausea (10.0%), vomiting (10.0%), anorexia (10.0%) and constipation (10.0%). No treatment-related deaths were observed.

Table 3 Toxicity (phase I study; $n=7$)

First course							
Toxicity	Dose level	No. of patients	Grade				Incidence of grade 3/4 (%)
			1	2	3	4	
Leukopenia	1	3	0	1	0	0	0
	2	4	1	1[c]	1[b]	0	25.0
Neutropenia	1	3	0	1	0	0	0
	2	4	1	2	0	0	0
Thrombocytopenia	1	3	0	0	0	0	0
	2	4	0	0	0	0	0
Decreased hemoglobin	1	3	1	0	0	0	0
	2	4	2	1	0	0	0
Diarrhea	1	3	0	1[c]	0	0	0
	2	4	2[a]	1	1[b]	0	25.0
Nausea	1	3	0	1	0	0	0
	2	4	2	0	2	0	50.0
Vomiting	1	3	0	1	0	0	0
	2	4	1	0	0	0	0
Anorexia	1	3	1	1	0	0	0
	2	4	2	0	2	0	50.0
Fatigue	1	3	0	0	0	0	0
	2	4	0	0	0	0	0
Stomatitis	1	3	0	0	0	0	0
	2	4	0	0	1[b]	0	25.0
Loss of hair	1	3	0	0	–	–	0
	2	4	0	0	–	–	0

[a]By diarrhea of grade 1, not able to do the second CPT-11 dosage by day 15.
[b]By Leukopenia decrease of grade 3, stomatitis and diarrhea of grade 3, not able to start the next course by day 29.
[c]By Leukopenia decrease of grade 2 and diarrhea of grade 2 not able to do the second CPT-11 dosage by day 15.

Dose intensity

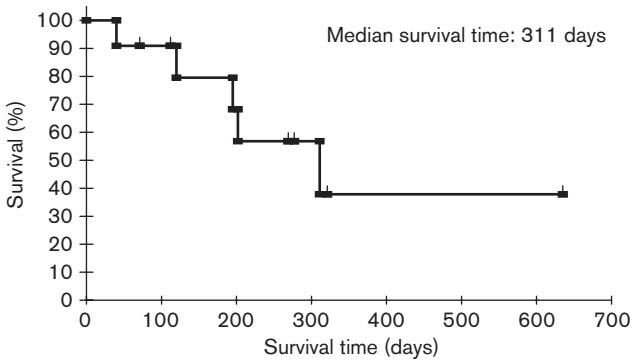
The actual administered dose in the first two courses was 52 mg/m^2/week for CPT-11 and 364 mg/m^2/week for S-1, which correspond to 97.6 and 97.5% of the planned doses. The drug administration was postponed or skipped in three patients on day 15 in the first cycle. Three patients delayed the start of the next cycle.

Discussion

In Japan, various regimens of 5-FU-based combination chemotherapy have been performed for the treatment of unresectable or recurrent gastric cancer. No regimen of chemotherapy exists that surpasses one with 5-FU and which could be called the standard treatment [5]. Therefore, expectations are placed on a new antitumor agent.

CPT-11 is an antitumor agent developed in Japan. Its mechanism of action involves inhibition of Topo I. It was found to be effective against advanced gastrointestinal

Fig. 1



Survival curve derived by Kaplan–Meier analysis.

Table 4 Response (phase II study)[a]

	No. of patients	CR		PR		SD		PD		NE	
		No.	%	No.	%	No.	%	No.	%	No.	%
Overall	10	0	0.0	2	20.0	4	40.0	4	40.0	0	0.0
Primary	8	0	0.0	1	12.5	7	87.5	0	0.0	0	0.0
Liver	4	0	0.0	0	0.0	2	50.0	2	50.0	0	0.0
Lymph nodes	8	0	0.0	2	25.0	4	50.0	2	25.0	0	0.0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.
[a]Included three cases of recommended dose in phase I.

Table 5 Toxicity (phase II study; $n=10$)[a]

Toxicity	Grade				Incidence of grade 3/4 (%)
	1	2	3	4	
Leukopenia	2	6	0	0	0
Neutropenia	3	3	0	0	0
Thrombocytopenia	0	0	0	0	0
Decreased hemoglobin	3	3	1	0	10.0
Diarrhea	3	0	1	0	10.0
Nausea	1	0	1	0	10.0
Vomiting	1	1	0	0	0.0
Anorexia	3	0	1	0	10.0
Fatigue	4	0	0	0	0.0
Stomatitis	1	0	0	0	0.0
Loss of hair	1	1	–	–	–
Constipation diarrhea	0	0	1	0	10.0
Pulmonary fibrosis	1	0	0	0	0.0

[a]Included three cases of recommended dose in phase I.

cancer in a clinical study. The recommended dosage regimen for this drug is 100 mg/m^2 given weekly or 150 mg/m^2 given biweekly [6,7]. The adverse events associated with this drug included leucopenia (42.1%) and diarrhea (22.4%), all of which were reversible. Therefore, expectations were placed on its use in combination with other chemotherapeutic agents [8]. Above all, it was reported that combination therapy with CPT-11 and CDDP produced high response rates of 42–59% and an MST of 365 days, which suggested the possibility of prolongation of survival time [11]. A problem of a high incidence of adverse events, however, remains, e.g. grade 3 or worse leucopenia was observed in 45% of patients, grade 4 neutropenia was observed in 37% of patients and grade 3 or worse diarrhea was observed in 20% of patients.

On the other hand, S-1, an oral 5-FU derivative developed in Japan, was designed to enhance the antitumor effect owing to an increase of blood 5-FU concentration and to reduce gastrointestinal toxicity. The response rate to monotherapy with S-1 was reported to be as high as 49–53.6% in patients with stomach cancer [15,16]. In addition, this therapy provides an MST of 8–10 months with low toxicity. Therefore, it is becoming a de-facto standard treatment for advanced recurrent gastric cancer. It was reported that neither the response rate nor the survival rate with administration of S-1 was influenced by the level of expression of TS or dihydropyrimidine dehydrogenase in patients with stomach cancer [24], whereas it was also reported that the effect of S-1 was related to the expression of TS in patients with stomach cancer because this drug is a 5-FU derivative [17]. Ichikawa *et al.* [18] also reported that S-1 produced significantly poorer therapeutic results in patients with high TS expression than in those with low TS expression and that there was no relation between expression of TS and the survival rate in a group that received combination therapy with S-1 and CPT-11. Beberjee *et al.* [25] reported that when the E2F-1 gene, the transcription factor, was introduced into 5-FU-sensitive cancer cells, the TS gene was expressed at a high level and developed 5-FU-resistance, whereas, it increased sensitivity to CPT-11. It was also reported that there was a positive correlation between TS expression and Topo I expression [26]. Considering the fact that the target enzyme of CPT-11 is Topo I, this report suggests the efficacy of combination therapy with CPT-11 in patients with high TS expression. It was also reported that CPT-11 reduced TS gene expression levels even in 5-FU-resistant cell lines [27]. As the effect of CPT-11 is specific to the S phase of the cell cycle, a report stating that combination of 5-FU and CPT-11 terminates the cell cycle in the S phase raises great expectations for combination therapy with CPT-11 and S-1 for advanced gastric cancer [28].

The major regimens of combination therapy with CPT-11 and S-1 that have been reported at present involve a combination of weekly or biweekly administration of CPT-11 and 2 weeks (days 1 to 14) or 3 weeks (days 1 to 21) of administration of S-1 [19–22]. In our study, one course of treatment lasted 21 days, during which CPT-11 was administered on days 1 and 8, and S-1 was administered for 2 weeks (days 1–14). This regimen is characterized by a dose intensity of S-1 equivalent to that approved for use in monotherapy with S-1 in Japan (28 consecutive days of oral administration and 14 days of drug withdrawal) and the additional effect of CPT-11. With regard to the dose of CPT-11 employed in this study, there was no dose-limiting toxicity at level 1 (80 mg/m^2 of CPT-11), whereas three of the four patients developed dose-limiting toxicity at level 2 (100 mg/m^2 of CPT-11). The dose-limiting toxicity included delayed administration owing to adverse reactions (leucopenia, diarrhea, etc.). Therefore, the MTD was found to be 100 mg/m^2 and the recommended dose was determined to be 80 mg/m^2 (level 1). These doses seem to be similar to those reported in studies of other regimens of combination therapy with CPT-11 and S-1 [19–22]. At present, chemotherapy is basically performed on an outpatient basis. During this study, grade 3 nausea, anorexia and diarrhea were observed, whereas there were no grade 4 adverse events. Therefore, the regimen employed in this study seems to be safe to prescribe to outpatients. Review of other reports for efficacy revealed that the response rate was 50% or more in both reports and that the MST was 423 or 581 days [20,21]. In this study, the response rate was 20%, which is not satisfactory. The tumor control rate (SD or better response), however, was 60% (6/10) and the MST was more than 10 months. These results are quite good. They also seem to present a standard of safety because this regimen can be prescribed on an outpatient basis, involves few adverse events, and thus can be continued.

A phase III controlled study of combination therapy with CPT-11 and S-1 should be conducted to objectively assess this therapy based on this study and other study results.

References

1 'Cancer Statistics in Japan' Editorial Board. *Cancer Statistics in Japan 2003*. Tokyo: Foundation for Promotion of Cancer Research; 2003.

2 Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72**:37–41.

3 Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoden PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994; **5**:189–190.

4 Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. 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* 1995; **71**:587–591.

5 Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, *et al.* 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* 2003; **21**:54–59.

6 Kawano Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Res* 1991; **51**:4187–4191.

7 Research Group of CPT-11 in Gynecologic Cancers. An early phase II trial of CPT-11 in patients with advanced gastrointestinal cancer. *J Jpn Soc Cancer Ther* 1992; **27**:2028–2035.

8 Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, *et al.* [Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-C11 Gastrointestinal Cancer Study Group]. *Gan To Kagaku Ryoho* 1994; **21**:1033–1038.

9 Shirao K, Shimada Y, Kondo H, Saito D, Yamao T, Ono H, *et al.* Phase I-II study of irinotecan hydrochloride combined with cisplatin in patients with advanced gastric cancer. *J Clin Oncol* 1997; **15**:921–927.

10 Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, *et al.* Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. *J Clin Oncol.* 1999; **17**:319–323.

11 Yoshida M, Boku N, Ohtsu A, Muto M, Nagashima F, Yoshida S. Combination chemotherapy of irinotecan plus cisplatin for advanced gastric cancer: efficacy and feasibility in clinical practice. *Gastric Cancer* 2001; **4**:144–149.

12 Yano T, Ohtsu A. Evaluation of newly developed agents for gastric cancer. *Jpn J Cancer Clin* 2003; **49**:583–588.

13 Fukushima T, Satake H, Uchida J, Shimamoto Y, Kato T, Takechi T, *et al.* Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluorouracil on human tumor xenografts. *Int J Oncol* 1998; **13**:693–698.

14 Shirasaka T, Nakano K, Takechi T, Satake H, Uchida J, Fujioka A, *et al.* Antitumor activity of 1 mol/l tegafur–0.4 mol/l 5-chloro-2,4-dihydroxypyridine-1 mol/l potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* 1996; **56**:2602–2606.

15 Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y, *et al.* An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. The S-1 Gastrointestinal Cancer Study Group. *Oncology* 1999; **57**:202–210.

16 Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 mol/l tegafur–0.4 mol/l gimestat–1 mol/l otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34**:1715–1720.

17 Lenz HJ, Leichman CG, Danenberg KD, Danenberg PV, Groshen S, Cohen H, *et al.* Thymidylate synthase mRNA level in adenocarcinoma of the stomach: a predictor for primary tumor response and overall survival. *J Clin Oncol* 1996; **14**:176–182.

18 Ichikawa W, Takahashi T, Suto K, Yamashita T, Nihei Z, Shirota Y, *et al.* Thymidylate synthase predictive power is overcome by irinotecan combination therapy with S-1 for gastric cancer. *Br J Cancer* 2004; **91**:1245–1250.

19 Takiuchi H, Narahara H, Tsujinaka T, Gotoh M, Kawabe S, Katsu K, *et al.* Phase I study of S-1 combined with irinotecan (CPT-11) in patients with advanced gastric cancer (OGSG 0002). *Jpn J Clin Oncol* 2005; **35**: 520–525.

20 Fujitani K, Takiuchi H, Narahara H. A phase I /II study of CPT-11 plus S1 in patients with advanced gastric cancer. *Jpn J Cancer Clin* 2003; **49**: 605–609.

21 Komatsu Y. A phase I and PK study of S-1 and irinotecan (CPT-11) in patients with advanced gastric cancer (AGC). *Proc Am Soc Clin Oncol* 2002; **21**:[Abstract 683].

22 Yamada Y, Yasui H, Goto A, Arai T, Ura T, Hamaguchi T, *et al.* Phase I study of irinotecan and S-1 combination therapy in patients with metastatic gastric cancer. *Int J Clin Oncol* 2003; **8**:374–380.

23 Japanese Research Society for Gastric Cancer. *Japanese classification of gastric carcinoma*. 1st English ed. Tokyo: Kanehara; 1995.

24 Miyamoto S, Boku N, Ohtsu A, Yoshida S, Ochiai A, Okabe H, *et al.* Clinical implications of immunoreactivity of thymidylate synthase and dihydropyrimidine dehydrogenase in gastric cancer treated with oral fluoropyrimidine (S-1). Study Group of S-1 for Gastric Cancer. *Int J Clin Oncol* 2000; **17**:653–658.

25 Baneree D, Schnieders B, Fu JZ, Adhikari D, Zhao SC, Bertino JR. Role of E2F-1 in chemosensitivity. *Cancer Res* 1998; **58**:4292–4296.

26 Ichikawa W. Topoisomerase I (Topo-I) expression correlates to thymidylate synthase (TS) expression in colorectal cancer (CRC). *Proc Am Soc Clin Oncol* 1999; [Abstract 946].

27 Que BG, Ardalan B, Richman S. Comptosar (CPT-11) reduced the thymidylate synthase gene expression in 5FU-resistant cell line. *Proc Am Assoc Cancer Res* 2002; **41**:[Abstract 4763].

28 Guichard S, Hennebelle I, Bugat R, Canal P. Cellular interactions of 5-fluorouracil and the camptothecin analogue CPT-11 (irinotecan) in a human colorectal carcinoma cell line. *Biochem Pharmacol* 1998; **55**: 667–676.