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ORIGINAL ARTICLE

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Phase I study of irinotecan and S-1 combination therapy in patients with metastatic gastric cancer

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Abstract
Background. Irinotecan plus intravenous 5-fluorouracil with leucovorin is effective against gastrointestinal cancer. S-1 is an oral fluoropyrimidine derivative combining tegafur with the modulators 5-chloro-2,4-dihydroxypyrimidine (a potent dihydropyrimidine dehydrogenase inhibitor), and potassium oxonate (an orotate phosphoribosyl transferase inhibitor), in a molar ratio of 1:0.4:1. S-1 has a high response rate, of about 40%, in advanced gastric cancer. A phase I study was conducted to assess the maximum tolerated dose and the recommended dose of the combination of irinotecan and S-1.
Methods. Irinotecan was given intravenously over the course of 90 min on day 1 and S-1 was given orally from days 1 to 14 of a 21-day cycle. The dose of S-1 was 80 mg/m^2 per day, given in two divided doses. The dose of irinotecan was escalated in a stepwise fashion from 100 mg/m^2 (level 1; $n = 3$), to 125 mg/m^2 (level 2; $n = 3$), and 150 mg/m^2 (level 3; $n = 6$).
Results. Dose-limiting toxicity did not occur during cycle 1, and the recommended dose for phase II studies was determined to be level 3, which was associated with grade 3 diarrhea in one patient, and with refusal to continue treatment because of prolonged fatigue in two patients. Grade 3 neutropenia developed in one of three patients at level 1 and level 2, and in two of six during cycle 1 of level 3. The recommended dose was determined to be 150 mg/m^2 of irinotecan on day 1 and 80 mg/m^2 per day of S-1 on days 1 to 14 of a 21-day cycle. Five of seven patients with measurable lesions had a partial response.
Conclusion. A combination of irinotecan and S-1 can be recommended for further phase II studies in patients with gastric cancer.

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Introduction

The 2-year survival rate of patients with metastatic gastric cancer is only 10%,[1] despite anticancer therapy. Monotherapy with 5-fluorouracil (5-FU), the mainstay of treatment for advanced gastric cancer for four decades, has a response rate of only 11% and a median survival time (MST) of 7.1 months.[1] In a recent randomized phase III trial conducted by the European Organization for Research and Treatment of Cancer, MSTs were approximately 7 months in patients with advanced gastric cancer who received a combination of etoposide, leucovorin, and bolus 5-FU; infusional 5-FU plus cisplatin; or a combination of 5-FU, doxorubicin, and methotrexate.[2] New anticancer agents are therefore needed to improve outcome in patients with metastatic gastric cancer.

S-1 is an oral fluoropyrimidine derivative that combines tegafur with two modulators of 5-FU metabolism, 5-chloro-2,4-dihydroxy pyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate, in a molar ratio of 1:0.4:1.[3] Tegafur, an oral prodrug of 5-FU, is gradually converted to 5-FU and rapidly catabolized by DPD in the liver. Potassium oxonate is an orotate phosphoribosyl transferase inhibitor and preferentially localizes in the digestive tract. This component of S-1 decreases the incorporation of 5-fluorouridine triphosphate into RNA in the gastrointestinal mucosa and reduces the incidence and severity of diarrhea. On the basis of the results of phase I and early phase II trials of S-1, 40 mg/m^2 twice daily was recommended for late phase II studies. The overall incidence of neutropenia associated with S-1 was 35% to 48%, and only 2% to 6% of patients had grade 3 or 4 neutropenia. Diarrhea occurred in 8% to 12% of patients, but the incidence of grade 3 diarrhea was only 2%.[4–7] In phase II trials of S-1, the response rate in patients with gastric cancer was 44% to 49%, with a good safety profile.

Irinotecan is a potent inhibitor of topoisomerase I. Preclinical studies of human cancer cell lines and tumor xenografts have suggested that the combination of irinotecan and 5-FU has additive-to-synergistic antitumor activity.[8,9] The response rate with irinotecan alone in patients with advanced gastric cancer was 23.3% (14/60).[10]

The primary objectives of this phase I study were to estimate the maximal tolerated dose (MTD) of irinotecan in combination with S-1 and to determine the recommended dose for phase II studies. We also evaluated the toxicity of this regimen, studied the pharmacokinetics of 5-FU, tegafur, irinotecan, and its metabolites SN-38 and SN-38 glucuronide (SN-38G), and assessed antitumor activity.

Patients and methods

Anticancer drugs

S-1 was available for clinical use as capsules. Each capsule contained 20 or 25 mg of tegafur (Taiho Pharmaceutical, Tokyo, Japan). Irinotecan was obtained from Daiichi Pharmaceutical (Tokyo, Japan).

Patient eligibility

Patients with histologically confirmed gastric cancer who had advanced or metastatic disease were eligible for the study. There was no restriction on prior chemotherapy or radiotherapy, other than a 4-week interval between the completion of such therapy and study entry. To be eligible, patients had to be between 20 and 75 years of age, with an Eastern Cooperative Group (ECOG) performance status of 0–2, and to have adequate baseline bone marrow (white blood cell [WBC] count, more than 3000/μl; hemoglobin, more than 8 g/dl; and platelets, more than 100000/μl); adequate hepatic function (serum bilirubin level, 1.5 mg/dl or less, and serum aspartate aminotransferase and alanine aminotransferase, 100 U/l or less); adequate renal function (blood urea nitrogen level, 25 mg/dl or less, and serum creatinine level, 1.5 mg/dl or less); and adequate respiratory function (arterial partial pressure of oxygen 60 mmHg or more); and a life expectancy of at least 8 weeks.

Patients were excluded if they had symptomatic brain metastasis, had previously received pelvic irradiation, had previously received chemotherapy with S-1 or irinotecan, had pre-existing diarrhea, or had a high risk of a poor outcome because of concomitant nonmalignant disease (cardiac, pulmonary, renal, or hepatic disease, or uncontrolled infection). This study was approved by the institutional review boards of the National Cancer Center hospital. All patients gave their written informed consent before entry.

Before enrollment, all patients underwent a physical examination (including documentation of measurable disease), a complete blood cell count with differential count, serum chemical analysis, chest radiography, electrocardiography, and computed tomographic (CT) scanning or magnetic resonance imaging (MRI).

Treatment plan

Patients received S-1 at a fixed dose of 80 mg/m^2 per day, in two divided doses, for 14 consecutive days of a 21-day cycle. S-1 was administered orally within an hour after breakfast and supper, at 9 a.m. and 9 p.m., at a dose of 40 mg for a body surface area (BSA) of less than 1.25 m^2, 50 mg for a BSA of 1.25 m^2 to 1.5 m^2, and 60 mg for a BSA of more than 1.5 m^2. Irinotecan was diluted in 250 ml of 5% glucose solution and given as a 90-min intravenous infusion, starting 30 min after the treatment with oral S-1, on day 1. All patients received premedication with a 5-hydroxytryptamine-3-receptor antagonist, or dexamethasone, or both, given as a 30-min drip infusion starting at 9 a.m. Treatment cycles were repeated every 3 weeks. Subsequent cycles of treatment were withheld until the WBC count and platelet count were greater than 3000/μl and 100000/μl, respectively. Treatment was repeated until the onset of disease progression or severe toxicity.

The dose was modified for each patient according to a nomogram, based on hematologic or nonhematologic toxicity. If the nadir of the WBC count was less than 500/μl or that of the platelet count was less than 10000/μl, the subsequent dose of irinotecan was reduced to 125 mg/m^2. If the WBC count on day 22 was less than 3000/μl or the platelet count was less than 100000/μl, further treatment was delayed for up to 1 week until recovery. Recombinant granulocyte colony-stimulating factor was injected subcutaneously if patients had a WBC count of less than 1000/μl or a neutrophil count of less than 500/μl for more than 5 days, or neutropenic fever, but this agent was not used routinely.

Dose-escalation schedule

Irinotecan was studied at dose levels of 100, 125, and 150 mg/m^2. If 150 mg/m^2 of irinotecan was tolerated, this dose became the recommended dose for treatment with S-1, because the maximum approved dose of irinotecan alone in Japan is 150 mg/m^2.

A minimum of three patients per group were studied per dose level. Dose-limiting toxicity (DLT) was defined as any of the following findings during cycle 1: (1) neutrophil count less than 500/mm^3 for 5 days or more, or febrile neutropenia; (2) platelet count less than 10000/mm^3, or less than 50000/mm^3 with a bleeding tendency; (3) grade 3 or 4 nonhematologic toxicity, excluding nausea, vomiting, and anorexia, according to the National Cancer Institute Common toxicity criteria (NCI-CTC); or (4) a greater than 1-week delay in treatment as a result of drug-related toxicity. If DLT occurred in one of the first three patients assigned to a given dose level, an additional three patients were assigned to receive that dose level. The MTD and recommended dose for phase II studies was defined as the dose that induced DLT during the first cycle in at least 50% of the subjects. Once the recommended dose was determined, six patients were enrolled to confirm tolerability. If a patient had DLT, the dose of irinotecan was decreased by one dose level.

Response and toxicity criteria

The response of measurable and assessable disease sites was assessed according to RECIST (*New guidelines to evaluate the response to treatment in solid tumors*[11]). Tumor measurement was assessed by CT scan or MRI after every treatment cycle. Partial response (PR) was defined as more than a 30% decrease in the sum of the products of the greatest perpendicular diameters of measurable lesions, without the development of any new lesions. Stable disease was defined as a steady state of response less than a PR or as progression of less than 20% over the course of at least 4 weeks. Progressive disease (PD) was defined as an unequivocal increase of at least 20% in the sum of the products of the greatest perpendicular diameters of individual lesions. The appearance of clinically significant new lesions also constituted PD. Toxicity was assessed according to the NCI-CTC, version 2.0.[12] During the study, all patients were evaluated on a weekly basis for signs and symptoms of toxicity. Complete blood cell counts, including differential count; liver function tests; measurement of urea nitrogen, creatinine, and electrolyte levels; and urinalysis were performed weekly in cycle 1 and every 3 weeks in subsequent cycles.

Pharmacokinetic study

During treatment with S-1, blood samples (BS) were collected on day 1 before the first dose of the day (BS1) and at 1 h (BS2), 2 h (BS3), 3 h (BS4), 4 h (BS5), 6 h (BS6), 10 h (BS7), 12 h (BS8), and 24 h (BS9). On day 8, blood samples were obtained at 0, 2, 4, and 10 h. With respect to irinotecan, blood samples obtained on day 1 corresponded to before the start of infusion (BS1), 30 min after the start of infusion (BS2), the end of infusion (BS3), and 1 h (BS4), 2 h (BS5), 4 h (BS6), 8 h (BS7), 10 h (BS8), and 22 h (BS9) after the end of infusion. Peripheral blood samples (6 ml) were collected into heparinized tubes and centrifuged at 1000 *g* for 15 min at 4°C. The plasma was stored at −20°C until analysis.

Levels of tegafur and 5-FU in plasma were analyzed as described by Matsushima et al.,[13] with minor modification. Tegafur was extracted with dichloromethane and analyzed by high-performance liquid chromatography (HPLC), with the use of an ultraviolet absorption spectrometer. 5-FU was extracted with ethyl acetate after washing with dichloromethane and was subjected to a reaction to induce trimethylsilyl derivatives. 5-FU was analyzed by electron impact ionization gas chromatography/mass spectrometry (GC-MS), using stable isotopes as internal references. For 5-FU, measurable plasma levels ranged from 1 to 400 ng/ml. Plasma concentrations of irinotecan, SN-38, and SN-38G were simultaneously measured by HPLC. Measurable ranges were 5 to 25 000 ng/ml for irinotecan, 5 to 2500 ng/ml for SN-38, and 2.5 to 500 ng/ml for SN-38G.

Maximum plasma concentration (Cmax) was determined from the highest observed concentration after treatment with oral S-1. The area under the time-concentration curve (AUC) from 0 to 10 h was calculated according to the trapezoidal rule, using a WinNonlin program (Ver. 3.1, Pharsight, Mountain View, CA, USA). Irinotecan, SN-38, and SN-38G plasma concentration data were analyzed by noncompartmental methods. Cmax and the time that Cmax occurred were determined by inspection of individual patients' irinotecan, SN-38, and SN-38G concentration-time curves. The AUC from 0 to 24 h after beginning the infusion of irinotecan was calculated by the linear trapezoidal rule. Clearance was calculated by dividing the total administered dose of irinotecan by the AUC.

Results

Patient characteristics

Twelve patients were enrolled. All patients received at least one cycle of study treatment. The patients' characteristics are summarized in Table 1. Four patients had previously received 5-FU-based chemotherapy to treat metastasis. One patient had received prior adjuvant chemotherapy with UFT. A total of 55 cycles of chemotherapy were administered, with a median of 5 cycles (range, 2 to 14) per patient at the recommended dose.

Dose-limiting toxicity and recommended dose

No DLT occurred in any patient during cycle 1. Dose-limiting diarrhea occurred in one of six patients treated with irinotecan 150 mg/m^2 during cycle 3. Two of six patients refused to continue therapy at level 3 after cycle 5 because of prolonged fatigue. Level 3 did not meet the criteria for MTD, and was deemed to be the recommended dose for a phase II trial.

Treatment was delayed for 1 week at least in 5 of the 12 patients. The reasons for treatment delay were fatigue in 7 patients, stomatitis in 3, anorexia in 2, and rash in 1. The median number of administered cycles was 5 (range, 2 to 14), and the total number of cycles during which patients received 150 mg/m^2 of irinotecan was 55. The relative dose intensity at level 3 was 91% for irinotecan and 92% for S-1.

Table 1. Patient characteristics

No. of patients		12
Male/female		9/3
Performance status (ECOG) 0/1		9/3
Age, years	Median	58
	Range	31–69
Metastatic sites		
Abdominal lymph nodes		7
Liver		4
Peritoneum		3
Lung		3
Previous therapy		
Gastrectomy		9
Chemotherapy		5
5-FU		
5-FU/cisplatin		1
Uracil/tegafur		1

ECOG, Eastern Cooperative Group; 5-FU, 5-fluorouracil

Table 2. Toxicity during first cycle

	Irinotecan dose level					
	1 (100 mg/m^2; $n = 3$)		2 (125 mg/m^2; $n = 3$)		3 (150 mg/m^2; $n = 6$)	
	G 1 or 2	G 3/4	G 1 or 2	G 3/4	G 1 or 2	G 3/4
Neutropenia	2	1/0	1	1/0	6	1/0
Leukopenia	1	0/0	1	0/0	6	0/0
Diarrhea	1	0/0	1	0/0	2	0/0
Fatigue	2	0/0	1	0/0	5	0/0
Anorexia	3	0/0	3	0/0	4	0/0
Nausea	0	0/0	1	0/0	4	0/0
Stomatitis	1	0/0	0	0/0	2	0/0
Rash	0	0/0	1	0/0	0	0/0
Infection without neutropenia	0	0/0	1	0/0	0	0/0

G, grade

Table 3. Nonhematologic toxicity during all cycles

	Irinotecan dose level					
	1 (100 mg/m^2; $n = 8$)		2 (125 mg/m^2; $n = 8$)		3 (150 mg/m^2; $n = 39$)	
	G 1 or 2	G 3/4	G 1 or 2	G 3/4	G 1 or 2	G 3/4
Diarrhea	3	0/0	2	0/0	5	1/0
Fatigue	3	0/0	2	0/0	15	0/0
Anorexia	3	0/0	4	0/0	10	0/0
Nausea	1	0/0	2	0/0	8	0/0
Vomiting	0	0/0	0	0/0	2	0/0
Stomatitis	4	0/0	3	0/0	4	0/0
Rash	0	0/0	1	0/0	0	0/0
Infection without neutropenia	0	0/0	1	0/0	0	0/0
Alopecia	4	–	1	–	20	–

Toxicity

Grade 3 neutropenia occurred in one of three patients at 100 and 125 mg/m^2 of irinotecan, respectively, and in two of six patients at 150 mg/m^2 (Table 2). Granulocyte colony-stimulating factor was not required in any patient. Grade 3 or 4 thrombocytopenia and anemia did not occur during any cycle.

Most treatment-related, nonhematologic adverse events were mild to moderate in intensity. The most frequent nonhematologic toxicities, other than alopecia, were fatigue and anorexia for all dose levels (Table 3).

Nausea and vomiting were mild. No patient had grade 2 or more severe nausea or vomiting at any dose level. Most cases of nausea and vomiting responded to dexamethasone and granisetron or other antiemetic drugs, and the patients could maintain good oral intake. Diarrhea was mild and infrequent. Grade 3 late diarrhea occurred in one patient. Delayed diarrhea was successfully managed with loperamide (Dainippon Pharmaceutical, Tokyo, Japan). Another mild, incidental finding, possibly related to treatment, was stomatitis (25%) during cycle 1.

A 54-year-old man with peritoneal carcinomatosis had an acute myocardial infarction 2 days after the start of cycle 2 of treatment (level 1) and died 4 days later. He had undergone a total gastrectomy for the primary lesion, with reconstruction by Roux-en-Y anastomosis. No ischemic episode had occurred previously. After the onset of the acute myocardial infarction, emergency coronary angiography revealed complete stenosis of the right coronary artery on the second day of cycle 2. The right coronary artery provided the dominant blood supply to the heart because of a congenital abnormality.

Pharmacokinetics

Complete sets of pharmacokinetic data were obtained in ten patients. Plasma pharmacokinetic parameters are shown in Tables 4 and 5. The peak plasma concentration of irinotecan was attained at the end of the 90-min intravenous infusion and declined with a harmonic mean $t_{1/2}$ of 7.8 h. As shown in Table 4, the AUC_{0-24h} of irinotecan increased linearly, parallel to the administered dose. The clearance

Table 4. Pharmacokinetic parameters of irinotecan and its metabolites on day 1

Dose of irinotecan	100 mg/m^2	125 mg/m^2	150 mg/m^2
No. of patients	3	3	4
Irinotecan			
Cmax (μg/ml)	1.2 ± 0.2	1.5 ± 0.2	2.3 ± 0.4
Tmax (h)	1.5	1.5	1.5
AUC_{0-24h} (μg·h/ml)	5.11 ± 0.62	7.38 ± 1.39	10.07 ± 1.71
Cl (ml/min)	456 ± 135	389 ± 115	354 ± 65
*t*1/2 (h)	8.8 ± 2.4	8.8 ± 1.2	6.6 ± 0.9
SN-38			
Cmax (μg/ml)	0.015 ± 0.008	0.029 ± 0.031	0.042 ± 0.039
Tmax (h)	2.2 ± 0.6	1.8 ± 0.6	2.5 ± 0.8
AUC_{0-24h} (μg·h/ml)	0.091 ± 0.048	0.161 ± 0.089	0.197 ± 0.062
*t*1/2 (h)	5.1 ± 1.2	15.3 ± 3.9	25.0 ± 24.1
SN-38G			
Cmax (μg/ml)	0.087 ± 0.011	0.061 ± 0.039	0.087 ± 0.038
Tmax (h)	2.8 ± 0.6	3.2 ± 2.1	2.5 ± 0
AUC_{0-24h} (μg·h/ml)	0.900 ± 0.308	0.764 ± 0.732	0.830 ± 0.229
*t*1/2 (h)	19.8 ± 9.4	35.0 ± 34.8	17.0 ± 7.2
Molar ratios (AUC_{0-24h} values)			
SN-38 to irinotecan (%)	1.8 ± 1.2	2.2 ± 1.2	1.9 ± 0.4
SN-38G to irinotecan (%)	17 ± 4.3	9.4 ± 7.8	8.3 ± 2.6
SN-38 to SN-38G (%)	13 ± 12	44 ± 37	24 ± 7.5

Cmax, maximum plasma concentration; Tmax, time to Cmax; AUC, area under the concentration-time curve; Cl, clearance, *t*1/2, plasma halflife

Table 5. Pharmacokinetic parameters of S-1 on days 1 and 8

Level	Dose of irinotecan (mg/m^2 per day)	Dose of S-1 (mg/m^2 per day)	No. of patients	Tegafur AUC_{0-10h} (μg·h/ml)[a]		5-FU AUC_{0-10h} (μg·h/ml)[a]	
				Day 1	Day 8	Day 1	Day 8
1	100	80	3	10.7 ± 3.1	17.8 ± 9.0	0.77 ± 0.25	0.93 ± 0.35
2	125	80	3	11.6 ± 2.8	20.3 ± 5.8	0.92 ± 0.25	1.35 ± 1.72
3	150	80	4	13.3 ± 4.0	22.6 ± 12.8	1.08 ± 0.41	1.35 ± 0.55
		P value[b]		0.636	0.875	0.511	0.314

[a] mean ± SD

[b] *P* value, the significance of differences between means was assessed using one-way analysis of variance (ANOVA; $P < 0.05$)

of irinotecan did not differ among the three dose levels. The AUCs of 5-FU and tegafur did not differ significantly between the three dose levels of irinotecan studied.

Response

Five of seven patients with measurable lesions had a PR. Two of these patients had previously received prior 5-FU-based chemotherapy for metastatic disease. PR was observed in two patients at level 2 and in three at level 3.

Discussion

The present investigation was undertaken to determine the recommended dose for phase II trials and to assess the feasibility of using triweekly irinotecan plus S-1 for the treatment of metastatic gastric cancer. The recommended dose was determined to be 150 mg/m^2 of irinotecan on day 1 and 80 mg/m^2 per day of S-1 on days 1 to 14 of a 21-day cycle. Toxicity was tolerable, and therapy was administered on an outpatient basis. DLT did not occur during cycle 1 of any dose level. Cumulative toxicity at 150 mg/m^2 of irinotecan included one patient with grade 3 diarrhea during cycle 3. Our results suggest that irinotecan plus S-1 holds promise of being a safe and effective treatment for metastatic gastric cancer.

Pozzo et al.[14] reported the results of a randomized phase II study comparing irinotecan plus 5-FU/leucovorin (LV) with irinotecan plus cisplatin in patients with gastric cancer. Irinotecan 80 mg/m^2 and LV 500 mg/m^2 were administered intravenously over the course of 2 h, followed by 5-FU 2000 mg/m^2 over the next 22 h. Treatment was given weekly for 6 weeks, followed by 1 week of rest. The response rate and MST were 28% and 6.9 months with irinotecan plus cisplatin and 34% and 10.7 months with irinotecan plus 5-FU/LV, respectively.[11] Grade 3 or 4 neutropenia according to the NCI-CTC developed in 25% of the patients with irinotecan plus 5-FU/LV , and grade 3 or 4 diarrhea developed in 24%. Because irinotecan plus 5-FU showed promising activity, Pozzo and Colleagnes[14] selected this regimen for an ongoing phase III study.

Other schedules for combination therapy with irinotecan and S-1 have been evaluated in gastric cancer. One study

assigned patients to receive irinotecan intravenously on days 1 and 15, and S-1 on days 1 to 14 of a 28-day cycle.[15] Irinotecan was administered at a recommended dose of 125 mg/m^2 and S-1 at a dose of 80 mg/m^2 per day. No DLT occurred during cycle 1 of treatment, even at 150 mg/m^2 of irinotecan; no information on toxicity during subsequent cycles, or on dose intensity was provided. In another phase I trial, irinotecan was given by intravenous infusion on days 1 and 15, and S-1 was given on days 1 to 21 of a 35-day cycle, every 5 weeks.[16] The DLTs were grade 3 rash and diarrhea, and the recommended dose was 80 mg/m^2 of irinotecan and 80 mg/m^2 per day of S-1. That study also did not report the results of subsequent treatment cycles. There are limitations in comparing the results of different studies. With our irinotecan plus S-1 combination therapy, only one clinic visit every 3 weeks is required for the administration of irinotecan, different from other scheduled regimens. We also found that both irinotecan and S-1 in our schedule could be administered at doses similar to those recommended for monotherapy with these drugs. Our limited experience suggests that triweekly treatment with irinotecan and S-1 may be more effective than currently available regimens.

The frequent nonhematologic toxicities were fatigue (36%); anorexia (31%); and diarrhea, stomatitis, and nausea (20% each). All cases of fatigue were grade 1 or 2. In our study, antiemetic therapy with a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone 8 mg was given intravenously on day 1, and dexamethasone 8 mg was given orally on days 2 to 4 to prevent delayed emesis, anorexia, and fatigue. Despite this treatment, two patients refused to continue chemotherapy after five cycles because of prolonged mild fatigue, although the relative dose intensity of both drugs was more than 90% at level 3. If we gain better compliance with the triweekly schedule, we consider this recommended dose and schedule as the appropriate regimen for both drugs.

The pharmacokinetic analysis showed no change in any pharmacokinetic parameter as compared with the expected values for irinotecan or S-1 as single agents. The mean SN-38/ irinotecan AUC ratio was approximately 2%. This value was similar to the ratio after the infusion of irinotecan alone.[17,18] A comparison of the pharmacokinetic data we obtained for irinotecan and its metabolites with such data reported by a previous study revealed that the plasma profiles of irinotecan, SN-38, and SN-38G were unaffected by the oral administration of S-1, though prior reports have suggested that 5-FU might inhibit the conversion of irinotecan to SN-38.[19,20] The AUCs of 5-FU and tegafur did not differ significantly between the three dose levels of irinotecan studied.

In conclusion, triweekly treatment with irinotecan plus S-1 holds the promise of being a safe and effective treatment for advanced gastric cancer. We believe that further clinical phase II studies of this combination are warranted.

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