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A Phase II Study of the Global Dose and Schedule of Capecitabine in Japanese Patients with Metastatic Colorectal Cancer

Ichinosuke Hyodo[1], Kuniaki Shirao[2], Toshihiko Doi[3], Kiyohiko Hatake[4], Yasuaki Arai[2], Kensei Yamaguchi[5], Takao Tamura[6], Shoji Takemiya[7], Hiroya Takiuchi[8], Kazuhiko Nakagawa[9] and Hideyuki Mishima[10]

[1]University of Tsukuba, Tsukuba, Ibaraki, [2]National Cancer Center Hospital, Tokyo, [3]National Cancer Center Hospital East, Kashiwa, Chiba, [4]Cancer Institute Hospital, Tokyo, [5]Saitama Cancer Center, Saitama, [6]Kobe University Graduate School of Medicine, Kobe, [7]Kanagawa Cancer Center, Yokohama, [8]Osaka Medical College, Takatsuki, Osaka, [9]Kinki University, Osakasayama, Osaka and [10]National Hospital Organization Osaka National Hospital, Osaka, Japan

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Background: Although the standard 3-week capecitabine regimen (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest) has shown superior activity and improved safety over bolus 5-fluorouracil/leucovorin in two large randomized phase III trials in Europe and in the United States, only a 4-week regimen of capecitabine (828 mg/m^2 twice daily for 3 weeks) has been studied in Japan. Therefore, we performed a phase II study to investigate the 3-week regimen of capecitabine in Japanese patients with metastatic colorectal cancer (MCRC).
Methods: Previously untreated patients with MCRC received oral capecitabine 1250 mg/m^2 twice daily for 2 weeks. Treatment was repeated every 3 weeks. Blood and urine samples were collected for pharmacokinetic analysis.
Results: Sixty patients were enrolled. The overall response rate was 35% [95% confidence interval (CI), 23–48%], and 52% of patients had stable disease. The median time to progression was 5.5 months (95% CI, 4.2–6.7 months). The median overall survival was 20.2 months (95% CI, 16.6–27.8 months). The most frequently occurring adverse drug reaction was hand-foot syndrome (all-grade 73%; grade 3 13%). Diarrhea, anorexia, nausea and stomatitis were each seen in 37% of patients. The pharmacokinetic profiles of capecitabine and its metabolites were similar to those reported in Caucasian patients.
Conclusions: The 3-week regimen of capecitabine was effective and well tolerated in Japanese patients with MCRC as well, and could be used as the basic regimen for future combination therapies.

Key words: capecitabine – colorectal cancer – phase II study

INTRODUCTION

For more than 40 years, 5-fluorouracil (5-FU) has been the mainstay of treatment for patients with metastatic colorectal cancer (MCRC). Many incremental improvements to 5-FU regimens, such as biomodulation with leucovorin (LV) and schedule modification, have been made. For example, infusional 5-FU offers not only improved response rates, but also a small survival benefit, compared with those of bolus 5-FU according to data from randomized trials and meta-analyses (1,2). However, continuous infusions require venous access lines and pumps with significant associated costs. Consequently, patients prefer to receive oral rather than intravenous chemotherapy (3,4).

Several new fluoropyrimidines, including uracil plus tegafur (UFT), capecitabine and S-1, have been developed and evaluated in the treatment of colorectal cancer. Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU predominantly to tumor cells. After oral administration, capecitabine is rapidly and extensively absorbed through the intestine as an intact molecule, and then metabolized to 5-FU in three steps. In the first step, capecitabine is hydrolyzed to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxylesterase primarily in the liver. 5′-DFCR is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase, which is highly active in

For reprints and all correspondence: Ichinosuke Hyodo, Division of Gastroenterology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan. E-mail: ihyodo@md.tsukuba.ac.jp

tumor cells and in the liver. Thymidine phosphorylase, which is significantly more active in tumor tissues than in adjacent normal tissues, finally converts 5′-DFUR to 5-FU (5,6). With each successive conversion step, the potential for systemic exposure to 5-FU is reduced while 5-FU delivery to tumor tissues is increased. Consequently, capecitabine avoids many of the gastrointestinal toxicities commonly observed with 5-FU.

Many clinical studies of capecitabine in MCRC have been conducted worldwide. In a Japanese phase I study using continuous administration of capecitabine, the maximum tolerated dose was 1255 mg/m^2 twice daily; skin fissures and gastric ulcers were noted as the dose-limiting toxicities (7). Another phase I study showed that a 1-week rest period appealed to patients and also maintained the activity of capecitabine therapy (8). From these findings, a 4-week intermittent regimen (3 weeks of capecitabine 828 mg/m^2 twice daily followed by a 1-week rest period) was recommended for Japanese phase II studies. This 4-week intermittent schedule of capecitabine was active and well tolerated in Japan, resulting in response rates of 25% (5/20) in a small pilot study (9), and 27% (15/56) in a phase II study (10) in patients with advanced or MCRC. However, it was a 3-week regimen of capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period) that was shown to have superior activity and improved safety over bolus 5-FU/LV (Mayo Clinic regimen) as the first-line therapy in two large randomized phase III studies (11–13), and has been approved for MCRC in Europe and in the United States. Since then, this 3-week regimen has been used as a platform for combination therapy with other active agents, such as irinotecan, oxaliplatin and bevacizumab (14–18).

To date, the efficacy and safety of the 3-week capecitabine regimen in Japan remains unclear. Therefore, we conducted this phase II trial as a registration trial, which included a pharmacokinetic analysis, of the 3-week capecitabine regimen in Japanese patients with previously untreated MCRC.

PATIENTS AND METHODS

Study Design

The primary endpoint of this open-label multicenter phase II study was response rate. Secondary endpoints were safety, time-to-tumor progression (TTP), survival and pharmacokinetic analysis. This study was conducted in accordance with the Good Clinical Practice guidelines for clinical trials in Japan and the Declaration of Helsinki. The study protocol was approved by the ethics committee of each institution. Written informed consent was obtained from all patients.

Patients

All patients had to have histologically confirmed colorectal adenocarcinoma with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) (19). Patients were also required to have the following laboratory values: neutrophils $\geq 1.5 \times 10^3$/mm^3; platelet count $>10 \times 10^4$/mm^3; serum creatinine $<1.5 \times$ upper limit of normal (ULN); serum bilirubin $<1.5 \times$ ULN; ALT (GPT), AST (GOT) $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases); alkaline phosphatase $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases or $\leq 10 \times$ ULN in the case of bone disease) and creatinine clearance >50 ml/min. Patients had received no chemotherapy for metastatic disease (excluding adjuvant chemotherapy completed more than 6 months before registration) and no radiotherapy to target lesions. Patients were not included if they had received radiotherapy within the previous 4 weeks, or had not fully recovered from the major surgery within 4 weeks. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; expected survival time of more than 3 months and age at enrollment of 20–74 years.

Exclusion criteria were as follows: pregnant or lactating women; sexually active men/women unwilling to practice contraception during the study; a history of hypersensitivity to 5-FU; organ allografts; clinically significant cardiac disease or myocardial infarction within the last 12 months; metastases of the central nervous system; a history of epilepsy; psychiatric disability precluding compliance with oral drug intake or giving informed consent; history of another malignancy within the last five years, except for cured basal cell carcinoma of skin, cured carcinoma *in situ* of uterine cervix, or cured esophago-gastric carcinoma removed by endoscopic procedures; serious uncontrolled infection; malabsorption syndrome; participation in any investigational drug study within 4 weeks preceding the start of treatment.

Evaluation of Response and Safety

Anti-tumor efficacy was evaluated by the investigators according to RECIST guidelines (19). An Independent Review Committee (IRC) confirmed tumor responses. Adverse events were assessed according to the National Cancer Institute—Common Toxicity Criteria, Version 2.0 (20). Hand-foot syndrome (HFS) was classified as follows: grade 1 (numbness, dysesthesia, painless swelling or erythema not disrupting daily living activities); grade 2 (erythema with painful swelling or disruption of daily living activities) or grade 3 (moist desquamation, ulceration, blistering or severe pain, or any symptoms leading to an inability to work or to perform daily living activities).

Study Assessments

Tumor responses were assessed every 2 cycles up to the cycle 10, and then every 3 cycles. Tumor markers (CEA and CA19-9) were also assessed at these times. Laboratory tests were performed before treatment, on day 8 of cycle 1 and on day 22 of each cycle. Drug compliance was reviewed at regular patient visits by checking unused tablets. Survival in all patients was monitored for 2 years after the last patient was enrolled.

Dosage and Dose Modifications

Capecitabine (Xeloda®) 1250 mg/m^2 was taken orally twice daily within 30 min after breakfast and dinner. The actual dose of capecitabine administered was determined according to the patient's body surface area (BSA) as follows: 3000 mg/day if BSA was <1.33; 3600 mg/day if BSA was between 1.33 and 1.56; 4200 mg/day if BSA was between 1.57 and 1.80; and 4800 mg/day if BSA was >1.80. Each cycle of therapy consisted of 2 weeks of capecitabine administration followed by a 1-week rest period. Patients received treatment unless they had disease progression or unacceptable toxicity, or withdrew consent.

Treatment interruption or dose reductions were made if patients experienced grade 2–4 toxicities, but not if the toxicity was considered unlikely to become serious or life-threatening. Treatment was interrupted in cases of grade 2 or grade 3 toxicities and was not resumed until adverse drug reactions improved to grade 1. The dose of capecitabine was not reduced for the subsequent treatment cycle in cases of the first appearance of grade 2 toxicity. Capecitabine dose was reduced by 25% when patients experienced any grade 2 toxicity for a second time or for any grade 3 toxicity. It was reduced by 50% when patients experienced any grade 2 toxicity three times, any grade 3 toxicity twice, or any grade 4 toxicity. Treatment was discontinued if such toxicities were observed despite dose reduction.

Statistical Methods

The target number of patients for accrual was 60. Given an expected response rate of 25%, a threshold response rate of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the analysis of response. The 95% confidence interval (CI) of the response rate was calculated by the exact method, assuming a binomial distribution of data. Treatment duration was defined as days from the first day of drug administration to the last regulated rest day of the final cycle. Dose intensity was calculated by dividing the cumulative dose/treatment duration by BSA. TTP was calculated as the time from the first administration of capecitabine to disease progression or death if the patient died before progression. Overall survival was defined as the time from study enrolment to death. These endpoints were calculated by the Kaplan–Meier method. Safety was evaluated in all patients who received capecitabine treatment.

Pharmacokinetic Analysis

Blood sampling was performed in the first 20 patients who gave consent to participate in the pharmacokinetic study. On day 1, the evening dose of capecitabine was not administered in order to quantify urinary recovery of capecitabine and its metabolites over a 24 h collection period. On days 1 and 14, 5 ml blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 11 h after the morning dose using vacutainers containing EDTA as an anticoagulant. Blood samples were centrifuged at 1500 *g* and 4°C for 10 min, and supernatant plasma was removed and stored in plastic tubes below −20°C until analysis. Urine was collected and pooled during the following time intervals: 0, 0–11 and 11–24 h on day 1; and 0–11 h on day 14. At the end of each interval, the total volume and the pH of urine were recorded; and a 15 ml aliquot was removed and stored at −20°C until analysis.

Plasma and urine concentrations of capecitabine and its metabolites were determined by a validated liquid chromatography with mass-spectrometry detection (LC/MS-MS). The lower limits of quantification (LLOQ) of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU and α-fluoro-β-alanine (FBAL) in plasma were 0.01, 0.01, 0.05, 0.002 and 0.011 μg/ml, respectively. The LLOQ of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, α-fluoro-β-ureidopropionic acid and FBAL in urine were 0.02, 0.02, 0.02, 0.1, 0.02 and 0.1 μg/ml, respectively.

Pharmacokinetic parameters were assessed by standard non-compartment analysis, using WinNonlin® professional version 4.1 (Pharsight Corporation). Maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined. Apparent half-life ($t_{1/2}$) was estimated from ln2/λ, where the apparent rate constant of elimination, λ, was estimated by linear regression on the logarithm of the plasma concentration versus time data. The area under the plasma concentration time curve from time 0 to infinity (AUC) was estimated from the sum of AUC_{0-t} and C_{tlast}/λ, where AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which a concentration above the limit of quantification was measured (C_{tlast}). AUC_{0-t} was estimated using the linear-log trapezoidal rule. Percentage of dose recovered in urine as capecitabine or one of its metabolites was calculated based on the dose administered, urinary concentration and volume of urine collected.

RESULTS

Patient Characteristics

Sixty patients were enrolled at 11 centers between January 2003 and November 2003. All patients met the eligibility criteria and received at least one dose of capecitabine. Therefore, both tumor response and safety were assessed in 60 patients. The baseline characteristics of patients are shown in Table 1. Median age was 60 years (range 34–71 years). A total of 33 patients (55%) had colon cancer, and 26 (43%) had rectal cancer. Metastatic sites affected were liver (73%), lung (58%), lymph node (47%) and others (17%).

Treatment Duration and Intensity

The median duration of treatment was 186 days (range 8–508 days). The median cumulative dose of capecitabine was 370 g (range 27–1255 g). The planned dose intensity was 1667 mg/m^2/day and the actual median dose intensity was 1420 mg/m^2/day (range 940–2220 mg/m^2/day). Approximately 57 and 35% of patients completed 8 and 10 cycles of therapy, respectively. The reasons for treatment discontinuation were progressive disease (54 patients), adverse reactions (5 patients) and salvage surgical therapy (1 patient).

Table 1. Baseline patient demographics (intent-to-treat population)

Parameter	No. of patients	%
No. patients enrolled	60	100
Sex		
Male	33	55
Female	27	45
Age (years)		
Median	60	
Range	34–71	
Primary site		
Colon	33	55
Rectum	26	43
Colon/rectum	1	2
ECOG performance status		
0	42	70
1	17	28
2	1	2
Metastatic sites		
Liver	44	73
Lung	35	58
Lymph node	28	47
Other	10	17
Number of metastatic sites		
1	18	30
2	31	52
≥3	11	18
Resection		
Yes	54	90
No	6	10
Prior radiotherapy	1	2
Prior 5-FU or 5-FU analog-based adjuvant chemotherapy	10	17

The median dose per cycle was >75% of the planned dose up to 10 cycles.

Efficacy

The objective response rate according to the IRC assessment was 35% (95% CI, 23–48%) (Table 2). Twenty-one patients had a partial response, and 31 (52%) had stable disease. Partial responses were observed in 11 out of 44 patients (25%) with liver metastases, 14 out of 35 patients (40%) with lung metastases and in 8 out of 28 patients (29%) with lymph nodes metastases. The median TTP was 5.5 months (95% CI, 4.2–6.7 months) (Fig. 1). Survival follow-up was performed at the cut-off date of October 2005. Thirty-five patients died of disease progression and there were no treatment-related deaths. The median overall survival was 20.2 months (95% CI, 16.6–27.8 months) and the 1-year survival rate was 70% (Fig. 1).

Table 2. Tumor responses ($N = 60$)

Response	No. of patients (%)	
	Assessed by investigators	Confirmed by Independent Review Committee
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	19 (32)	21 (35)
Stable disease (SD)	33 (55)	31 (52)
Progressive disease (PD)	7 (12)	8 (13)
Not evaluable	1 (2)	0 (0)
Overall response rate	32% (95% CI, 20–45%)	35% (95% CI, 23–48%)
Disease control (CR + PR + SD)	87% (95% CI, 75–94%)	87% (95% CI, 75–94%)

CI: confidence interval.

Safety

The common adverse drug reactions (all grades) were HFS (73%), pigmentation (38%), diarrhea (37%), anorexia (37%), nausea (37%) and stomatitis (37%) (Fig. 2). The most frequent grade 3/4 adverse drug reaction was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. No grade 4 diarrhea was observed, and grade 3 diarrhea was seen in only one patient. Ileus occurred in one patient. As for grade 3/4 laboratory abnormalities, the common events were elevated total bilirubin (12%) and elevated AST (10%). One patient had grade 3 leucopenia, and 5 patients had grade 3 neutropenia. One patient had grade 4 hyperglycemia.

Treatment was interrupted due to adverse drug reactions in 48 patients (80%). The median time to the first interruption was 43 days. The major cause of treatment interruption was HFS (25 patients). Dose reduction was needed in 32 patients (53%), and 10 patients had the second dose reduction. The median time to the first dose reduction was 78 days, and to second dose reduction was 162 days. Nineteen patients had dose reductions due to HFS. Five patients discontinued treatment because of adverse events: ileus (grade 4, treatment related); hepatitis C (grade 3, not related, an accidental acute infection); liver function abnormality (grade 2, not related, due to the progression of liver metastasis); hydronephrosis (grade 4, not related) and HFS (grade 3, treatment related).

Pharmacokinetics

Plasma concentrations for capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU and FBAL) are shown in Fig. 3. The pharmacokinetic parameters are summarized in Table 3. Peak plasma concentrations of capecitabine and its metabolites

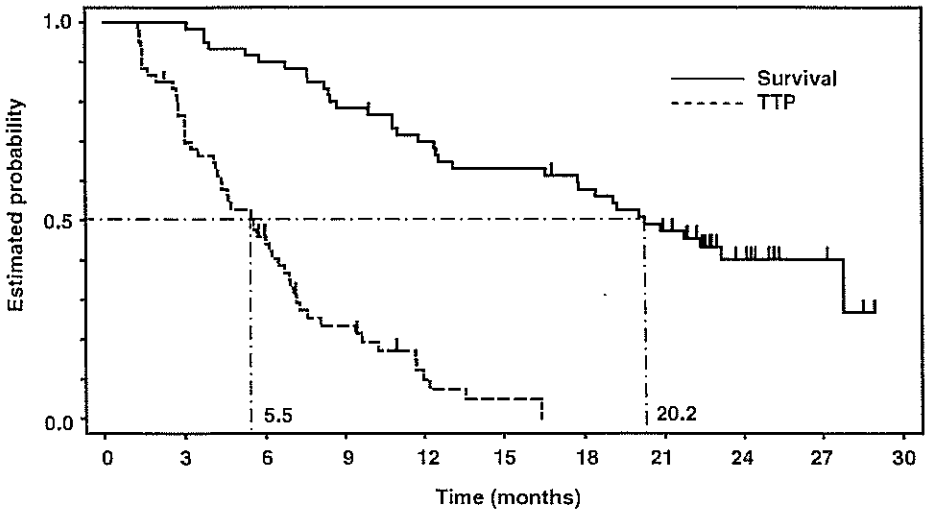

Figure 1. Time to disease progression (TTP) and overall survival.

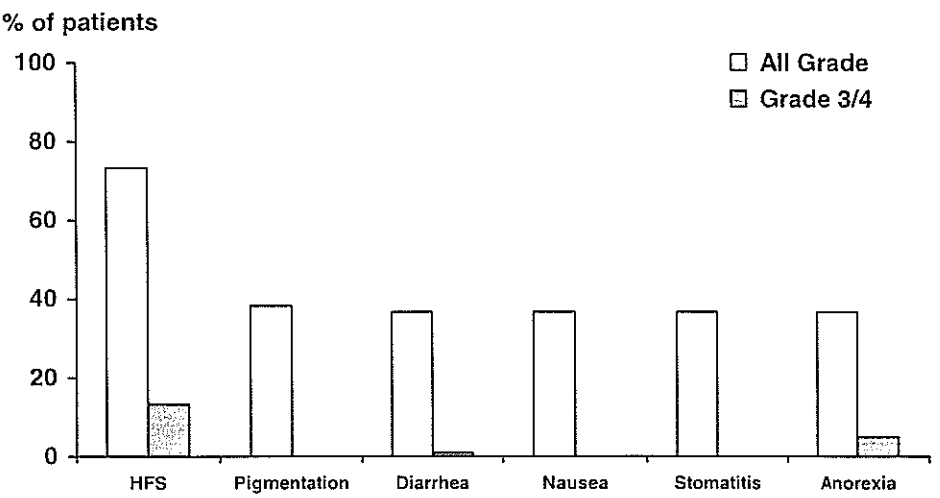

Figure 2. Common adverse drug reactions (≥20% of patients). HFS: hand-foot syndrome.

were reached rapidly at approximately 1.5–4 h after oral administration. Plasma concentrations of capecitabine, 5′-DFCR, 5′-DFUR and 5-FU were below the LLOQ at 8, 11, 8 and 8 h on day 1, respectively, and at 6, 11, 6 and 8 h on day 14, respectively. $T_{1/2}$ were generally short at <1 h, except for FBAL (around 2.5 h). After a single dose of capecitabine 1250 mg/m^2, the AUC for 5-FU was almost 30 times lower than its precursor 5′-DFUR on day 1. Comparing day 1 versus day 14, there was no significant accumulation of capecitabine and its metabolites except for 5-FU. The AUC for 5-FU on day 14 was 1.6 times higher than that on day 1.

The mean urinary excretion ratio of capecitabine and its metabolites are presented in Table 4. The mean proportions for the urinary recovery of capecitabine and its metabolites were 78% on day 1 and 80% on day 14. FBAL was the main urinary metabolite accounting for 50% on day 1 and 50% on day 14. The urinary excretion ratio of unmetabolized capecitabine was low at around 3%.

DISCUSSION

Two large randomized phase III studies have shown that capecitabine is more active than bolus 5-FU/LV in terms of tumor response (26 versus 17%), and equivalent to 5-FU/LV in terms of TTP and overall survival time in the first-line treatment of MCRC (11,13). Furthermore, a combined analysis of these randomized phase III studies revealed that capecitabine conferred a clinically meaningful advantage over 5-FU/LV in terms of safety (12). On the basis of these data, capecitabine was approved for the treatment of MCRC in Europe and in the US as an alternative to 5-FU/LV.

The results of the present study are similar to those observed in the pivotal phase III trials. The response rate in our study

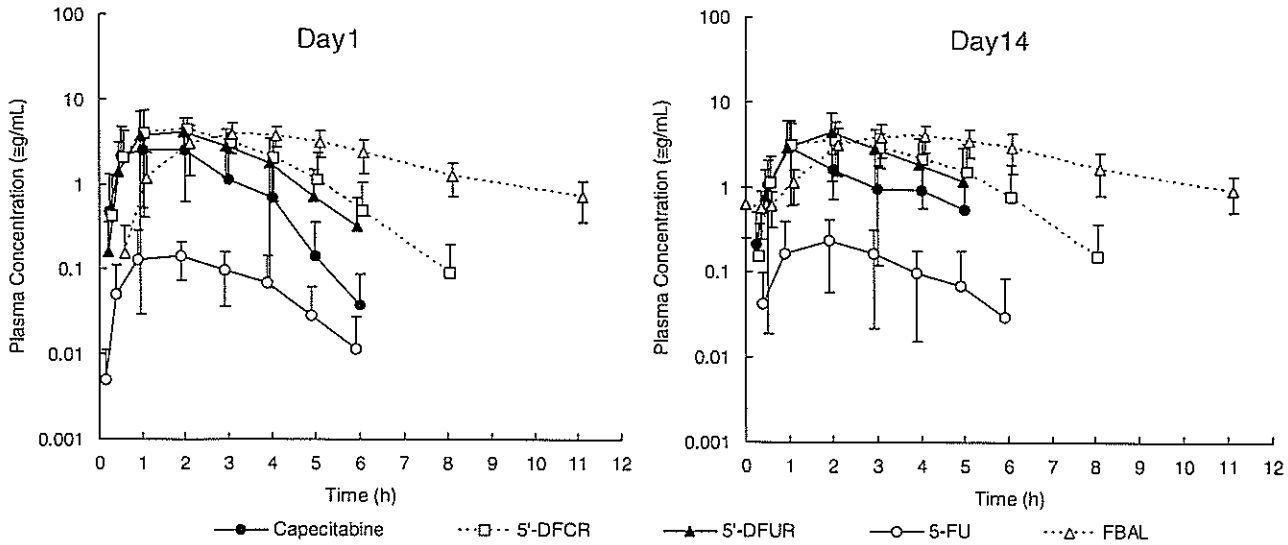

Figure 3. Plasma concentrations (mean ± standard deviation) for capecitabine and its metabolites 5′-deoxy-5-fluorocytidine (5′-DFCR), 5′-deoxy-5-fluorouridine (5′-DFUR) and α-fluoro-β-alanine (FBAL).

Table 3. Pharmacokinetic parameters of capecitabine and its metabolites

	Parameter	Day 1		Day 14	
		N	Mean ± SD	*N*	Mean ± SD
Capecitabine	C_{max} (μg/ml)	20	4.80 ± 1.75	19	4.19 ± 2.55
	T_{max} (h)	20	1.68 ± 0.99	19	1.90 ± 1.40
	AUC (μg·h/ml)	18	7.06 ± 2.46	15	6.73 ± 1.71
	$t_{1/2}$ (h)	18	0.545 ± 0.245	15	0.478 ± 0.152
5′-DFCR	C_{max} (μg/ml)	20	5.95 ± 2.50	19	5.20 ± 1.90
	T_{max} (h)	20	2.00 ± 1.07	19	2.53 ± 1.27
	AUC (μg·h/ml)	20	15.2 ± 4.32	19	14.1 ± 4.60
	$t_{1/2}$ (h)	20	0.810 ± 0.112	19	0.855 ± 0.199
5′-DFUR	C_{max} (μg/ml)	20	6.02 ± 2.49	19	6.59 ± 2.83
	T_{max} (h)	20	2.25 ± 1.16	19	2.69 ± 1.21
	AUC (μg·h/ml)	19	13.1 ± 3.69	17	13.2 ± 3.40
	$t_{1/2}$ (h)	19	0.711 ± 0.140	17	0.689 ± 0.199
5-FU	C_{max} (μg/ml)	20	0.217 ± 0.121	19	0.376 ± 0.211
	T_{max} (h)	20	2.30 ± 1.25	19	2.74 ± 1.20
	AUC (μg·h/ml)	19	0.455 ± 0.180	17	0.719 ± 0.235
	$t_{1/2}$ (h)	19	0.732 ± 0.291	17	0.755 ± 0.258
FBAL	C_{max} (μg/ml)	20	4.50 ± 1.01	19	4.84 ± 1.20
	T_{max} (h)	20	3.35 ± 1.09	19	3.85 ± 1.31
	AUC (μg·h/ml)	20	24.5 ± 7.40	16	27.0 ± 7.84
	$t_{1/2}$ (h)	20	2.56 ± 0.690	16	2.72 ± 0.506

5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FBAL, α-fluoro-β-alanine.

was 35%, which compares favorably with the combined response rate reported in the phase III studies (26%) (11,13) and in a previous Japanese phase II study (27%) using the 4-week regimen (10). Comparing the patients' background, the number of patients who had more than 3 metastatic sites in this study was less than that in the phase III studies (18 versus 52%) (12), and our patients had better PS (PS 0, 70%). These better backgrounds might bring out slightly higher response rate in our study. The rate of stable disease was 52% in the current study and 38% with the 4-week regimen (10). Consequently, the disease control rate was superior in the present study than with the 4-week regimen (87 versus 64%). Moreover, the median TTP was similar to that reported in the phase III studies (5.5 months versus 4.6 months) using the same 3-week schedule, and was longer than that in the previous Japanese phase II study (2.2 months, unpublished data) using the 4-week regimen. Notwithstanding the limitations of comparing data between trials, these data strongly suggest that the capecitabine 3-week regimen is superior to the 4-week regimen. One of the reasons for these better results might be attributed to the higher dose intensity of the 3-week regimen than that of the 4-week regimen.

In terms of safety, most adverse events were reversible and manageable, and the tolerability of this regimen in a Japanese patient population seemed similar to that observed in Western patient populations. Compared with the randomized phase III studies (12), the rate of HFS, the most frequently reported adverse drug reaction, was higher in the present study (73 versus 54%), but grade 3 HFS appeared a little lower (13 versus 17%). However, HFS was controlled easily by interruption or dose reduction and it is not a life-threatening toxicity. Only one patient withdrew from the study due to this adverse reaction (2%), but none of the patients required hospitalization for the treatment of HFS. In the phase III studies (12), 2% of patients withdrew because of HFS, a rate that was similar to our study. The rate of diarrhea (all-grade and grade 3/4) was less frequent in the present study compared with that of the phase III data (all-grade 37 versus 48%; grade 3/4

Table 4. Urinary excretion of capecitabine and its metabolites

	Urinary excretion (% of dose)			
	Day 1		Day 14	
	N	Mean ± SD	*N*	Mean ± SD
Capecitabine	16	3.21 ± 2.04	19	3.42 ± 1.48
5′-DFCR	16	8.39 ± 3.73	19	8.42 ± 3.44
5′-DFUR	16	12.1 ± 4.34	19	14.6 ± 5.35
5-FU	16	0.691 ± 0.835	19	0.782 ± 0.642
FUPA	16	2.78 ± 0.808	19	2.98 ± 1.05
FBAL	16	50.3 ± 9.66	19	49.5 ± 11.3
Total	16	77.5 ± 14.8	19	79.6 ± 16.9

5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FUPA, α-fluoro-β-ureidopropionic acid; FBAL, α-fluoro-β-alanine.

2 versus 13%) (12). Though pigmentation, which was not reported more than 5% in the phase III trials, was frequently observed in this study (38%), all events of pigmentation were grade 1 and did not lead to interruption or reduction. The rate of other adverse drug reactions in our study was almost identical to that reported in the phase III trials (12). With regard to severe abnormalities in laboratory parameters, AST elevation was more frequently observed in the present study (10 versus 1%), although the rate of hyperbilirubinemia was similar to phase III observations (12 versus 23%) (12). Dose reduction was executed more frequently than the phase III trials (53 versus 34%), but the rate of dose reduction to second level was almost similar (17 versus 12%). Median time to reduction to the first level was similar to phase III trials (2.6 months versus 2.5 months), and median time to reduction to the second level was longer in our study (5.3 months versus 3.6 months). From these results, the current 3-week regimen seems quite feasible for the treatment of MCRC in Japan.

The pharmacokinetic findings in the present study were basically similar to those reported in Caucasian patients (8,21). Pharmacokinetic analysis of plasma concentrations and urinary excretion showed rapid gastrointestinal absorption of capecitabine and efficient conversion to its metabolites. Peak concentrations of capecitabine and its metabolites, including 5-FU, were reached shortly after drug administration and declined exponentially with a half-life of approximately 1 h. Pharmacokinetic data obtained on days 1 and 14 showed no difference in pharmacokinetics over time and there was no clinically significant accumulation of capecitabine and its metabolites, except for 5-FU. The AUC of 5-FU on day 14 was 1.6 times higher than on day 1. A similar increase of 5-FU with multiple administration has been also reported in other clinical studies of capecitabine (7,8,21).

From these results, we conclude that the 3-week regimen of capecitabine is effective and well tolerated in Japanese patients with MCRC. Capecitabine has been reported to show good activity when combined with irinotecan (14,15) and oxaliplatin (16,17). Further investigation of this 3-week schedule is warranted in Japan.

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References

1. de Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997;15:808–15.
2. Anon. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-analysis Group In Cancer. *J Clin Oncol* 1998;16:301–8.
3. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;15: 110–5.
4. Borner MM, Schoffski P, de Wit R, Caponigro F, Comella G, Sulkes A, et al. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2002;38:349–58.
5. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumors by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998;34: 1274–81.
6. Ishikawa T, Utoh M, Sawada N, Nishida M, Fukase Y, Sekiguchi F, et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. *Biochem Pharmacol* 1998;55:1091–7.
7. Saeki T, Takashima S, Terashima M, Satoh A, Toi M, Osaki A, et al. A Japanese phase I study of continuous oral capecitabine in patients with malignant solid tumors. *Int J Clin Oncol* 2005;10:51–7.
8. Mackean M, Planting A, Twelves C, Schellens J, Allman D, Osterwalder B, et al. Phase I and pharmacologic study of intermittent twice-daily oral therapy with Capecitabine in patients with advanced and/or metastatic cancer. *J Clin Oncol* 1998;16:2977–85.
9. Kondo Y, Terashima M, Sato A, Taguchi T. A pilot phase II study of capecitabine in advanced or recurrent colorectal cancer. *Jpn J Clin Oncol* 2004;34:195–201.
10. Sakamoto J, Kondo Y, Takemiya S, Sakamoto N, Nishisho I, on behalf of the clinical study group of capecitabine. A phase II Japanese study of a modified capecitabine regimen for advanced or metastatic colorectal cancer. *Anti-Cancer Drugs* 2004;15:137–43.
11. Twelves C. Capecitabine as first-line treatment in colorectal cancer: pooled data from two large, phase III trials. *Eur J Cancer* 2002;38(Suppl. 2):15–20.
12. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, et al. Capecitabine Colorectal Cancer Study Group. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002;13:566–75.
13. Van Cutsem E, Hoff PM, Harper P, Bukowski RM, Cunningham D, Dufour P, *et al.* Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomized, phase III trials. *Br J Cancer* 2004;90:1190–7.
14. Tewes M, Schleucher N, Achterrath W, Wilke HJ, Frings S, Seeber S, et al. Capecitabine and irinotecan as first-line chemotherapy in patients with metastatic colorectal cancer: results of an extended phase I study. *Ann Oncol* 2003;14:1442–8.

15. Borner MM, Bernhard J, Dietrich D, Popescu R, Wernli M, Saletti D, et al. A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. *Ann Oncol* 2005;16:282–8.
16. Diaz-Rubio E, Evans TR, Tabernero J, Cassidy J, Sastre J, Eatock M, et al. Capecitabine (Xeloda) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. *Ann Oncol* 2002;13:558–65.
17. Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, et al. XELOX (Capecitabine Plus Oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol* 2004;22:2084–91.
18. Fernando N, Yu D, Morse M, Blobe G, Odogwu L, Crews J, et al. A phase II study of oxaliplatin, capecitabine and bevacizumab in the treatment of metastatic colorectal cancer. *J Clin Oncol* 2005;23:6S(Abst. 3556).
19. Therasse P, Arbuck S, Eisenhauer E, Wanders J, Kaplan R, Rubinstein L, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. *J Natl Cancer Inst* 2000;92: 205–16.
20. National Cancer Institute–Common Toxicity Criteria (NCI-CTC Version 2.0, April 30, 1999).
21. Reigner B, Watanabe T, Schuller J, Lucraft H, Sasaki Y, Bridgewater J, et al. Pharmacokinetics of capecitabine (Xeloda) in Japanese and Caucasian patients with breast cancer. *Cancer Chemother Pharmacol* 2003;52:193–201.

APPENDIX

List of participating centers: NHO Shikoku Cancer Center, National Cancer Center Hospital, National Cancer Center Hospital East, Cancer Institute Hospital, Aichi Cancer Center, Saitama Cancer Center, Kobe University Graduate School of Medicine, Kanagawa Cancer Center, Osaka Medical College, Kinki University, NHO Osaka National Hospital.

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A Phase I Study of Irinotecan in Combination with Amrubicin for Advanced Lung Cancer Patients

HIROYASU KANEDA, TAKAYASU KURATA, KENJI TAMURA, HISAO UEJIMA, KAZUHIKO NAKAGAWA and MASAHIRO FUKUOKA

Department of Medical Oncology, Kinki University School of Medicine, Osaka 589-8511, Japan

Abstract. *Background: A combination phase I study was conducted in a cohort of lung cancer patients to determine the maximum tolerated dose (MTD) and toxicities of irinotecan (CPT-11), a topoisomerase I inhibitor, in combination with amrubicin (AMR), a topoisomerase II inhibitor, and to observe their antitumor activities. Patients and Methods: Patients with lung cancer received AMR (35 – 40 mg/m^2 given intravenously over 5 min) for 3 consecutive days, and CPT-11 (50 – 60 mg/m^2 given intravenously over 90 min) after the completion of AMR infusion on days 1 and 8, every 3 weeks. Results: In total, eleven patients were enrolled in this study. The most frequent toxicities were bone marrow suppression, particularly leucopenia and neutropenia, followed by infection, diarrhea and pneumonitis. As a consequence of these toxicities, the MTD and the recommended dose could not be determined. There were two partial responses, which included one patient with small cell lung cancer (SCLC) who had previously received chemotherapy and the other with previously untreated non-small cell lung cancer (NSCLC). Conclusion: These data suggest that the combination of CPT-11 and AMR is not tolerated, as it mediates an unexpectedly strong myelosuppressive effect, and is inactive against both NSCLC and SCLC.*

Lung cancer is the leading cause of cancer deaths worldwide. In spite of the development of new anticancer agents, such as paclitaxel, docetaxel, irinotecan (CPT-11) and gemcitabine, the prognosis of lung cancer is still poor. New agents and new combination chemotherapy regimens are warranted in order to improve the outcome for lung cancer patients. The DNA topoisomerases are essential nuclear enzymes that catalyze the breakage and rejoining of DNA. There are two classes of DNA topoisomerases, type I (topo I) and type II (topo II), which alter the topology of single- and double-stranded DNA, respectively, and are concerned with genetic reactions including DNA replication, transcription and DNA repair (1). To date, several DNA topoisomerase inhibitors, including CPT-11, the anthracyclines and etoposide, have played an important role in lung cancer chemotherapy (2, 3). Moreover, some investigators have reported that the combination of topo I and topo II inhibitors resulted in a synergistic effect in preclinical studies (4). This synergistic effect may be related to their complementary functions. However, other investigators have reported, conversely, that inhibition of both topo I and topo II led to an antagonistic effect (5, 6). Thus, the inhibition of both topoisomerases seems to be a very attractive strategy in the context of lung cancer chemotherapy, although it is not clear whether the combination results in a synergistic, additive or antagonistic effect. Amrubicin (AMR) is a novel, totally synthetic, 9-aminoanthracycline derivative that inhibits topo II. It has more potent antitumor activity and less heart, liver and renal toxicities than doxorubicin, according to *in vivo* studies. Amrubicinol, the C-13 alcohol metabolite of AMR, which also inhibits topo II, has 10 to 100 times more antitumor activity than the parent compound. Based on preclinical study data, intravenous (*i.v.*) administration on 3 consecutive days every 3 weeks was recommended for use in a phase I/II study involving previously untreated advanced non-small cell lung cancer (NSCLC) patients. The dose-limiting toxicities (DLTs) were leucopenia, thrombocytopenia and gastrointestinal disturbance and the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies were 50 mg/m^2/day and

Abbreviations: NSCLC, non-small cell lung cancer; ED-SCLC, extensive-disease small cell lung cancer; PS, performance status; topo I, topoisomerase I; topo II, topoisomerase II; CPT-11, irinotecan; AMR, amrubicin; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; RD, recommended dose; MST, median survival time; JCOG, Japan Clinical Oncology Group; FACS, Four Arm Cooperative Study; AUC, area under the concentration-time curve; C_{max}, concentration$_{max}$.

Correspondence to: Masahiro Fukuoka, Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan. Tel: +81-72-366-0221, Fax: +81-72-360-5000, e-mail: mfukuoka@med.kindai.ac.jp

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45 mg/m^2/day, respectively. Two phase II studies for NSCLC showed response rates of 27.9% and 18.3%, while a phase II study for extensive-disease small cell lung cancer (ED-SCLC) had a response rate of 75.8% and a median survival time (MST) of 11.7 months. Based on these results, AMR seems to be active for both NSCLC and ED-SCLC.

CPT-11, a camptothecin derivative, is a semi-synthetic topo I inhibitor and is one of the most active drugs used in the treatment of NSCLC and SCLC (7, 8). Recently, the Japan Clinical Oncology Group (JCOG) indicated that the combination of cisplatin and CPT-11 allows for significantly better survival than the combination of cisplatin and etoposide for previously untreated ED-SCLC (9). Moreover, Kubota *et al.* recently reported the results of the Four Arm Cooperative Study (FACS), which showed that cisplatin plus CPT-11 had comparative activity to carboplatin plus paclitaxel, cisplatin plus gemcitabine and cisplatin plus vinorelbine for the treatment of advanced NSCLC(10). Therefore, in Japan, the combination of cisplatin and CPT-11 is considered to be one of the standard chemotherapy regimens for NSCLC and ED-SCLC.

With the aim of improving therapeutic effects, a phase I study of AMR and CPT-11, as a combined topo I/II-targeting chemotherapy regimen for advanced lung cancer, was conducted. The objectives of this phase I study were: (a) to determine the MTD of both drugs and the RD for phase II studies; (b) to evaluate the toxicity profile of this regimen; (c) to investigate the pharmacokinetics of CPT-11, SN-38, AMR and amrubicinol; and (d) to observe the antitumor activity.

Patients and Methods

Patient eligibility. Patients with histological or cytological confirmation of locally advanced or metastatic NSCLC or ED-SCLC, who had received either no prior chemotherapy or one previous chemotherapy regimen, were eligible. The eligibility criteria were as follows; (a) ≥20 but <75 years old; (b) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; (c) adequate organ function [white blood cell count (WBC) ≥4000 μl^{-1}, neutrophil count ≥2000 μl^{-1}, platelet count ≥100,000 μl^{-1}, hemoglobin concentration ≥9.5 gdl^{-1}, serum total bilirubin ≤1.5 mgdl^{-1}, serum transaminase ≤2.5 x upper normal limits, serum creatinine ≤ upper normal limits, PaO_2 ≥ 60 mmHg]. At least 4 weeks had to have passed after the completion of prior therapy and the patients had to have recovered from any toxic effects of such therapy. The exclusion criteria comprised pulmonary fibrosis or interstitial pneumonitis with symptoms or apparent abnormalities on chest X-ray, massive pleural effusion, pericardial effusion, or ascites, pregnancy, lactation, symptomatic brain metastases, active concurrent malignancies, severe drug allergies, severe heart disease, cerebrovascular disease, uncontrollable diabetes mellitus, severe infection or active peptic ulcer. This study was performed at the Kinki University School of Medicine, Japan, and was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Table I. *Dose modification schemes.*

Dose	Amrubicin (mg/m^2)	Irinotecan (mg/m^2)	No. of patients (courses)
–2	30	50	3(8)
–1	30	60	5(14)
1	40	50	3(11)

Pretreatment and follow-up studies. Prior to entry, a full history and physical examination were completed, including age, height, weight, PS, histological diagnosis, tumor stage, nature of previous treatment and presence of a complication. The pretreatment laboratory examinations included a complete blood cell count, differential WBC count, hemoglobin, platelet count, serum electrolytes, total protein, albumin, total bilirubin, transaminase, alkaline phosphatase, lactate dehydrogenase, BUN, creatinine, blood gas analysis and electrocardiogram. After the initiation of therapy, a complete blood cell count with a differential WBC count was performed at least twice a week. Blood chemistry profiles and chest X-rays were obtained weekly. The lesion measurements were performed during every second course at least. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 and tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (11).

Drug administration and dose escalation. The treatment schedule included AMR, diluted with 20 ml of 5% glucose fluid, given *i.v.* over 5 min for 3 consecutive days, and CPT-11 with 500 ml of normal saline, given *i.v.* over 90 min after the completion of AMR infusion on days 1 and 8, every 3 weeks. All patients were allowed to receive antiemetics with dexamethasone and granisetron. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was not administered. Doses of CPT-11 on day 8 were given if the WBC count was >2,500 μl^{-1}, the platelet count was >75,000 μl^{-1}, no episode of diarrhea had been experienced, pneumonitis incidents were less than grade 2 and the other non-hematological toxicities were less than grade 3. The subsequent courses were started if the WBC count was >3,000 μl^{-1}, the platelet count was >100,000 μl^{-1}, serum total bilirubin ≤1.5 mgdl^{-1}, serum transaminase ≤2.5 x upper normal limits, no episode of diarrhea had been experienced and pneumonitis incidents were less than grade 2. The doses of both drugs were decreased by one dose level if DLTs occurred. In the case of the initial dose level, the dose reduction was not permitted and this study was canceled.

The dose escalations were performed as listed in Table I. Intra-patient dose escalation was not allowed. At least three patients were treated at each dose level, and three additional patients were entered at the same dose level if DLT was observed in one or two of the first three patients. The MTD was defined as the dose level at which three out of three patients, or more than three out of six patients experienced DLT. The definition of DLT was: (a) grade 4 neutropenia for more than 4 days, (b) grade 3 febrile neutropenia, (c) thrombocytopenia <20,000 μl^{-1}, (d) grade 3 non-hematological toxicity except for nausea/vomiting, appetite loss and pneumonitis, (e) more than grade 2 pneumonitis, (f) delay of administration of CPT-11 on day 8 over a week, or delay of subsequent courses over 2

Table II. *Patient characteristics.*

No. of patients	11
Age	
Median(range)	61.5 (49-72)
Gender	
Male/Female	8/3
Performance status	
0/1	3/8
Histology	
Adeno/Small	7/4
Stage	
IIIB/IV	3/8
Prior therapy	
None	8
Chemotherapy	3
Cisplatin-based	2
Non-platinum	1

weeks for toxicities and (g) inability to administer AMR for 3 consecutive days.

Pharmacokinetics. Pharmacokinetic (PK) studies for both AMR and CPT-11 were performed for all patients during their first course. Heparinized venous blood samples (3 ml) for AMR PK were taken to obtain plasma for the analysis of the parent compound and to isolate blood cells for the analysis of the active metabolite, amrubicinol, before administration, at the end of infusion and 15 min, 1 h, 1 h 55 min, 2 h 55 min, 4 h, 6 h 55 min, 10 h 55 min and 23 h 55 min post-infusion. CPT-11 PK (parent compound and SN-38) samples were taken in heparinized tubes before administration, at the end of infusion and 15, 30 min and 1, 3, 4, 5, 7, 9 and 22 h post-infusion. The plasma and blood cell samples were separated by centrifugation (3000xg for 10 min at 4°C) and were stored below –20°C until analysis. The AMR (Sumika Chemical Analysis Service, Ltd., Osaka, Japan), amrubicinol, CPT-11 (Yakult Honsha Co., Ltd., Tokyo, Japan) and SN-38 levels were assayed by high-performance liquid chromatography and mass spectrometry. The PK parameters were determined on the basis of non-compartment analysis (WinNonlin Professional ver. 4.1, Pharsight Corp.). The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule.

Results

Patient characteristics. Between January 2003 and June 2004, eleven patients were enrolled in this study and their characteristics are listed in Table II. The median age was 62 years (range: 49 to 72 years). There were eight males and eight patients with PS of 1. Four had SCLC, while eight had not received prior treatment (level 1, two patients; level 1, three patients; level 2, three patients). Of the three previously treated patients, two had received cisplatin-based chemotherapy, while the remaining patient having received a non-platinum regimen. The total number and the median number of courses were 33 and 3 (range 1-8), respectively.

Table III. *Hematological toxicity following first course of amrubicin and irinotecan.*

		WBC grade	ANC grade	Plt grade	Hb grade
Dose level	No. of patients	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
–2	3	0 2 0 0 1	0 0 1 1 1	2 1 0 0 0	0 1 2 0 0
–1	5	0 2 2 0 1	0 0 1 1 3	4 1 0 0 0	0 3 1 1 0
1	3	0 0 0 3 0	0 0 0 0 3	2 1 0 0 0	0 2 1 0 0

WBC, white blood cell count; ANC, absolute neutrophil count; Plt, platelet; Hb, hemoglobin.

Table IV. *Non-hematological toxicity following first course of amrubicin and irinotecan.*

		Nausea	Vomiting	Fatigue	Transaminase
Dose level	No. of patients	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
–2	3	1 2 0 0 0	2 1 0 0 0	0 3 0 0 0	1 2 0 0 0
–1	5	1 1 3 0 0	2 3 0 0 0	3 1 1 0 0	4 1 0 0 0
1	3	1 2 0 0 0	2 1 0 0 0	1 2 0 0 0	2 1 0 0 0
		Infection	Appetite loss	Diarrhea	Pneumonitis
Dose level	No. of patients	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
–2	3	2 0 0 1 0	1 2 0 0 0	1 1 1 0 0	1 0 0 2 0
–1	5	3 0 0 2 0	1 1 3 0 0	0 3 0 1 1	5 0 0 0 0
1	3	1 0 0 2 0	1 2 0 0 0	2 1 0 0 0	3 0 0 0 0

Table V. *Toxicity following all courses of amrubicin and irinotecan.*

	Grade				
	0	1	2	3	4
WBC	2	13	5	10	3
ANC	0	3	12	4	14
Hb	1	20	8	4	0
Plt	26	6	1	0	0
Nausea	15	15	3	0	0
Vomiting	27	6	0	0	0
Appetite loss	18	9	6	0	0
Fatigue	21	10	2	0	0
Transaminase	22	10	1	0	0
Diarrhea	21	7	3	1	1
Infection	28	0	0	5	0
Pneumonitis	31	0	0	2	0

WBC, white blood cell count; ANC, absolute neutrophil count; Plt, platelet; Hb, hemoglobin.

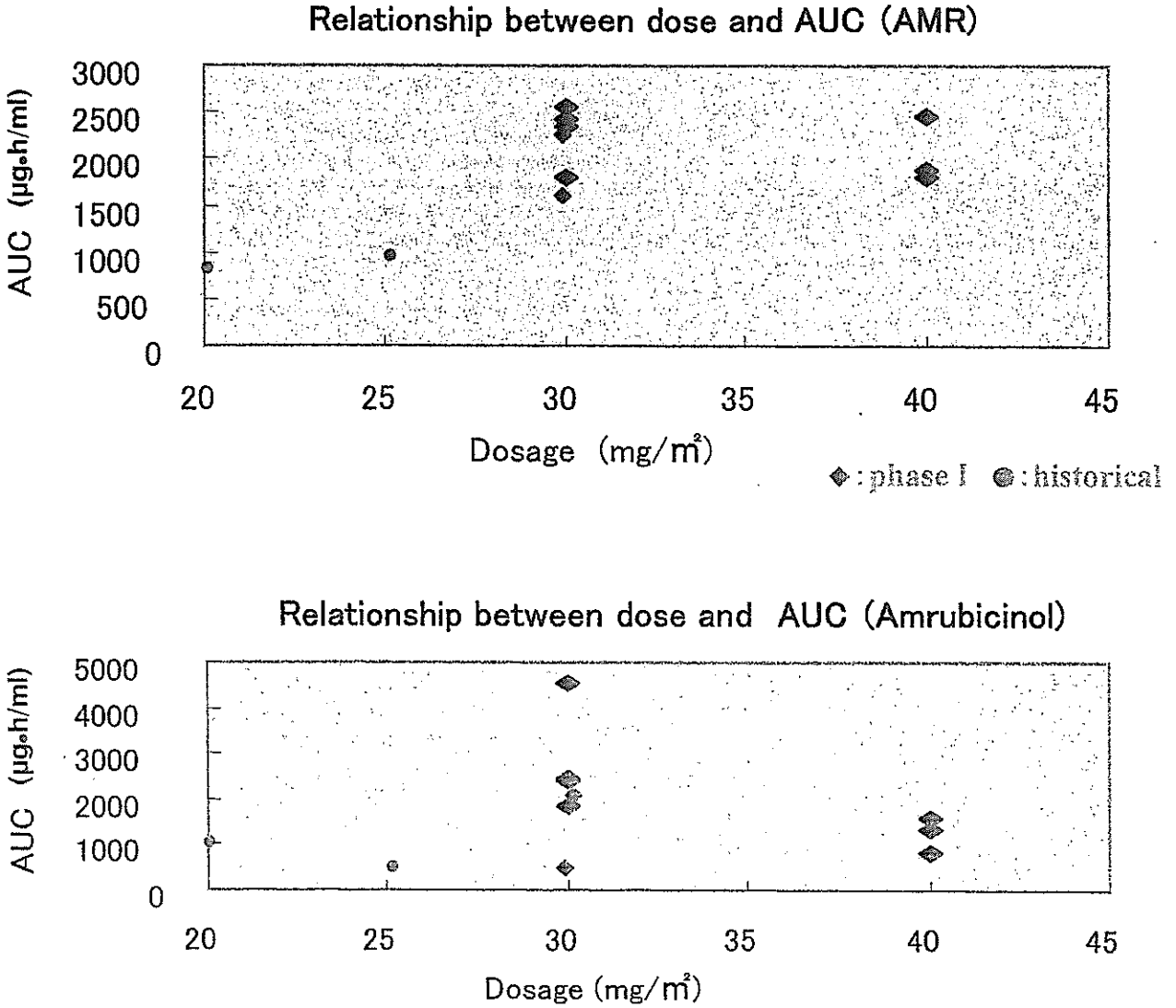

Figure 1. *Relationship between dose (mg/m²) and area under the concentration-time curve (AUC) (μg•h/ml) of (A) amrubicin; (B) amrubicinol.*

Toxicities. All patients were assessable for toxicity. The hematological and non-hematological toxicities developed during the first course are shown in Tables III and IV, respectively. Myelosuppression, especially neutropenia, was frequently observed. At level 1, two out of three patients developed febrile neutropenia and the other patient had grade 4 neutropenia which lasted for 7 days. At level 1, one patient developed febrile neutropenia and two out of five patients had grade 4 neutropenia; however, this did not last for more than 4 days. One patient had grade 3 anemia but did not receive a blood transfusion. At level 2, one patient experienced febrile neutropenia and pneumonia.

Non-hematological toxicities were comparatively mild, except for diarrhea and pneumonitis. None of the patients experienced more than grade 3 non-hematological toxicities in the first course. All five patients at dose level 1 suffered from diarrhea, two patients experiencing grades 3 and 4. The patient with grade 3 water diarrhea, experienced on day 10, was accompanied by infection and required *i.v.* antibiotic therapy. The other patient with grade 4 diarrhea, experienced on day 5, required continuous *i.v.* hydration therapy. This patient was not able to receive CPT-11 from day 8 because of severe grade 4 diarrhea.

Eight out of eleven patients received two or more courses, but three patients did not receive the second course because two had severe water diarrhea and the other had febrile neutropenia. The toxicities following all courses are listed in Table V. The incidences of more than grade 3 leucopenia and neutropenia were 39.4% and

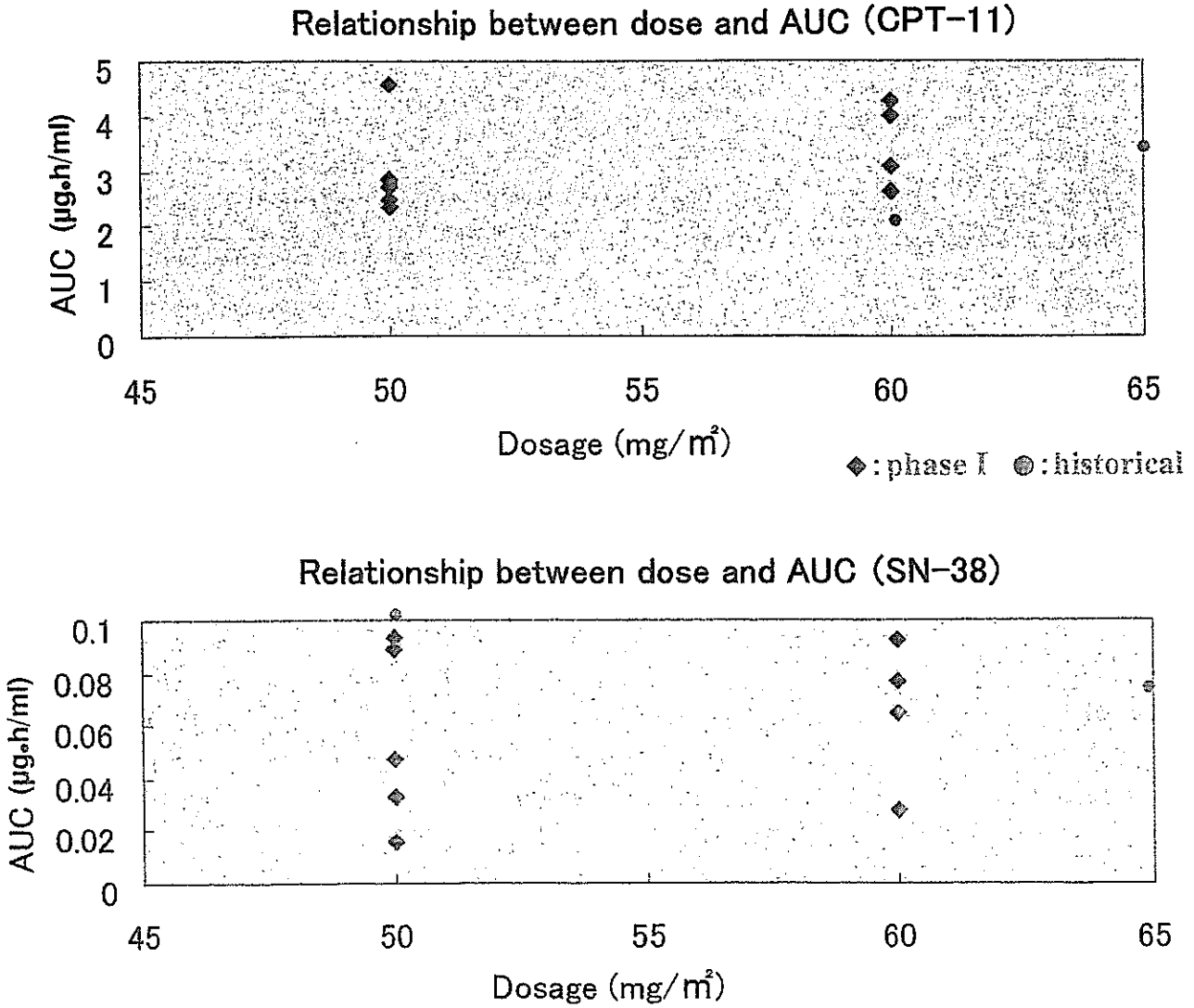

Figure 2. *Relationship between dose (mg/m^2) and area under the concentration-time curve (AUC) (μg•h/ml) of (A) irinotecan; (B) SN-38.*

54.5%, respectively, while that of febrile neutropenia was 21.2%. At level 2, two out of three patients suffered from grade 3 pneumonitis. Pneumonitis occurred during the second and third courses, respectively, which improved after the administration of steroid therapy. There was no treatment-related death.

MTD and DLTs. At level 1, all three patients had developed DLT for febrile neutropenia, with those showing grade 4 neutropenia lasting for more than 7 days. Therefore, the dosages of CPT-11 and AMR were changed to 60 mg/m^2 and 30 mg/m^2, respectively, as level 1. At level 1, three out of five patients had developed DLTs. Two patients experienced grades 3 and 4 diarrhea, while the other experienced a febrile neutropenia. In addition, the dosage of CPT-11 was decreased to 50 mg/m^2 as level 2. At level 2, one patient developed a DLT with febrile neutropenia. Two patients had not developed DLTs during their first courses; however, pneumonitis appeared after the second and third courses, respectively. Although pneumonitis is not a DLT according to conventional criteria, such pneumonitis events are included in the criteria of DLTs as they are fatal toxicities. Therefore, we were unable to establish the MTD and to determine the RD in this trial as all three levels were found to be intolerable.

Response. Nine patients were assessable for response. There were two partial responses, which included one patient with previously treated SCLC and the other with previously untreated NSCLC.

Table VIa. *C_{max}, AUC and clearance of plasma levels of amrubicin and metabolites.*

	30 mg/m^2 (mean)	40 mg/m^2 (mean)
No. of patients	6	3
AMR (plasma)		
C_{max} (μg/ml)	3735.5	3533.3
AUC (μg•h/ml)	2231.4	2235.1
CL (l/h/m^2)	15.29	18.33
AMR (blood cells)		
C_{max} (μg/g)	2582.8	2248.6
AUC (μg•h/g)	2035.7	2044.3
Metabolite (plasma)		
C_{max} (μg/ml)	29.9	21.4
AUC (μg•h/ml)	362.4	1036.1
Metabolite (blood cells)		
C_{max} (μg/g)	115.3	90.0
AUC (μg•h/g)	2368.3	1244.1

Table VIb. *C_{max}, AUC and clearance of plasma levels of CPT-11 and SN-38.*

	50 mg/m^2 (mean)	60 mg/m^2 (mean)
No. of patients	5	4
CPT-11		
C_{max} (μg/ml)	0.83	1.12
AUC (μg•h/ml)	3.01	3.489
CL (l/h/m^2)	17.65	17.89
SN-38		
C_{max} (μg/ml)	0.02	0.029
AUC (μg•h/ml)	0.05	0.066

C_{max}, concentration$_{max}$, CPT-11, irinotecan; AMR, amrubicin; AUC, area under the concentration-time curve; CL, clearance.

Pharmacokinetics. Plasma samples were obtained from nine patients during the first course. The relationships between the mean concentration-time curve of CPT-11, SN-38, AMR and amrubicinol are shown in Figures 1 and 2. The pharmacokinetic parameters derived from the plotted data are listed in Tables VIa and b. Though only two dose levels for CPT-11 and SN-38 were examined, there seemed to be a linear association between dose and AUC. However, no similar association was apparent for AMR and amrubicinol. Moreover, the PK parameters for AMR showed marked inter-patient variability.

Discussion

A phase I study was conducted regarding the combined use of CPT-11 and AMR, as a topo I and II inhibitor, respectively, for advanced lung cancer, which demonstrated that the combination of CPT-11 and AMR was inactive against both NSCLC and SCLC. It was indicated that the combination of CPT-11 and AMR is not tolerated. As this combination mediated an unexpectedly strong myelosuppressive effect, the MTD and the RD for combination therapy with CPT-11 and AMR could not be determined.

JCOG compared cisplatin plus CPT-11 with cisplatin plus etoposide within a standard regimen in patients with previously untreated ED-SCLC. The response rate and MST for the patients treated with cisplatin plus CPT-11 were 84.4% and 12.8 months, respectively, which are considered a good outcome. On the other hand, Masuda *et al.* conducted a phase II trial of CPT-11 and etoposide with rhG-CSF in patients with previously treated SCLC. The response rate was 71% and the MST was 8.9 months. CPT-11-containing regimens, such as CPT-11 plus cisplatin and etoposide, seem to generate high response rates for both previously treated and untreated patients with SCLC. Our study showed that only two out of eleven patients responded to treatment. The overall response rate of 18.1% was lower than expected. Of the four patients with previously untreated SCLC, only one responded to treatment. In the case of the SCLC patients, the response rate was 25%, but was 14.3% in the cohort of NSCLC patients. Although several recent trials have reported that the efficacy of a non-platinum regimen is equivalent to that of a platinum regimen for advanced NSCLC (12, 13), the results of the present study were disappointing. These response rates were lower than those found historically and than those shown in a phase II study of CPT-11 and AMR monotherapy. An attempt was made to rationalize the underlying basis of these phenomena. Firstly, it was reasoned that the combination therapy with CPT-11 and AMR did not appear to have an additive or synergistic effect. Secondly, the dosage of either drug was not increased since the effects of CPT-11 and AMR on myelosuppression overlapped when used in combination. In the present study, CPT-11 and AMR were used as a combination therapy to inhibit topo I and II. Preclinical and phase I studies have shown that the combined use of topo I and II inhibitors has a synergistic or antagonistic effect. Although cross-resistance between topo I and topo II inhibitors is uncommon in drug-resistant cell lines (14-16), topo I inhibitors were reported to have shown competitive activity in the presence of topo II inhibitors *in vitro* (6). Furthermore, the dose could not be increased since toxicity was marked at all dose levels. The most severe adverse reactions were bone marrow toxicities, particularly leucopenia and neutropenia, followed by infection, diarrhea and pneumonitis. The incidence of more than grade 3 leucopenia was 39% and that of neutropenia was 55%. Four out of eleven patients developed febrile neutropenia in the first course. At level 2, no DLTs occurred in the first course, but two patients experienced interstitial pneumonia in the second and third courses.

None of the patients with previously untreated SCLC were able to complete four courses of treatment. Several studies have investigated combination therapy with CPT-11 and etoposide and some have reported marked toxicity after simultaneous administration of the two drugs (17, 18). This suggests that, when using topo I and II inhibitors in combination, it may be better to administer the drugs sequentially rather than simultaneously. The present study supports these theories. Myelosuppression may be overcome with G-CSF. If G-CSF is used prophylactically, the adverse event of myelosuppression is surmountable, perhaps allowing dosage increases.

The PK investigation showed no difference in the AUC and C_{max} of CPT-11 and SN-38 when compared with historical data. Moreover, CPT-11 did not display a drug-drug interaction with AMR. The PK parameters for AMR showed marked inter-patient variability. The parameters in blood cells were measured since these cells contain the same reductase as found in tumors; however, no relationship between the PK, toxicity and efficacy data could be demonstrated. Although there was no correlation between the PK parameters and toxicity in this study, this schedule cannot be recommended. Future studies should investigate combination therapies with G-CSF or sequential administration.

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References

1 Wang JC: DNA topoisomerases. Annu Rev Biochem *54*: 665-697, 1985.
2 Van Maanen JM, Retel J, de Vries J and Pinedo HM: Mechanism of action of antitumor drug etoposide: a review. J Natl Cancer Inst *80*: 1526-1533, 1988.
3 Masuda N, Kudoh S and Fukuoka M: Irinotecan (CPT-11): pharmacology and clinical applications. Crit Rev Oncol Hematol *24*: 3-26, 1996.
4 Kano Y, Suzuki K, Akutsu M, Suda K, Inoue Y, Yoshida M, Sakamoto S and Miura Y: Effects of CPT-11 in combination with other anti-cancer agents in culture. Int J Cancer *50*: 604-610, 1992.
5 D'Arpa P, Beardmore C and Liu LF: Involvement of nucleic acid synthesis in cell killing mechanisms of topoisomerase poisons. Cancer Res *50*: 6919-6924, 1990.
6 Kaufmann SH: Antagonism between camptothecin and topoisomerase II-directed chemotherapeutic agents in a human leukemia cell line. Cancer Res *51*: 1129-1136, 1991.
7 Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Negoro S, Nishioka M, Nakagawa K and Takada M: CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol *10*: 1225-1229, 1992.
8 Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S and Masuda N: A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol *10*: 16-20, 1992.
9 Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T and Saijo N: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. New Engl J Med *346*: 85-91, 2002.
10 Kubota K, Nishiwaki Y, Ohashi Y, Saijo N, Ohe Y, Tamura T, Negoro S, Ariyoshi Y, Nakagawa K and Fukuoka M: The Four-Arm Cooperative Study (FACS) for advanced non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 22: 7006a, 2004.
11 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst *92*: 205-216, 2000.
12 Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas Ph and Vlachonikolis I: Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomized multicenter trial. Lancet *357*: 1478-1484, 2001.
13 Pectasides D, Mylonakis N, Farmakis D, Nikolaou M, Koumpou M, Katselis I, Gaglia A, Kostopoulou V, Karabelis A and Kosmas C: Irinotecan and gemcitabine in patients with advanced non-small-cell lung cancer, previously treated with cisplatin-based chemotherapy. A phase II study. Anticancer Res *23*: 4205-4211, 2003.
14 Ferguson PJ, Fisher MH, Stephenson J, Li DH, Zhou BS and Cheng YC: Combined modalities of resistance in etoposide-resistant human KB cell lines. Cancer Res *48*: 5956-5964, 1988.
15 Matsuo K, Kohno K, Takano H, Sato S, Kiue A and Kuwano M: Reduction of drug accumulation and DNA topoisomerase II activity in acquired teniposide-resistant human cancer KB cell lines. Cancer Res *50*: 5819-5824, 1990.
16 Tsuruo T, Matsuzaki T, Matsushita M and Yokokura T: Anticancer effect of CPT-11, a new derivative of camptothecin, against pleiotropic drug-resistant tumors *in vitro* and *in vivo*. Cancer Chemother Pharmacol *21*: 71-74, 1988.
17 Karato A, Sasaki Y, Shinkai T, Eguchi K, Tamura T, Ohe Y, Oshita F, Nishio M, Kunikane H and Arioka H: Phase I study of CPT-11 and etoposide in patients with refractory solid tumors. J Clin Oncol *11*: 2030-2035, 1993.
18 Oshita F, Noda K, Nishiwaki Y, Fujita A, Kurita Y, Nakabayashi T, Tobise K, Abe S, Suzuki S, Hayashi I, Kawakami Y, Matsuda T, Tsuchiya S, Takahashi S, Tamura T and Saijo N: Phase II study of irinotecan and etoposide in patients with metastatic non-small-cell lung cancer. J Clin Oncol *15*: 304-309, 1997.

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Phase I and Pharmacokinetic Study of Combination Chemotherapy Using Irinotecan and Paclitaxel in Patients with Lung Cancer

Gyo Asai, MD, PhD, Nobuyuki Yamamoto, MD,* Takayasu Kurata, MD, PhD,† Kenji Tamura, MD,† Hisao Uejima, MD, PhD,† Kazuhiko Nakagawa, MD, PhD,† and Masahiro Fukuoka, MD, PhD†*

The purpose of this study was to investigate the maximum tolerated doses, dose-limiting toxicities, efficacy, and pharmacokinetic profiles in the combination of irinotecan and paclitaxel. Eligibility criteria included age 75 years or younger, good performance status, adequate organ function, and unresectable non–small cell or extensive disease of small cell lung cancer. Irinotecan was administered on days 1 and 8 over 90 minutes, and paclitaxel was administered on day 8 over 3 hours after 90 minutes from the end of the irinotecan infusion. Irinotecan and paclitaxel were dose-escalated from 40 and 135 mg/m^2 and repeated every 4 weeks. The authors also administered a higher dosage with preventive granulocyte colony-stimulating factor support from day 9. Thirty-one patients were assessed for toxicities and responses. Dose-limiting toxicities were neutropenia and febrile neutropenia. The dose of irinotecan 60 mg/m^2 and paclitaxel 200 mg/m^2 with preventive granulocyte colony-stimulating factor support was tolerable and suitable for a phase II trial. Nine of 25 (36%) patients with non–small cell and all six patients with small cell carcinoma achieved partial response. The areas under the concentration versus time curves of irinotecan and its metabolites on day 8 were significantly higher than on day 1. This combination therapy must be planned only after careful consideration of the drug–drug interaction.

Key Words: Lung cancer, Irinotecan, Paclitaxel, Phase I, Pharmacokinetics.

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Chemotherapy for non–small cell lung cancer (NSCLC) has recently improved survival by using platinum compounds and new drugs (e.g., vinorelbine, gemcitabine, taxanes, and irinotecan).[1] Chemotherapy for extensive disease of small cell carcinoma (ED-SCLC) has also improved survival using cisplatin and irinotecan.[2] Although these regimens statistically improved survival, the benefits are far from satisfactory. There are comparatively few reports of nonplatinum regimens, and we do not have sufficient knowledge about these regimens regarding maximum tolerated doses (MTD), toxicities, responses, and pharmacokinetic profiles. However, irinotecan and paclitaxel have shown antitumor activity for both non–small cell and small cell carcinoma as a single agent.[3–6] This combination is also reported to have additive or supra-additive antitumor effects for lung cancer cells in vitro by using an isobologram.[7,8] Therefore, we conducted this combination phase I study to evaluate MTD, dose-limiting toxicities (DLTs), and pharmacokinetics in this combination therapy. We also evaluated the response rate and pharmacokinetic profiles.

Before planning this study, we performed this combination trial by another administration schedule.[9] In the prior trial, irinotecan was administered over 90 minutes on days 1, 8, and 15 and paclitaxel was given by infusion over 3 hours on day 2. Starting doses of irinotecan and paclitaxel were 50 and 135 mg/m^2, respectively. DLTs were neutropenia and febrile neutropenia, and MTD was the starting dose. Furthermore, most of the patients could not receive irinotecan on days 8 and 15 because of neutropenia. Although the neutropenia from this combination regimen was intolerable, an antitumor response was seen in the majority of the patients, suggesting that this combination might provide good antitumor activity and that an alternative administration schedule was needed to use these drugs. In this new trial, we therefore modified the administration schedule to escalate dose intensity while avoiding severe toxicities.

PATIENTS AND METHODS

Patient Selection

Patients with unresectable NSCLC or ED-SCLC were eligible for the trial. Pathologic confirmation and assessable lesions were necessary before study entry. Previous chemotherapy or radiotherapy, if given, must have been completed at least 4 weeks before entry. Other eligibility criteria included age 20 to 75 years, Eastern Cooperative Oncology Group performance status of 0 to 1, estimated life expectancy of at least 3 months, and adequate organ function defined as follows: white blood cell count greater than or equal to 4000 cells/μl, absolute neutrophil count greater than or equal to

*Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka; and †Department of Medical Oncology, Kinki University School of Medicine, Osaka, Japan.

Address for correspondence: Gyo Asai, MD, PhD, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi, Sunto-gun, Shizuoka 411-8777, Japan; email: gyoa@gmx.net.

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2000 cells/μl, platelet count greater than or equal to 100,000 cells/μl, serum creatinine less than or equal to 1.2 mg/dL, bilirubin less than or equal to 1.5 mg/dL, serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) less than twice the upper limit of normal, and PaO_2 greater than or equal to 60 mmHg. Patients with interstitial pneumonia, active infection, unstable cardiac disease, uncontrolled diabetes mellitus, pleural or cardiac effusion that required drainage, or symptomatic brain metastasis were ineligible. Our hospital institutional review committee approved this study, and all patients provided written informed consent.

Treatment

Irinotecan was administered on days 1 and 8 over 90 minutes, and paclitaxel was administered on day 8 over 3 hours after 90 minutes from the end of irinotecan infusion (Figure 1). All patients received premedication for paclitaxel and vomiting. The treatment was repeated every 4 weeks. The latter therapy was permitted using preventive granulocyte colony-stimulating factor (G-CSF) support from day 9 if patients experienced DLT of leukopenia or neutropenia and achieved partial response or stable disease on the previous course. The criteria for administration on day 8 were white blood cell count greater than or equal to 3000 cells/μl and other eligibility criteria before study entry. If patients did not clear this criteria for day 8, their treatment was cancelled and they were excluded from the evaluation of toxicities and responses.

Dose Escalation

The dose escalation schedule is shown in Table 1. Evaluation of DLTs for dose escalation was performed for the first course of chemotherapy. DLTs were defined using National Cancer Institute Common Toxicity Criteria (version 2.0)[10] as grade 4 neutropenia lasting 5 days or more, other grade 4 hematologic toxicities, neutropenic fever, or grades 3 and 4 toxicities in other organ systems except for nausea and vomiting. Three patients were assigned to each dose level. When all three patients did not experience DLT, we shifted to the next dose level. If one or two patients experienced DLT, an additional three patients were entered at the dose level before dose escalation. When at least three patients were found to have DLT, the dose was defined as the MTD. After the MTD was determined without preventive G-CSF support, we continued this study with preventive G-CSF support from day 9 until the recovery of neutropenia. We permitted the latter therapy by using preventive G-CSF support if patients who experienced DLT achieved stability or a partial response. Intrapatient dose escalation was not permitted. World Health Organization tumor evaluation criteria were used for tumor response evaluation.[11,12]

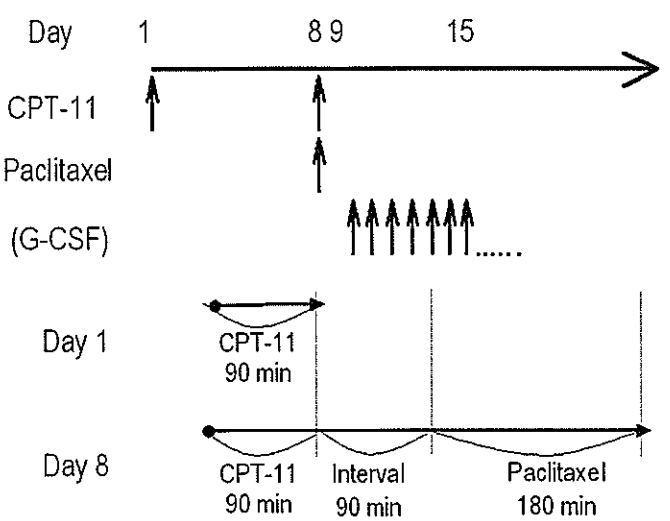

FIGURE 1. Treatment schedule of irinotecan and paclitaxel.

TABLE 1. Dose Escalation Schedule

Dose Level	CPT-11 (mg/m²)	Paclitaxel (mg/m²)
1	40	135
2	50	135
3	60	135
4	60	150
5	60	175
6	60	200

CPT-11, irinotecan.

Pharmacokinetic Analysis

Blood samples for pharmacokinetic analysis were obtained on days 1 and 8 in the first course. We collected samples by means of a peripheral venous catheter at the following times from the end of irinotecan infusion: 0, 15, 30, 90, 180, 240, 300, 420, 540, and 1410 minutes on day 1; and 0, 15, 30, 90, 180, 240, 270, 285, 300, 360, 420, 540, 630, and 1410 minutes on day 8, respectively. To analyze the pharmacokinetics of paclitaxel and the influence on the pharmacokinetics of irinotecan by paclitaxel, several processes were

TABLE 2. Patient Characteristics

Characteristic	Value
No. of patients enrolled	31
Median age (range) (yr)	62 (36–75)
Sex	
Male	23
Female	8
PS	
0	4
1	27
Prior chemotherapy	
Yes	2
No	29
Type of lung cancer	18
Adenocarcinoma	6
Squamous cell carcinoma	1
Large cell carcinoma	6
Small cell carcinoma	
Median no. of courses (range)	2 (1–5)

PS, performance status.

TABLE 3. Major Toxicities

	Level 1	Level 2	Level 3	Level 3' (G-CSF)	Level 4 (G-CSF)	Level 5 (G-CSF)	Level 6 (G-CSF)
No. of patients	3	6	3	2* + 1	6	6	6
Neutropenia							
G3	1	0	0	1	2	0	1
G4 (<5 days)	1	4	3	1	2	2	1
G4 (≥5 days)	0	0	0	0	0	0	0
Neutropenic fever	0	1	2*	0	1	1	1
AST or ALT							
G2	0	0	0	0	0	0	0
G3	0	1	0	0	0	0	0
Diarrhea							
G2	0	1	1	0	1	0	1
G3	0	0	0	0	0	1	0
DLT patients	0	2	2*	0	1	2	1

*Two patients who had neutropenic fever in level 3 were treated with preventive G-CSF support in second courses as level 3'. Level 3' was tolerable for them. G, National Cancer Institute Common Toxicity Criteria grade; DLT, dose-limiting toxicity.

added on day 8. Heparinized tubes were used, and the plasma was immediately separated by centrifugation and stored at −20°C until analysis. Plasma concentrations of irinotecan, its metabolites (SN-38 and SN-38G), and paclitaxel were measured using high-performance liquid chromatography on the reported conditions.[13,14]

The area under the plasma concentration-time curve (AUC) of irinotecan, its metabolites, and paclitaxel were calculated by the trapezoidal method with extrapolation to infinity using WinNonlin (version 1.1; Scientific Consulting, Inc., Apex, NC).

The AUC of irinotecan, SN38, and SN-38G on day 1 were compared with those on day 8 using paired *t* test and Wilcoxon matched-pairs signed ranks test. Clearance of paclitaxel was compared with reported data in monotherapy.

RESULTS

Patient Characteristics

Twenty-six men and eight women were enrolled in the study and were treated between March of 1999 and November of 2002 at Kinki University Hospital in Osaka, Japan. Two men in level 3 and one man in level 4 were excused because of the criteria for administration of day 8. One showed grade 3 elevation of ALT and ileus, another showed grade 2 elevation of ALT, and the other exhibited grade 2 rash. These patients were excluded from evaluation of toxicities and responses at each dose escalation. Finally, 31 patients were evaluated for their toxicities and responses, and blood samples were drawn on both day 1 and day 8 from 31 patients. The characteristics of the 31 patients are listed in Table 2.

Toxicities and Dose Escalation

Major toxicities are hematologic toxicities, diarrhea, and elevation of AST and ALT. Other nonhematologic toxicities are mild. Details are listed in Table 3. In level 2, one patient developed grade 3 liver dysfunction and the other developed neutropenic fever. In level 3, all patients developed grade 4 neutropenia and two of three patients developed neutropenic fever. Although level 3 had not reached the definition of MTD at this point, we judged that the dose of level 3 was probably MTD, and that further continuation of level 3 was dangerous. However, two patients who had neutropenic fever did not develop DLT in the second course of level 3 with preventive G-CSF support. We decided, therefore, to continue this study with preventive G-CSF support from level 3. One patient added to level 3 with preventive G-CSF support did not develop DLT. Most patients received second or later courses on schedule in each level. Although the schedules were delayed in a few patients, the reasons were not toxicities. This study was subsequently continued until level 6, and the dose did not reach the MTD with preventive G-CSF support. Although level 6 with G-CSF support was tolerable, this phase I study was discontinued because each dose was close to the recommended dose for monotherapy in Japan. We estimated that the recommended dose for phase II study was irinotecan 60 mg/m^2 (days 1 and 8) and paclitaxel 200 mg/m^2 (day 8) with preventive G-CSF support from day 9.

TABLE 4. Tumor Responses

Level	Patients	PR	SD	PD
1	3		3	
2	6	2 + 1*	2	1
3	4	1	1	2
4	6	0 + 3*	2	1
5	6	4 + 2*		
6	6	2	2	2

*Patients with ED-SCLC. †NSCLC (25 patients): PR, 9 (36%; 95% CI, 18–57%). ED-SCLC (6 patients): PR, 6 (100%; 95% CI, 61–100%). PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

TABLE 5. Comparison of AUCs of Day 1 and Day 8

	CPT-11	SN-38	SN-38G
Average (μg/min/ml) ± SD			
Day 1	223.3 ± 73.6	5.92 ± 5.30	70.24 ± 70.40
Day 8 (with paclitaxel)	296.3 ± 92.0	8.31 ± 7.13	102.71 ± 123.14
Paired *t* test (*p* value)	<0.0001	0.0271	0.0136
Wilcoxon matched-pairs signed ranks test (*p* value)	<0.0001	0.0044	0.0001

SD, standard deviation; CPT-11, irinotecan.

Tumor Responses

Nine of 25 (36%) patients with NSCLC achieved partial response, and all six patients with ED-SCLC achieved partial response (Table 4).

Pharmacokinetics

Pharmacokinetic analyses were conducted on 31 patient blood samples. AUCs of irinotecan and its metabolites on day 8 were significantly higher than on day 1 (Table 5). Clearance of paclitaxel (day 8) was 14.3 ± 5.3 liters/hr/m^2.

DISCUSSION

Several other studies of this combination were reported.[15–17] Both paclitaxel and irinotecan were administered weekly in some studies, and patients were given paclitaxel on day 1 and irinotecan on days 1, 8, and 15 in some studies. DLTs and other major toxicities were hematotoxicities and diarrhea. These toxicities were similar to those in this study. Administration of irinotecan on day 8 or 15 was generally skipped in the weekly schedule, or administration of paclitaxel on day 1, because of hematotoxicities. This study schedule was designed to avoid skipping administration on day 8 and to elevate dose intensity and its efficacy by using G-CSF without any risky administration on day 15. Other studies did not increase the dosage with G-CSF and did not treat patients with ED-SCLC. This combination showed comparatively stronger hematologic toxicity than the other platinum combination regimens or nonplatinum regimens as indicated from our results and the other reports on this combination.

Platinum-based combinations with third-generation drugs are standard regimens in the treatment of advanced NSCLC.[1,18,19] However, a recent meta-analysis has reported that 1-year survival was not significantly prolonged when platinum-based therapies were compared with third-generation–based combination regimens.[20] Platinum-free doublet regimens are expected to offer improved survival without decreasing quality of life. Although this trial showed a response rate similar to other nonplatinum regimens, hematotoxicities were stronger than those of the other regimens. Therefore, this combination therapy might not be suitable for the treatment of NSCLC.

In the treatment of small cell lung cancer, the regimen of cisplatin and irinotecan ensures better survival than the regimen of cisplatin and etopside.[2] There have been very few reports of platinum-free doublet regimens based on third-generation drugs in small cell lung cancer. The response rate of this study regimen was noteworthy. Although the number of patients with small cell carcinoma was limited, all patients achieved partial response (95% confidence interval, 61–100%). This combination showed similar or better response than the combination of cisplatin and etoposide, and this regimen might be as effective as the combination of cisplatin and irinotecan. Therefore, this combination is proposed as an attractive regimen for small cell lung cancer chemotherapy.

In this trial, three persons were withdrawn from treatment by the criteria of day 8 and thus excluded from evaluation. We know from our previous study that this combination may cause severe neutropenia and that some patients occasionally show stronger toxicities for irinotecan than most. For example, it has been suggested that the polymorphism of UDP-glucuronosyltransferase might raise severe toxicities.[21,22] If only single administration of low-dose irinotecan produced toxicities that conflicted with the criteria of day 8, we can regard that patient as an anomaly regarding irinotecan. At this point, our administration schedule seems to be safe for this combination.

In the pharmacokinetic study, AUCs of irinotecan and its metabolites on day 8 were significantly higher than those of day 1. Clearance of paclitaxel was similar to that in many previously reported studies. We observed a 90-minute interval between irinotecan infusion and paclitaxel infusion to avoid severe drug interactions. We concluded that the mechanism of drug elimination is competitive because we had found indications of interaction from the pharmacokinetic investigation in our previous study. Irinotecan and its metabolite are mainly excreted by P-glycoprotein and cMORT in the liver, and paclitaxel or its vehicle (Cremophor EL) will compete in some stage of excretion. Noninterval administration of paclitaxel and irinotecan would heighten the AUC and the risk of toxicities. It has been advised in phase II trials that the administration time schedule of a phase I study be retained because it is very likely that the MTDs are different in each administration schedule. If the interval between irinotecan and paclitaxel administration is shorter or the order of administration is reversed, the possible pharmacokinetic interaction and toxicities might be much stronger. This combination therapy must be planned carefully with due consideration of the drug–drug interaction.

REFERENCES

1. Baggstrom MQ, Socinski MA, Hensing TA, et al. Third generation chemotherapy regimens (3GR) improve survival over second generation

regimens (2GR) in stage IIIB/IV non-small cell lung cancer (NSCLC): a meta-analysis of the published literature (Abstract). *Proc Am Soc Clin Oncol* 2002; 21: 306a.
2. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
3. Fukuoka M, Niitani H, Suzuki A, et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* 1992;10:16–20.
4. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992;10:1225–1229.
5. Murphy WK, Fossella FV, Winn RJ, et al. Phase II study of taxol in patients with untreated advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1993;85:384–388.
6. Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *Br J Cancer* 1998;77:347–351.
7. Kano Y, Akutsu M, Tsunoda S, et al. In vitro schedule-dependent interaction between paclitaxel and SN-38 (the active metabolite of irinotecan) in human carcinoma cell lines. *Cancer Chemother Pharmacol* 1998;42:91–98.
8. Pei XH, Nakanishi Y, Takayama K, et al. Effect of CPT-11 in combination with other anticancer agents in lung cancer cells. *Anticancer Drugs* 1997;8:231–237.
9. Yamamoto N, Negoro S, Chikazawa H, et al. Pharmacokinetic interaction of the combination of paclitaxel and irinotecan in vivo and clinical study (Abstract). *Proc Am Soc Clin Oncol.* 1999; 18: 718.
10. National Cancer Institute. Cancer Evaluation Reporting Program [Web site]. Available at: http://ctep.cancer.gov/reporting/ctc.html. Accessed .
11. WHO Handbook for Reporting Results for Cancer Treatment. Geneva, Switzerland: World Health Organization Offset Publication No. 48, 1979.
12. Miller AB, Hogestraeten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
13. Grem JL, Tutsch KD, Simon KJ, et al. Phase I study of taxol administered as a short i.v. infusion daily for 5 days. *Cancer Treat Rep* 1987;71:1179–1184.
14. Kurita A, Kaneda N. High-performance liquid chromatographic method for the simultaneous determination of the camptothecin derivative irinotecan hydrochloride, CPT-11, and its metabolites SN-38 and SN-38 glucuronide in rat plasma with a fully automated on-line solid-phase extraction system, PROSPEKT. *J Chromatogr B Biomed Sci Appl* 1999;724:335–344.
15. Murren JR, Peccerillo K, DiStasio SA, et al. Dose escalation and pharmacokinetic study of irinotecan in combination with paclitaxel in patients with advanced cancer. *Cancer Chemother Pharmacol* 2000;46: 43–50.
16. Kasai T, Oka M, Soda H, et al. Phase I and pharmacokinetic study of paclitaxel and irinotecan for patients with advanced non-small cell lung cancer. *Eur J Cancer* 2002;38:1871–1878.
17. Hotta K, Ueoka H, Kiura K, et al. A phase I study and pharmacokinetics of irinotecan (CPT-11) and paclitaxel in patients with advanced non-small cell lung cancer. *Lung Cancer* 2004;45:77–84.
18. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
19. Kubota K, Nishiwaki Y, Ohashi Y, et al. The Four-Arm Cooperative Study (FACS) for advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2004; 22:618s.
20. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2006;23: 2926–2936.
21. Ando Y, Saka H, Asai G, et al. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. *Ann Oncol* 1998;9:845–847.
22. Ando Y, Saka H, Ando M, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res* 2000;60:6921–6926.