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Relationship between the Pharmacokinetics of Irinotecan and Diarrhea during Combination Chemotherapy with Cisplatin

Shinzoh Kudoh,[1] Masahiro Fukuoka,[2] Noriyuki Masuda,[1] Atsuko Yoshikawa,[1] Yoko Kusunoki,[1] Kaoru Matsui,[1] Shun-ichi Negoro,[2] Nobuhide Takifuji,[2] Kazuhiko Nakagawa,[1] Tomonori Hirashima,[1] Takashi Yana[1] and Minoru Takada[1, 3]

[1]Department of Internal Medicine, Osaka Prefectural Habikino Hospital, 3-7-1 Habikino, Habikino 583 and [2]Department of Internal Medicine, Osaka Municipal Momoyama Citizen's Hospital, 2-25 Fudegasakicho, Tennoji-ku, Osaka 543

Two phase I trials of irinotecan (CPT-11) in combination with cisplatin were conducted. In both cases, the dose-limiting toxicities were leukopenia and/or diarrhea. During these trials the pharmacokinetics of CPT-11 and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), were investigated to evaluate the relationship between pharmacokinetic parameters and diarrhea, since this is an unpredictable and severe toxicity of combination chemotherapy using CPT-11 and cisplatin. Twenty-three previously untreated patients with advanced lung cancer were evaluated in the pharmacokinetic study. Ten patients received CPT-11 at 80 or 90 mg/m² plus cisplatin at 60 mg/m². The other 13 patients received CPT-11 at 80 or 90 mg/m² plus cisplatin at 80 mg/m² with the granulocyte colony-stimulating factor support (2 μg/kg × 16 days). CPT-11 was given as a 90-min intravenous infusion on days 1, 8, and 15. Cisplatin was given on day 1. The pharmacokinetics of CPT-11 and SN-38 were analyzed on day 8 during the first course of treatment. The maximum tolerated dose of CPT-11 was 90 mg/m² in both phase I trials. The severity of diarrhea was best correlated with the peak plasma concentration of SN-38 among the pharmacokinetic parameters tested. In addition, patients with a plasma SN-38 level >12.4 ng/ml at 1.75 h after the start of CPT-11 infusion had a higher incidence of Eastern Cooperative Oncology Group grade 3–4 diarrhea than those with a lower SN-38 level ($P=0.0003$). Stepwise logistic regression analysis identified the SN-38 concentration as a significant contributor to the development of diarrhea ($P=0.0021$). We conclude that there is a clear relationship between the SN-38 concentration and diarrhea during chemotherapy with CPT-11 plus cisplatin.

Key words: CPT-11 — Pharmacokinetics — Diarrhea

CPT-11 is a water-soluble semisynthetic derivative of camptothecin, an antitumor alkaloid isolated from *Camptotheca acuminata*.[1, 2] The molecular target of CPT-11 has been identified as DNA topoisomerase I, a nuclear enzyme implicated in DNA replication and transcription.[3–7] The mechanism of topoisomerase I inhibition involves the formation of a reversible enzyme-drug-DNA ternary complex. Preclinical studies of CPT-11 have demonstrated a strong antitumor activity of this agent in a variety of experimental tumor models.[2, 8] Phase I studies identified leukopenia and diarrhea as the dose-limiting toxicities.[9–13] In phase II trials, CPT-11 has also been found to be active against carcinoma of the lung,[14–16] cervix,[17] ovary,[18] and colon and rectum[19] as well as against leukemia and lymphoma.[20]

Enhancement of *in vitro* and *in vivo* antitumor activity was observed when CPT-11 was administered in combination with cisplatin or etoposide in our preclinical studies.[21, 22] We performed three phase I trials of escalating doses of CPT-11 combined with a fixed dose of cisplatin in patients with advanced non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[23–25] The major dose-limiting toxicities of this combination chemotherapy were also diarrhea and/or leukopenia, and marked interpatient variability of these toxicities was observed. The prediction of toxicity, especially diarrhea, was very difficult. We therefore undertook a pharmacokinetic study of CPT-11 and its active metabolite, SN-38, to evaluate whether there was a relationship between any pharmacokinetic parameters and diarrhea during combination chemotherapy with CPT-11 and cisplatin.

PATIENTS AND METHODS

Patients Patients with previously untreated histologically proven stage IIIB or IV lung cancer were entered into this study. The eligibility criteria have been described previously.[25] In brief, they were (1) an age ≤75 years, (2) a performance status (PS) of 2 or better on the Eastern Cooperative Oncology Group (ECOG) scale, and (3) adequate organ function (leukocyte count ≥4,000/μl, platelet count ≥100,000/μl, hemoglobin ≥9

[3] To whom requests for reprints should be addressed.

g/dl, bilirubin $\leq$1.5 mg/dl, transaminases $\leq$ twice the upper limit of normal, creatinine $\leq$1.4 mg/dl, 24-h creatinine clearance $\geq$60 ml/min). All subjects gave written informed consent to the study. Patients underwent staging evaluation as described previously.[25] Prior to the first course of treatment, a complete blood count (including a differential white cell count and platelet count), biochemistry tests (renal and hepatic function, and electrolytes), and urinalysis were performed. The blood count, biochemistry tests, urinalysis, and chest X-ray were repeated at least once a week after this initial evaluation. Other investigations were repeated as necessary to evaluate marker lesions. After the completion of chemotherapy, each patient was restaged with all the tests used during the initial work-up. The eligibility, evaluability, and response of each patient were assessed by extramural review. Tumor response and the duration of each response were evaluated. ECOG common toxicity criteria were used to grade organ damage.

Treatment schedule Cisplatin was administered intravenously on day 1 at a fixed dose of 60 mg/m^2 (in the first phase I trial), or 80 mg/m^2 (second trial). Escalating doses of CPT-11 (60, 70, 80, or 90 mg/m^2) were given intravenously on days 1, 8, and 15, and the regiman was repeated every 28 days. CPT-11 (Daiichi Pharmaceutical Co., Ltd. and Yakult Honsha Co., Ltd., Tokyo) was dissolved in 500 ml of normal saline and given as a 90-min intravenous infusion, while cisplatin was given intravenously over 30 min at 2 h after CPT-11 administration. To avoid cisplatin-induced renal damage, patients were intravenously hydrated on day 1 with 2,600 ml of 5% dextrose in 0.45% sodium chloride, and diuresis was induced with mannitol and furosemide. Intravenous hydration with 800 ml of 5% dextrose in 0.45% sodium chloride was continued for another 48 h.

Pharmacokinetics The pharmacokinetics of CPT-11 and SN-38 were analyzed on day 8 of the first course of treatment. Heparinized blood samples (2 ml) for the preparation of plasma were obtained before infusion, at 30 and 60 min of infusion, at the end of infusion, and at 5, 15, and 30 min as well as 1, 2, 4, 8, 10, and 24 h after the end of infusion. The samples were immediately centrifuged and the plasma thus obtained was stored frozen at -20°C until analysis. Plasma CPT-11 and SN-38 concentrations were determined according to the method of Kaneda *et al.*[1] using high-performance liquid chromatography. The limit of determination was about 1 ng/ml for CPT-11 and about 5 ng/ml for SN-38. The linearity of the calibration curves was very good. The coefficients of correlation were more than 0.999 and the coefficients of variation were less than 7 %, both intraday and interday. Pharmacokinetic parameters were calculated by fitting the plasma concentration data to a two-compartment model. The area under the curve for plasma concentration versus time (AUC) was calculated by use of the trapezoidal rule from time zero to the last data point, and then was extrapolated to infinity with a terminal rate elimination constant. The significance of differences in the pharmacokinetic parameters was determined by using the unpaired Student's t test. Other statistical analysis was performed using Fisher's exact probability test. All reported P values were based on two-tailed statistical tests. Multivariate analysis using a logistic regression model was performed to select the subset of variables most closely related to ECOG grade 3–4 diarrhea.

RESULTS

From July 1991 to November 1992, we conducted two dose escalation studies of CPT-11 in combination with cisplatin.[24, 25] A total of 34 patients were entered into both studies and the pharmacokinetics of CPT-11 were studied in 23 of them (Table I). Ten patients received CPT-11 plus 60 mg/m^2 of cisplatin without granulocyte colony-stimulating factor (G-CSF) support and 13 patients received CPT-11 plus 80 mg/m^2 of cisplatin with G-CSF support. Pharmacokinetic studies were only performed in patients receiving 80 and 90 mg/m^2 of CPT-11. The mean plasma elimination curves for CPT-11 and SN-38 are shown in Fig. 1. The plasma concentration of CPT-11 rose progressively during drug infusion, after which it decayed in a biexponential fashion. The terminal half-life of CPT-11 at doses of 80 and 90 mg/m^2 was 13.38$\pm$8.74 h (range: 3.35–31.12 h) and 15.21$\pm$10.90 h (range: 6.01–41.39 h), respectively. The peak plasma concentration (C_{max}) at doses of 80 and 90 mg/m^2 was achieved at 1.363 h (range: 1.00–1.583 h) and 1.213$\pm$0.275 h (range: 1.00–1.583 h), respectively, which was approximately the end of the infusion. SN-38 was rapidly formed from the parent compound, but the C_{max} was observed at different points and 14 patients had two

Table I. Characteristics of Patients

		CPT-11+cisplatin	CPT-11+cisplatin+G-CSF
No. of patients		10	13
Male/Female		7/3	9/4
ECOG PS 0–1/2		7/3	12/1
Median age (range)		60 (43–71)	59 (44–66)
Tumor type			
NSCLC/SCLC		8/2	13/0
Stage IIIB/IV		5/5	2/11
CPT-11 dose	80 mg/m^2	7	7
	90 mg/m^2	3	6

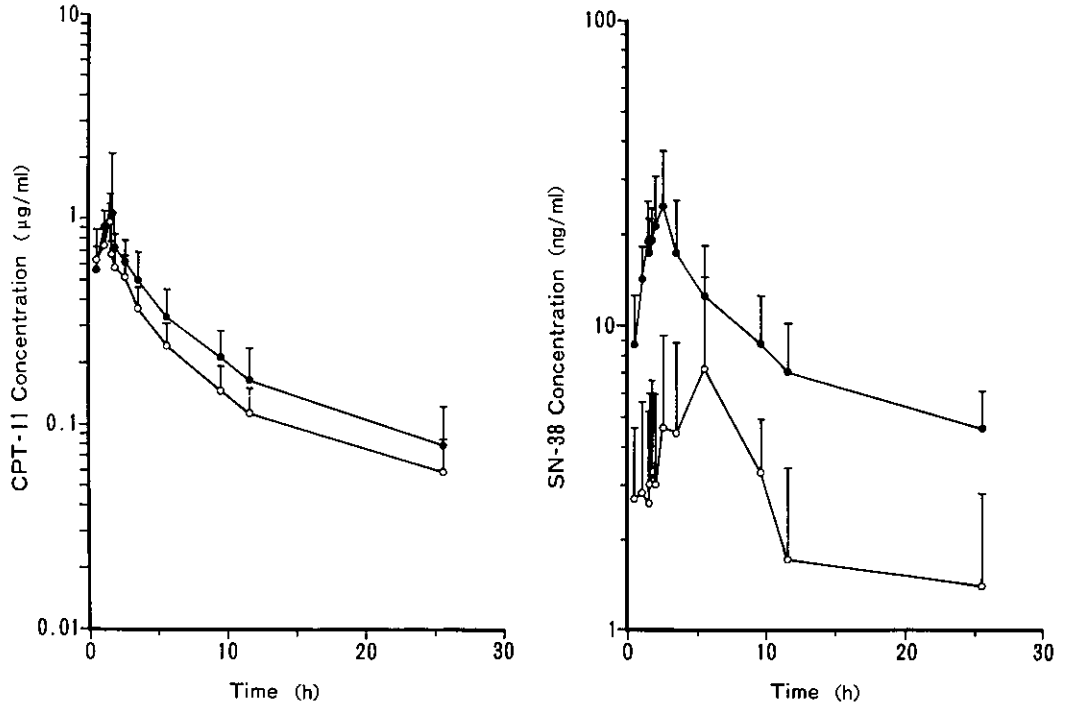

Fig. 1. Mean plasma disposition curves of CPT-11 and SN-38 in patients treated at 80 mg/m^2 (○) or 90 mg/m^2 (●). Data points are the mean+SD.

Table II. Pharmacokinetic Parameters of CPT-11 and SN-38

	CPT-11		SN-38	
(mg/m^2)	80	90	80	90
C_{max}[a] (ng/ml)	1016±211[b]	1330±906	15.70±6.15*	27.78±11.85*
C_{max} time (h)	1.363±0.239	1.231±0.275	2.855±1.389	2.416±0.707
$t_{1/2}$[c] (h)	13.38±8.74	15.21±10.90	20.83±12.30	21.82±12.32
$AUC_{0-25.5}$[d] (ng h/ml)	4336±1736	6886±3819	136.22±53.68**	258.36±122.26**
$AUC_{0-\infty}$[e] (ng h/ml)	6137±1581	8.847±5.467		
CL_t[f] (liter/h/m^2)	14.53±5.32	12.65±5.14		
V_d[g] (liter/m^2)	241.32±131.89	226.57±84.88		

a) Peak plasma concentration.
b) Values are mean±SD.
c) Half-life of terminal phase.
d) Area under the curve for plasma concentration of drug×time between 0 and 25.5 h from the start of drug infusion.
e) Area under the curve for plasma concentration of drug×time from 0 h (start of infusion) to infinity.
f) Total body clearance.
g) Volume of distribution.
*P=0.0041, **P=0.0031.

peaks of SN-38. At doses of 80 and 90 mg/m^2, the C_{max} of SN-38 was seen at 2.855±1.389 h (range: 1.00–5.50 h) and 2.418±0.707 h (range: 1.50–3.50 h), respectively. The elimination curve for SN-38 was fitted by a one-compartment model at each dose of CPT-11. The plasma concentration of SN-38 decreased more slowly than that of CPT-11, with a terminal half-life of 20.83±12.30 h (range: 7.42–45.62 h) at a dose of 80 mg/m^2. When the

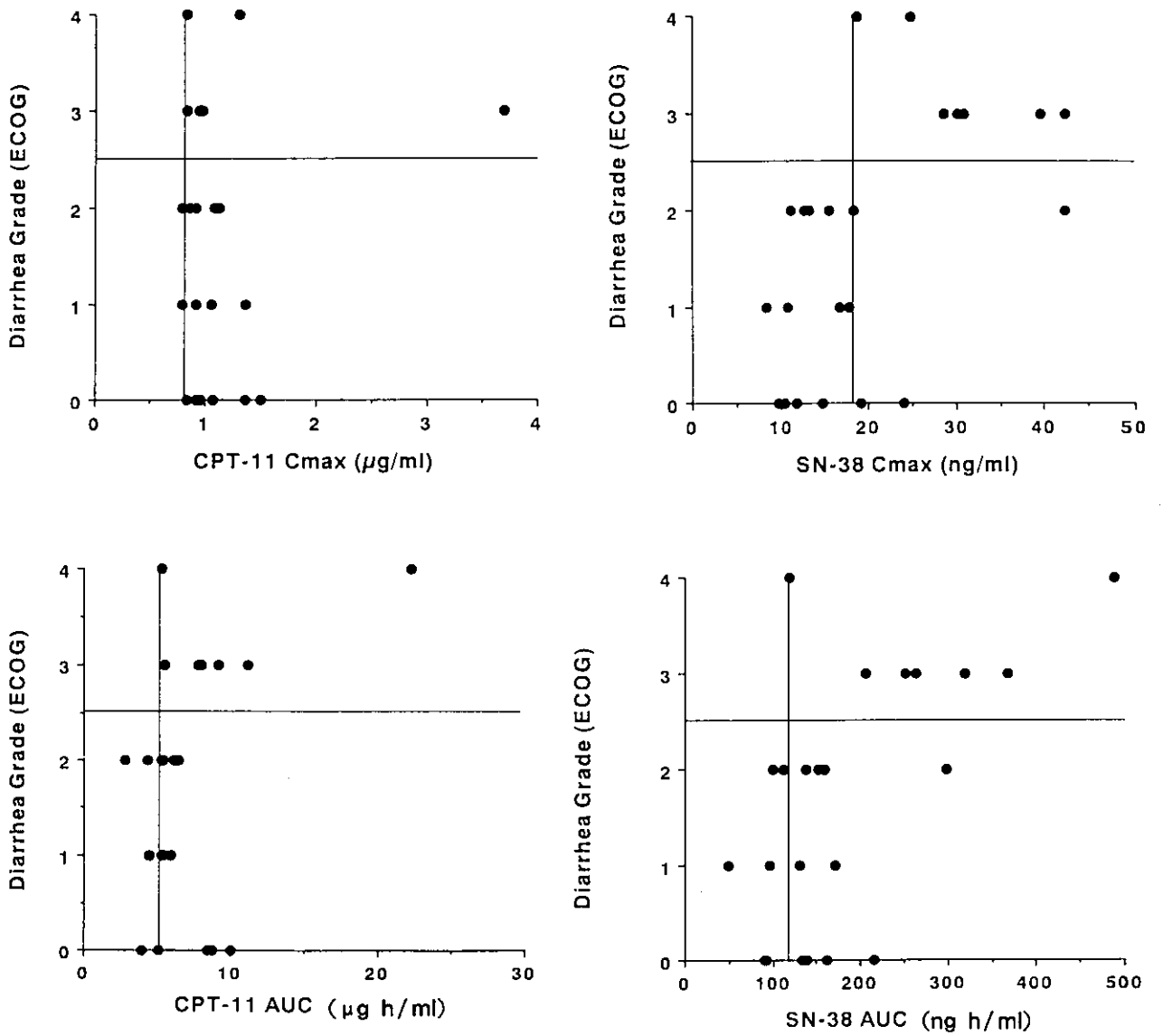

Fig. 2. Scatterplots depicting the severity of diarrhea (ECOG grade) versus the pharmacokinetic parameters (C_{max} and AUC) for CPT-11 and SN-38 during the first course of therapy.

dose of CPT-11 was increased from 80 to 90 mg/m^2, the plasma concentration curve of CPT-11 did not increase much, but that of SN-38 increased significantly (Fig. 1). Pharmacokinetic parameters for CPT-11 and SN-38 are summarized in Table II. The C_{max} and the AUC for SN-38 increased nearly twofold (C_{max} = 15.7 ng/ml vs. 27.78 ng/ml (P=0.0041), AUC = 136.22 ng h/ml vs. 258.36 ng h/ml (P=0.0031)) when the CPT-11 dose was raised from 80 mg/m^2 to 90 mg/m^2.

The relationship between pharmacokinetic parameters and diarrhea are shown in Fig. 2. The severity of diarrhea was divided into grades 0–2 and grades 3–4. Pharmacokinetic parameters such as C_{max} and AUC were also divided into 2 groups on the basis of the minimum value which caused grade 3–4 diarrhea. A close relationship was found between the C_{max} of SN-38 and the occurrence of diarrhea (P=0.0003), and the AUC of SN-38 also showed a good correlation with diarrhea (P= 0.0595). In contrast, there was no significant relationship between the C_{max} or AUC of CPT-11 and the development of diarrhea (P=0.3276, P=0.0946). These findings suggested that the C_{max} of SN-38 might be usable as a

Table III. Relationship between the SN-38 Concentration and Diarrhea

Time[a] (h)	r^{b}	SN-38 concentration cut-off value[c] (ng/ml)	P value[d]
1.0	0.714	11.7	0.0016
1.5	0.763	12.8	0.0016
1.583	0.749	12.9	0.2929
1.75	0.794	12.4	0.0016
2.0	0.680	9.1	0.1711
2.5	0.617	11.5	0.0656

a) Time after the start of CPT-11 infusion.
b) Correlation coefficient.
c) Minimum plasma SN-38 concentration which caused grade 3–4 diarrhea.
d) Fisher's exact probability test.

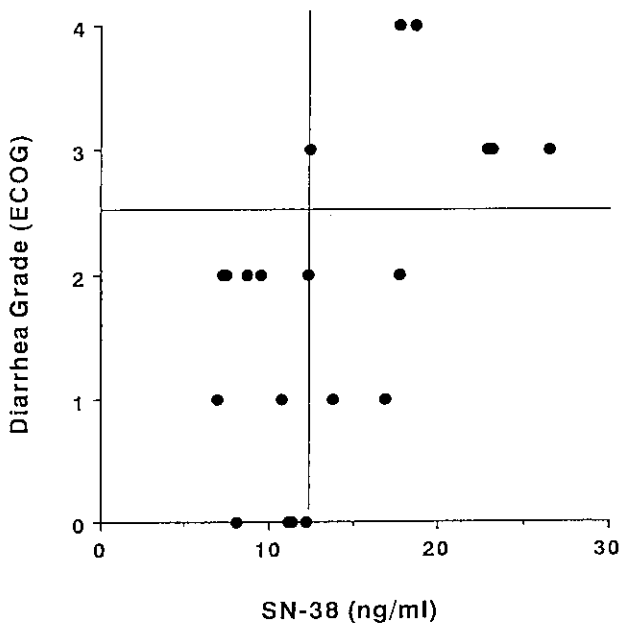

Fig. 3. Scatterplots depicting the severity of diarrhea (ECOG grade) versus the SN-38 concentration at 1.75 h after the start of CPT-11 infusion during course 1.

predictor of the severity of diarrhea during combination chemotherapy with CPT-11 and cisplatin. When the C_{max} of SN-38 is more than 18.6 ng/ml, the risk of grade 3–4 diarrhea is markedly increased. However, the time of C_{max} varied from 1.0 to 5.5 h after the start of infusion, making it difficult accurately to determine the C_{max} value. Accordingly, we investigated the relationship between the SN-38 concentration at each sampling time and diarrhea. Table III shows P values calculated by Fisher's exact probability test and the cut-off value of SN-38 at each sampling time, which was determined as the minimum concentration which caused grade 3–4 diarrhea. On the basis of these data, the SN-38 concentration measured at 1.75 h after the start of CPT-11 infusion can be used to predict the severity of diarrhea. When the SN-38 concentration at this time is more than 12.4 ng/ml, grade 3–4 diarrhea seems likely to develop.

There are many factors that may influence the onset of diarrhea. We analyzed various factors, including the SN-38 concentration, PS, age, creatinine clearance, CPT-11 dose, cisplatin dose, CPT-11 AUC, CPT-11 C_{max}, SN-38 AUC, and G-CSF support using the stepwise method of logistic regression analysis. An SN-38 concentration $\geq$12.4 ng/ml at 1.75 h was significantly correlated with an increased risk of grade 3–4 diarrhea ($r=3.1835$, standard error = 1.0366, odds ratio = 24.1, 95% confidence interval = 3.164–184.055, and P value = 0.0021), while the other variables did not significantly affect the probability of grade 3–4 diarrhea.

DISCUSSION

Topoisomerase I inhibitors such as CPT-11 and topotecan are very promising agents for cancer chemotherapy either alone or combined with other drugs. The dose-limiting toxicities of CPT-11 alone or in combination with cisplatin are diarrhea and/or leukopenia,[11–15, 20, 23–25] and the interpatient variability of these toxicities is very large. Rowinsky *et al.* have demonstrated a positive correlation between the mean percent change in the absolute neutrophil count and the AUC of SN-38, and they found that a sigmoidal E_{max} model well described the relationship.[13] Other investigators have pointed out a positive correlation between the white blood cell count and the AUC of SN-38[26] or CPT-11.[27]

Although leukopenia can be minimized by G-CSF, it is still very difficult to control the diarrhea caused by CPT-11. The relationship between diarrhea and various pharmacokinetic parameters has not previously been clarified. Sasaki *et al.* pointed out that during administration of CPT-11 as a weekly infusion of 100 mg/m^2, there was a good relationship between the AUC of SN-38 and the occurrence of diarrhea ($r=0.606$).[27] In the present study the AUC of SN-38 also showed a good correlation with diarrhea ($r=0.588$, $P<0.01$, and $P=0.0595$ by Fisher's exact probability test). However, the C_{max} of SN-38 showed a better correlation with the occurrence of diarrhea than the AUC. Unfortunately, the C_{max} of SN-38 did not always coincide with the end of CPT-11 infusion and its timing varied between patients. Thus we could not obtain the C_{max} of SN-38 by one-point sampling. Accordingly, we investigated the relationship between the concentration of SN-38 at each sampling time and the occurrence of diarrhea. Our findings showed that the concen-

tration of SN-38 at 1.75 h after the start of CPT-11 infusion could be used to predict the severity of diarrhea. Using this pharmacodynamic relationship, we may be able to individualize the dose of CPT-11 during combination therapy with cisplatin. This may allow an increase in the dose intensity of CPT-11 therapy without increasing the toxicity, which should lead to better results with this regimen.

We experienced grade 3–4 diarrhea in 7 (30.4%) out of 23 patients. Two types of diarrhea have been reported as a result of CPT-11 treatment.[12, 28] One is early diarrhea that occurs during or immediately after drug infusion, and this is considered to be due to increased cholinergic activity and/or a vasoactive response. It is readily controlled by atropine sulfate and by premedication with ondansetron and diphenhydramine. The other type is late diarrhea which develops around the third week of therapy and sometimes coincides with severe neutropenia. This diarrhea is usually refractory to anticholinergic agents and to other antidiarrheal agents, including albumin tannate, codeine phosphate, loperamide, and the somatostatin analogue, sandostatin. Our pharmacodynamic study was concerned with this refractory late diarrhea. The SN-38 concentration on day 8 was found to be similar to that on day 1 (data not shown). Therefore, the SN-38 concentration at 1.75 h after the start of infusion on day 1 should be measured, and if the level is $\geq$12.4 ng/ml, it may be possible to prevent severe diarrhea by reduction of the next dose of CPT-11. If the level of SN-38 is quite low, increasing the next dose of CPT-11 should raise the dose-intensity of therapy and improve the response without causing severe diarrhea.

Marked interpatient variability in the pharmacokinetics of CPT-11 and SN-38 has been reported, and there appear to be profound interindividual differences in the metabolism and/or elimination of these drugs.[11–13, 24, 25, 27] CPT-11 is a prodrug which is converted to SN-38 by carboxylesterase.[29] This enzyme appears to be present in the liver, the mucosa of the small intestine, and tumor cells in humans. SN-38 is produced immediately after the infusion of CPT-11, but the peak concentration and the duration for which it is maintained vary between patients. In the present study, interpatient variability of elimination of SN-38 was also large and the elimination curve of SN-38 had two peaks in 14/23 patients, as was also observed in another study.[12] This marked interpatient variability is possibly due to differences in the content and/or activity of the converting enzyme, carboxylesterase. Since it is difficult to assess the content and activity of carboxylesterase in individual patients, more investigation is needed into carboxylesterase and the mechanism of SN-38 toxicity.

Rothenberg *et al.*[12] and Rowinsky *et al.*[13] have evaluated the pharmacokinetics of the lactone and hydroxy acid forms of CPT-11 and SN-38. In the present study, only the total concentrations of CPT-11 and SN-38 were measured. Hydrolysis of the lactone ring of CPT-11 produces a hydroxy acid form, which is a less potent inhibitor of topoisomerase I and has much weaker antitumor activity. They reported that the lactone AUC to total AUC ratio was relatively constant for both CPT-11 (33.9 and 44%) and SN-38 (44.7 and 50%). Therefore, pharmacodynamic and pharmacokinetic studies using the total concentration of CPT-11 and SN-38 may be useful.

In the present study we used CPT-11 combined with cisplatin. The maximum tolerated dose of CPT-11 was reduced from 100 mg/m^2 to 90 or 70 mg/m^2 by the addition of cisplatin,[11, 23–25] since it enhances the toxicity of CPT-11 as well as the antitumor effect. However, the mechanisms of the interaction between cisplatin and CPT-11 or SN-38 are still unknown.

In conclusion, the severity of diarrhea during combined therapy with CPT-11 and cisplatin was significantly correlated with the C_{max} of SN-38 and with the SN-38 concentration at 1.75 h after the start of CPT-11 infusion. These findings may allow the individualization of CPT-11 therapy. To confirm this, we are now evaluating the relationship between the SN-38 concentration and the occurrence of diarrhea in a phase II study of CPT-11 plus cisplatin in patients with previously untreated small-cell lung cancer.

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