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A Pharmacokinetic and Pharmacodynamic Analysis of CPT-11 and Its Active Metabolite SN-38

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In the present study, an attempt was made to determine the precise pharmacokinetics of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38). The relationship between pharmacokinetic parameters and pharmacodynamic effects was also investigated to elucidate the cause of interpatient variation in side effects. Thirty-six patients entered the study. CPT-11, 100 mg/m^2, was administered by IV infusion over 90 min weekly for four consecutive weeks. The major dose-limiting toxicities were leukopenia and diarrhea. There was a positive correlation between the area under the concentration-time curve (AUC) of CPT-11 and percent decrease of WBC ($r=0.559$). On the other hand, episodes of diarrhea had a better correlation with the AUC of SN-38 ($r=0.606$) than that of CPT-11 ($r=0.408$). Multivariate analysis revealed that the AUC of SN-38, AUC of CPT-11 and indocyanine green retention test were significant variables for the incidence of diarrhea and that both performance status and AUC of CPT-11 were significant variables for percent decrease of WBC. The large interpatient variability of the degree of leukopenia and diarrhea is due to a great plasma pharmacokinetic variation in CPT-11 or SN-38. The AUCs of CPT-11 and SN-38 obtained from the first administration of CPT-11 correlate with toxicities, but it is impossible to predict severe side effects before the administration of CPT-11 at the present time.

Key words: CPT-11 — SN-38 — Pharmacokinetics — Pharmacodynamics — AUC

During the 1980s, the introduction of cisplatin, etoposide and vinca alkaloids improved the clinical outcome in patients with solid tumors. Although the number of long-term survivors with chemosensitive tumors has been increased by these agents, the survival benefit of using anticancer agents against chemoresistant tumors is still marginal or unclear. Development of new agents, scientific evaluation and establishment of effective and safe administration schedules are essential to generate a breakthrough in the chemotherapy of solid tumors.

Camptothecin (CPT), obtained from the Chinese tree *Camptotheca accuminata*, is an alkaloid with a novel ring structure.[1] Although CPT showed promising antitumor effects *in vitro* and *in vivo*,[2,3] its clinical application was disappointing because of its low therapeutic efficacy and severe toxicity to the intestine, bladder and bone marrow.[4–8] To improve the therapeutic index in the clinical setting, various derivatives of CPT have been semisynthesized. 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) is a promising water-soluble camptothecin derivatives that was developed in Japan.[9] The anticancer activity of CPT-11, an inhibitor of type I DNA topoisomerase (topoisomerase I), was demonstrated not only in murine tumor models,[10,11] but also in a variety of human tumors, including lung cancer,[12,13] malignant lymphoma,[14] cervical cancer,[15] ovarian cancer[16] and colorectal cancer[17] in clinical use. A phase II multi-institutional study of CPT-11 on advanced non-small cell lung cancer was conducted in Japan and the clinical response was reported to be more than 30%.[13] The dose of CPT-11 in this phase II study was 100 mg per m^2 and the drug was administered by intravenous drip infusion over 90 min, once a week six consecutive weeks. This administration schedule of CPT-11 is commonly used at present. The major toxicities in patients treated with CPT-11 are myelosuppression and gastrointestinal toxicity, especially leukopenia and diarrhea. In addition, some patients experienced life-threatening toxicity after receiving CPT-11, even though they had good performance status before receiving this agent in our preliminary study.

As to the pharmacokinetics of CPT-11, Kaneda *et al.* have reported nonlinear pharmacokinetic models of

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CPT-11 in rats, and found that CPT-11 is metabolized and converted into a major active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which is thought to be relevant to the antitumor activity and side effects.[18–20] A recent study suggested that carboxylesterase in the liver plays an important role in this enzymatic conversion.[21]

Based on these findings, we conducted a prospective pharmacokinetic and pharmacodynamic study of CPT-11 at the National Cancer Center of Japan. The objectives of the study were: (1) to determine the precise pharmacokinetic parameters of CPT-11 and SN-38, (2) to evaluate the interpatient variability in the pharmacokinetics of CPT-11 and SN-38, (3) to analyze the relationships between plasma pharmacokinetics of CPT-11 and SN-38 and grades of toxicities, (4) to examine patients' characteristics that may influence the degree of toxicities and (5) to evaluate the efficacy of CPT-11 in previously treated patients.

PATIENTS AND METHODS

Selection of patients All patients had to have documented histologic evidence of advanced malignancy for which routine treatments were not or had not been effective, or no standard chemotherapy existed. Patient requirements included (1) at least 18 years of age, (2) ambulatory with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, (3) a life expectancy of at least 3 months, (4) at least 4 weeks since prior cytotoxic chemotherapy (6 weeks for nitrosoureas and mitomycin) or at least 3 weeks since any major surgical procedure, (5) adequate bone marrow function (leucocytes $>3{,}000/\mu l$, platelets $>100{,}000/\mu l$, Hb >10.0 g/100 ml), renal function (blood urea nitrogen concentration $<1.5\times$normal, creatinine <2.0 mg/dl or creatinine clearance (Ccr) >50 ml/min), cardiac function (normal ECG) and hepatic function (total bilirubin <2.0 mg/ml, GOT or GPT level $<2\times$normal). Patients were ineligible if they: (1) had had prior treatment with radiation therapy to $>1/3$ of the bone marrow or pelvic irradiation, (2) had an active infectious process, (3) had a history of congestive heart failure requiring medical therapy (NYHA Class III and IV), (4) had psychiatric disorder or neurologic disease, were pregnant or lactating woman, (5) were HTLV-I-positive or HBSag-positive. There was no restriction on the amount of prior chemotherapy with respect to study eligibility. Creatinine clearance (Ccr) and indocyanine green (ICG) retention test at 15 min (R_{15}) were also examined to evaluate renal and hepatic functions, respectively. Ccr was determined by the 24-h method. ICG at a dose of 0.5 mg/kg was injected as a bolus and blood was sampled 15 min after injection. R_{15} was calculated by use of the following equation:

$$R_{15}=C_{15}/1.00\times 100(\%)$$

where C_{15} = plasma ICG concentration at 15 min after the injection (mg/ml), and 1.00 is the theoretical ICG concentration at 0 min (mg/ml). This protocol was a separate pharmacological study for prospective analysis of the relation between pharmacokinetics and pharmacodynamics. The protocol was approved by the Institutional Review Board of the National Cancer Center. Written informed consent was obtained from all patients after they had been informed of the procedure to be followed, the experimental nature of the treatment, potential benefits, side effects, risks and discomfort.

Treatment regimen CPT-11 is supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo) as a solution in vials (40 mg/2 ml or 100 mg/5 ml). These vials were kept at room temperature in a shaded place. The contents of the vial were reconstituted in 250 ml of 5% glucose solution in a plastic bottle. The dose, 100 mg/m^2 of CPT-11, was administered by intravenous drip infusion over 90 min using an electric infusion pump (Termo, Tokyo). There was no premedication for nausea, vomiting or diarrhea, and granulocyte colony-stimulating factor was not used in this study. CPT-11 administration was repeated once a week for 4 consecutive weeks. After a two-week rest period, the patients received the same course of treatment until disease progression was documented or intolerable side effects were observed.

Criteria for assessment of toxicity and response Toxicities were evaluated according to the ECOG Common Toxicity Criteria. The total number of episodes of diarrhea in a week after the initiation of CPT-11 and percent decrease of white blood cell (WBC) nadir (%ΔWBC) as compared with the WBC before treatment were used to evaluate the degree of diarrhea and leukopenia, respectively. Patients were removed from the present study if they experienced unacceptable toxicity, defined as grade 4 hematological toxicity or grade 3 or greater non-hematological toxicity. The ECOG criteria[22] were used for evaluating tumor response. Briefly, complete response was defined as disappearance of all evidence of tumor for at least 4 weeks; partial response was defined as decrease by at least 50% in the sum of the products of the longest perpendicular diameters of all measurable lesions; no change meant a decrease of less than 50% or an increase of less than 25% in any measurable lesion; progressive disease was defined as an increase of more than 25%. Appearance of a new lesion in any other response category was also considered as progressive disease.

Blood and urine sampling and pharmacokinetic analysis Blood samples in heparinized tubes were collected before infusion and at 30, 60 and 90 min after the start of the infusion, and at 5, 15, 30, 60, 120, 240, 360, 480, 720,

1440 min after the end of the infusion. The 48-h urine samples were collected and monitored for excreted CPT-11 and SN-38 in each 6-h period.

Concentrations of both CPT-11 and SN-38 were measured with a reverse-phase, high-performance liquid chromatography (HPLC) technique using a modification of the method reported previously.[18,19] Briefly, plasma was isolated by low speed (2,000 rpm for 10 min at −5°C) centrifugation as soon as possible following sample collection. Two (2) ml of plasma was stored at −40°C until analysis for total CPT-11 and SN-38. Plasma samples were injected under nitrogen gas pressure into a C18 cassette of an advanced automated sample processor (AASP) (Analytichem International, Harbor City, CA); the cassette was wetted with methanol and water before application, followed by rinsing with 1.5 ml of water. The HPLC system (Shimadzu, Kyoto) was linked to the AASP, which performed as an auto-sampler. A C18 reversed-phase column ODS-80TM (250×4.6 mm ID) (Tosoh Co., Tokyo) with an ODS 120-T guard column (15×3.2 mm ID) (Tosoh Co.) was used for separation. CPT was used as an internal standard. The mobile phases consisted of acetonitrile/ethanol/0.8% ammonium carbonate (2/1/1, v/v) and acetonitrile/water (1/4, v/v) for CPT-11 and SN-38, respectively, at flow rates of 1.0 ml/min and 2.0 ml/min. A Hitachi 650-10LC fluorospectrometer (Hitachi, Tokyo) was set at an excitation wavelength of 373 nm and an emission wavelength of 428 nm for CPT-11, and at 380 nm and 540 nm for SN-38. The detection limits of CPT-11 and SN-38 were 5 ng/ml and 0.5 ng/ml, respectively. The highest actual concentration was taken to be the peak plasma concentration (Cmax). Pharmacokinetic parameters of both CPT-11 and SN-38 were determined on the basis of 2-compartmental and non-compartmental models, respectively, using a computer program, MULTI.[23] The area under the concentration-time curve (AUC) from the initiation of the infusion to 24 h after finishing the infusion was calculated by the trapezoidal method.

Pharmacodynamics To determine if a quantative relationship exists between exposure to CPT-11 or SN-38 and the magnitude of leukopenia and diarrhea, scatter plots of AUCs of CPT-11 or SN-38 vs. the percentage decrease in white blood cell (%ΔWBC) or episodes of diarrhea in the first week were examined by simple linear regression analysis.

Statistical analysis Forms of univariate and multivariate analysis were used to determine the main factors that affect %ΔWBC or episodes of diarrhea due to the use of CPT-11.

RESULTS

Characteristics of patients From April 1990 to March 1991, 36 patients with good performance status entered the pharmacokinetic/pharmacodynamic study. The patients' characteristics are shown in Table I. All patients

Table I. Characteristics of Patients

	No. of patients
Patients	36
Male	28
Female	8
Median age (years)	60
Range	29–75
Median performance status (ECOG[a])	1
Range	0–2
Prior therapy	
Operation	26
Chemotherapy	16
Radiation	5
Radiation and chemotherapy	11
None	4
Diagnosis	
Lung (NSCLC[b])	16
Lung (SCLC[c])	2
Colon	9
Head and neck	4
Uterus	2
Other	3

a) ECOG, Eastern Cooperative Oncology Group.
b) NSCLC, non-small cell lung cancer.
c) SCLC, small cell lung cancer.

Table II. Toxicities of CPT-11

Toxicity criteria[a]		No. of patients
Leukopenia		
WBC	0	7
	1	12
	2	12
	3	4
	4	1
Gastrointestinal		
Nausea	0	3
	1	13
	2	16
	3	4
Vomiting	0	23
	1	4
	2	6
	3	1
	4	2
Diarrhea	0	14
	1	8
	2	6
	3	3
	4	5

a) ECOG common toxicity criteria.

except 4 had received prior treatments and 16 patients, including two with small cell lung cancer, had received prior chemotherapy. Sixteen patients had non small cell lung cancer, 9 had colon cancer and 4 had head and neck cancer.

Toxicity and clinical response Leukopenia and gastrointestinal toxicities were dose-limiting factors (Table II). Grade 3 or 4 leukopenia and diarrhea on the ECOG scale were observed in 5 and 8 patients, respectively. Toxicities other than leukopenia and diarrhea were mild and were well tolerated, with ECOG common toxicity criteria of less than 3 (data not shown). CPT-11 was scheduled to be administered once a week for 6 consecutive weeks if possible, but when the tolerability of CPT-11 was examined in terms of dose intensity, which indicates the administered dose per week in the first month, only half of the patients received 4 consecutive courses of CPT-11 chemotherapy (Table III). Four patients received only one course of treatment with a dose intensity of 25 mg/m^2/week/month because of excessive toxicity (diarrhea and/or leukopenia). Thirty-five patients had evaluable lesions for assessing clinical response to CPT-11 treatment. Two and six patients achieved partial and minor response (less than 50% tumor regression), respectively. The disease status of twenty-one patients was stable and disease progression was observed in six patients.

Table III. Variability of Dose Intensity

Dose intensity (mg/m^2/week/month)	No. of patients
100	17
75	6
68.7	1
62.5	1
50	7
25	4

Pharmacokinetics A total of 1080 samples were planned for the analyses of both CPT-11 and SN-38, and 97% of scheduled blood sampling was achieved from the 36 patients. The total concentrations of CPT-11 and SN-38 were analyzed in this study, because the assay method for the lactone forms of CPT-11 and SN-38 had not been established then. The plasma concentration-time curves for CPT-11 and SN-38 are presented in Fig. 1. The peak plasma concentration of CPT-11 was observed just after the end of drug infusion and declined in a bi-exponential mode with a half life (T1/2β) of 7.2 h. The mean volume of distribution for CPT-11 was 266 liters. On the other hand, the peak plasma concentration of SN-38 was detected within 2 h after the end of drug infusion with a half life of 10.5 h. The standard deviation of the plasma concentration of SN-38 was greater than that of CPT-11.

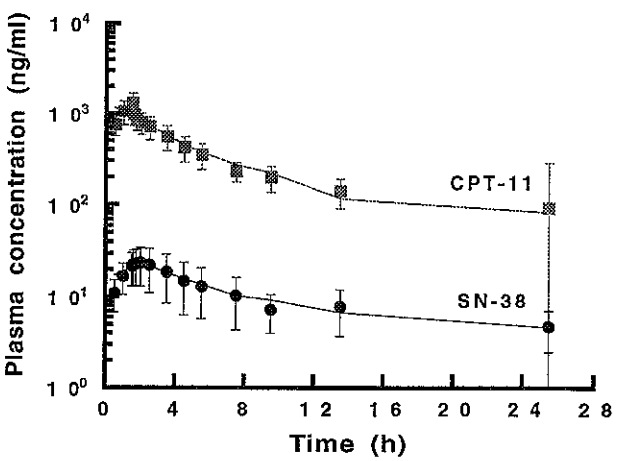

Fig. 1. Plasma concentration-time curves of CPT-11 and SN-38 determined by HPLC in 36 patients treated with CPT-11 at the dose of 100 mg/m^2 per 90 min. Points represent means±SD.

Table IV. Pharmacokinetic Variability of CPT-11 and SN-38 in 36 Patients

	CPT-11		SN-38		%AUC SN-38/CPT-11
	AUC[a] (μg/ml h)	Cmax[b] (μg/ml)	AUC (μg/ml h)	Cmax (ng/ml)	
Mean	6.41	1.35	236.14	26.20	3.70
Maximum	12.05	2.31	348.27	68.41	6.41
Minimum	4.14	0.74	97.00	10.70	1.39
SD	1.66	0.36	91.90	11.55	1.21
CV[c]	25.97	26.97	38.91	44.06	32.62

a) AUC, area under the concentration vs. time curve.
b) Cmax, peak plasma concentration.
c) CV, coefficient of variation.

The interpatient variability of pharmacokinetic parameters of CPT-11 and SN-38 is shown in Table IV. The coefficients of variation for AUC and peak plasma concentration of CPT-11 were 25.97 and 26.97, respectively, and those of SN-38 were 38.91 and 44.06, respectively. The pharmacokinetic interpatient variability was shown to be large for both CPT-11 and SN-38. While the peak plasma concentration of CPT-11 correlated with that of SN-38 (Fig. 2A), the correlation between the AUC of CPT-11 and that of SN-38 was weaker than the correlation of peak plasma concentrations (Fig. 2B). The major excretion route of CPT-11 is thought to be non-renal. Urinary excretion was measured in 14 patients. Almost 15% of CPT-11 was excreted in the urine within 48 h (Fig. 3).

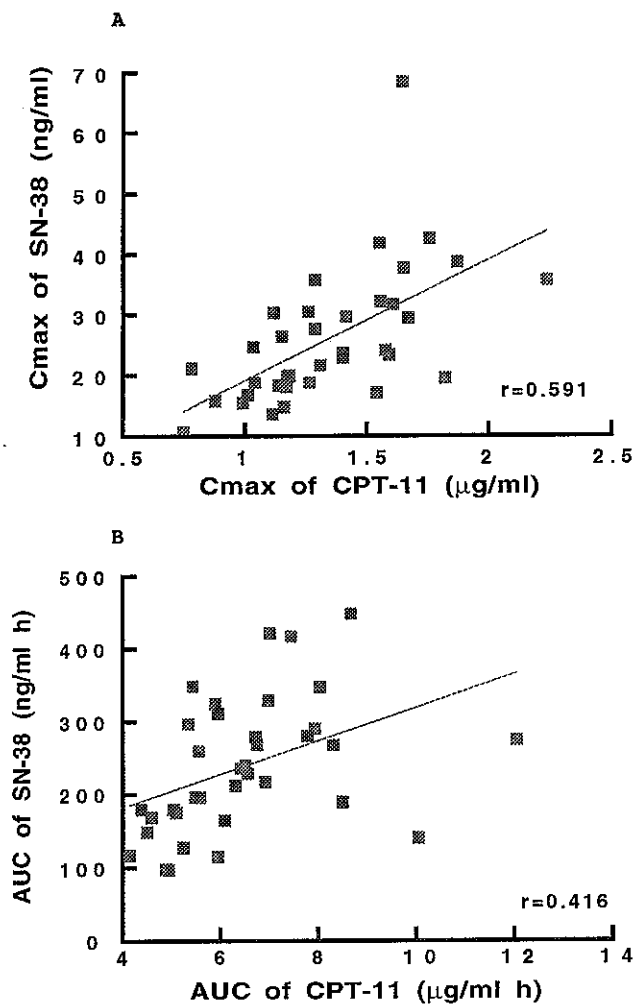

Fig. 2. The relationship between Cmax of CPT-11 and SN-38 (A), and AUCs of CPT-11 and SN-38 (B) in 36 patients treated with CPT-11 at the dose of 100 mg/m^2 per 90 min.

Pharmacodynamics The relationship between AUC as a pharmacokinetic parameter and the level of toxicity as a pharmacodynamic effect was analyzed. A stronger correlation between the AUC of CPT-11 and %ΔWBC than that between the AUC of SN-38 and %ΔWBC was observed (Fig. 4). On the other hand, the number of episodes of diarrhea had a better correlation with the AUC of SN-38 than that of CPT-11 (Fig. 5).

Predictability of toxicity To analyze whether leukopenia and incidence of diarrhea can be predicted, univariate and multivariate analyses were performed between the patients' characteristics (including sex, age, performance status, disease, actual CPT-11 dose, total protein, plasma albumin, hemoglobin, WBC, platelets, ICG test and Ccr) and pharmacokinetic parameters of CPT-11 and SN-38 (episodes of diarrhea and %ΔWBC). Although several factors were identified as significant variables for diarrhea and %ΔWBC by univariate analysis, multivariate analysis revealed that the AUC of SN-38, AUC of CPT-11 and ICG test were significant variables for the incidence of diarrhea, and both performance status and AUC of CPT-11 were significant variables for %ΔWBC (Tables V and VI). In addition, both age and WBC count before treatment influence the AUC of CPT-11, and ICG result influences the AUC of SN-38; however, these factors were not significant variables for diarrhea and %ΔWBC (Tables V, VI and VII). The incidence of diarrhea in the patients with colon cancer and other GI malignancies was negligible. The history of prior chemotherapy (including alkylating agent) was not a significant factor for either leukopenia or diarrhea. Prior use of fluoropyrimidines or cisplatin had no significant influence on the incidence of diarrhea (data not shown).

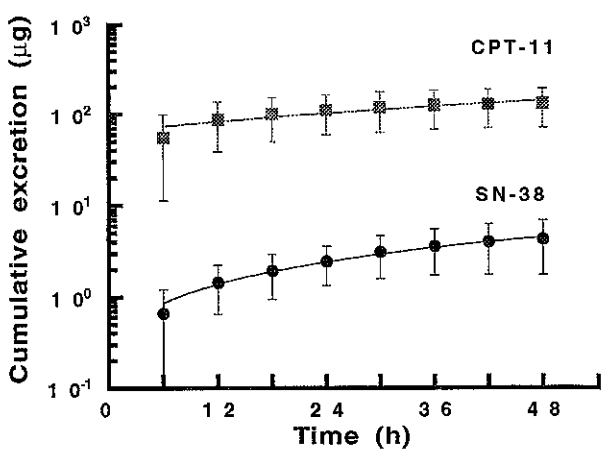

Fig. 3. Cumulative urinary excretion of CPT-11 and SN-38 determined by HPLC in 14 patients treated with CPT-11 at the dose of 100 mg/m^2 per 90 min. Points represent means±SD.

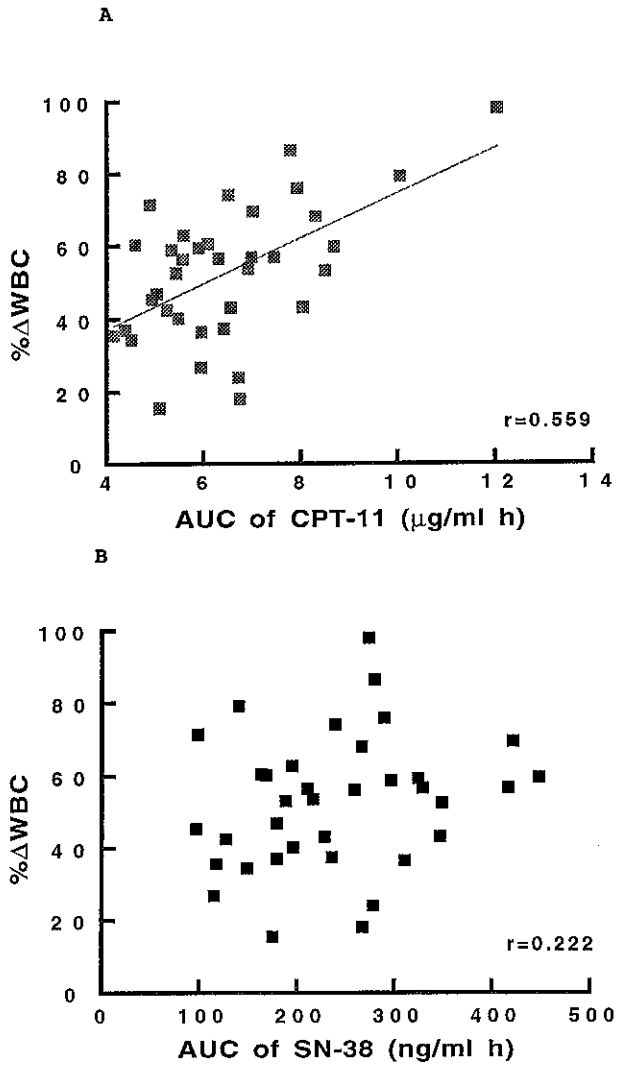

Fig. 4. The relationship between AUCs of CPT-11 (A) or AUCs of SN-38 (B) and %ΔWBC in 36 patients treated with CPT-11 at the dose of 100 mg/m^2 per 90 min.

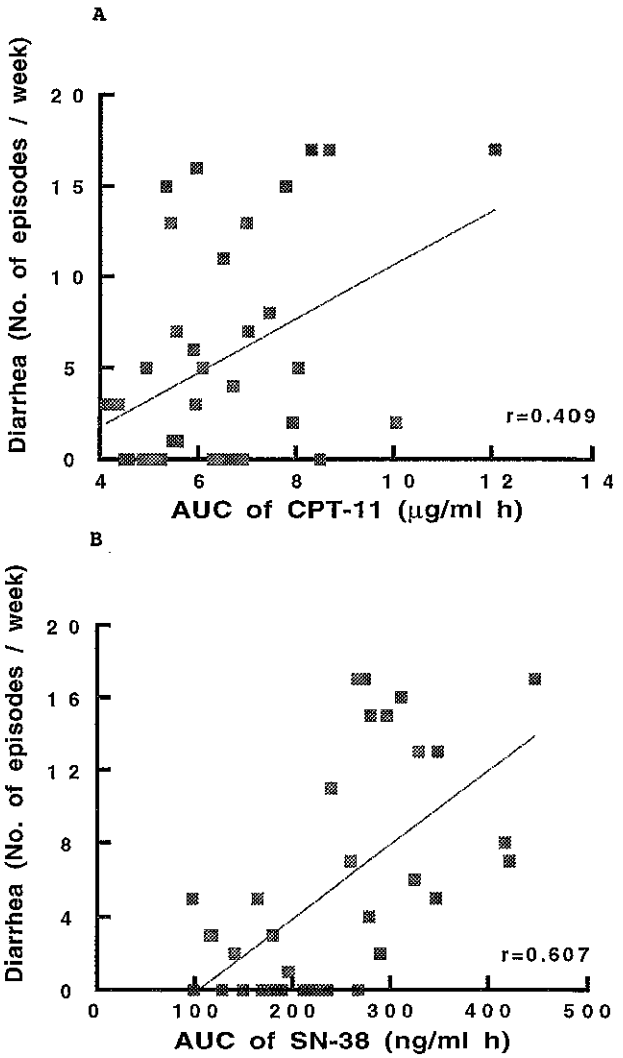

Fig. 5. The relationship between AUCs of CPT-11 (A) or AUCs of SN-38 (B) and episodes of diarrhea in the first week in 36 patients treated with CPT-11 at the dose of 100 mg/m^2 per 90 min.

DISCUSSION

Although CPT-11 produces a high clinical response in a variety of tumor types, dose-limiting toxicities include myelosuppression and diarrhea, as experienced in the present study and reported previously.[12] Based on dose intensity, only half of the patients received CPT-11 for 4 consecutive weeks. The major causes of the discontinuation of the drug administration were severe diarrhea and/or leukopenia, although most of the patients, who had received previous treatment, were ambulatory with performance status of 0, 1 and 2. On the other hand, more than half of the patients experienced mild myelosuppression and/or gastrointestinal toxicities. In addition to the wide interpatient variability in pharmacodynamics, especially for leukopenia and diarrhea, interpatient variability in pharmacokinetics was also shown to be great. The interpatient differences in AUC and Cmax of CPT-11 were 2.9 times and 3.12 times and those of SN-38 were 3.9 and 6.4, respectively. CPT-11 is metabolized by carboxylesterase in the liver,[21] but the activity of this enzyme is hardly detected in the human plasma. The higher correlation observed between the Cmax of CPT-11 and that of SN-38 than between the AUCs of CPT-11 and that of SN-38 is thought to be due to the difference in

Table V. Pearson Correlation Coefficient between Patients' Characteristics and Episodes of Diarrhea or %ΔWBC

Variable	Diarrhea		%ΔWBC[a]	
	Correlation coefficient	*P*	Correlation coefficient	*P*
Sex	−0.040	NS[b]	−0.354	<0.05
Age	0.229	NS	0.208	NS
PS	0.184	NS	0.429	<0.01
Disease	0.036	NS	−0.171	NS
Dose of CPT-11	0.138	NS	0.155	NS
Total protein	−0.063	NS	−0.126	NS
Albumin	−0.306	<0.1	−0.478	<0.01
Hemoglobin	−0.272	NS	−0.340	<0.05
WBC	0.216	NS	0.583	<0.001
Neutro.	0.189	NS	0.582	<0.001
Platelet	−0.043	NS	0.030	NS
ICG	−0.037	NS	0.086	NS
Ccr	0.138	NS	−0.090	NS
AUC/CPT-11	0.409	<0.05	0.559	<0.001
Cmax/CPT-11	0.345	<0.05	0.273	NS
AUC/SN-38	0.607	<0.001	0.222	NS
Cmax/SN-38	0.448	<0.01	0.224	NS

a) %ΔWBCS, percent decrease of WBC.
b) NS, not significant.

Table VI. Multivariate Analysis between Patients' Characteristics and Episodes of Diarrhea or %ΔWBC

Dependent	Independent	Coefficient (SE)	*P*	Multiple R
Diarrhea				0.733
	Constant	−6.77		
	AUC[a]/SN-38	0.045 (0.0093)		<0.001
	AUC/CPT-11	0.99 (0.49)	<0.05	
	ICG[b]	−0.67 (0.22)	<0.01	
%ΔWBC[c]				0.637
	Constant	8.67		
	AUC/CPT-11	5.38 (1.53)	<0.001	
	PS[d]	7.10 (3.12)	<0.05	

Multivariate analysis was used to determine the significant factors that affect %ΔWBC or episodes of diarrhea due to the use of CPT-11.
a) AUC, area under the concentration vs. time curve.
b) ICG, indocyanine green.
c) %ΔWBCS, percent decrease of WBC.
d) PS, performance status.

metabolism from CPT-11 to SN-38 in each patient. This finding also suggested a difference in glucuronic acid conjugation of SN-38. The observations that the AUC of CPT-11 is more responsible for %ΔWBC than that of SN-38 and that the AUC of SN-38 is more responsible for the episodes of diarrhea than that of CPT-11 are interesting. CPT-11 was believed to be a masked compound, because the antitumor activity of SN-38 was one hunderd to one thousand times stronger than that of CPT-11. However, for most anticancer agents, %ΔWBC is closely correlated with anticancer effects. In addition, the plasma concentration of CPT-11 was shown to be one hundred times higher than that of SN-38. These observation suggested that not only SN-38 but also CPT-11 is important for the anticancer activity as well as the side effects. In the present study, we analyzed the pharmacokinetic/pharmacodynamic relationship by using a simple linear model, but more complicated analyses that co-

Table VII. Multivariate Analysis between Patients' Characteristics and AUC of CPT-11 or AUC of SN-38

Dependent	Independent	Coefficient (SE)		P	Multiple R
AUC[a]/CPT-11					0.76
	Constant	1.15			
	Age	0.083	(0.02)	<0.001	
	Neutro.	0.0011	(0.00028)	<0.001	
	WBC	−0.00064	(0.00026)	<0.05	
AUC/SN-38					0.43
	Constant	163.71			
	ICG[b]	10.35	(3.73)	<0.01	

Multivariate analysis was used to determine the significant factors that affect AUC of CPT-11 or AUC of SN-38.

a) AUC, area under the concentration vs. time curve.

b) ICG, indocyanine green.

model Cmax or AUC of CPT-11 and SN-38 simultaneously may be necessary. Kudo *et al.*[24] reported similar work on CPT-11 pharmacokinetic and pharmacodynamics one year after our first report. They concluded that there is a clear relationship between Cmax of SN-38 and diarrhea for CPT-11 in combination with cisplatin. However, we consider that their work has several weak points, as follows: (1) their data were taken from two independent phase I studies including heterogeneously treated patient populations, and were not analyzed prospectively, (2) the number of patients was rather smaller than in our prospective study, (3) they performed no pharmacokinetic analysis for cisplatin, although diarrhea is sometimes observed in patients treated with cisplatin alone and (4) they administered CPT-11 and cisplatin on day 1 and they performed pharmacokinetic analysis of CPT-11 on day 8, when the second course of CPT-11 was administered.[24]

As to the assay procedures for CPT-11 and SN-38, lactone and hydroxy acid of CPT-11 and SN-38 were not measured separately in this series, because suitable assay methods were not available when this study was conducted. Rowinsky *et al.* reported the pharmacokinetics and pharmacodynamics of topotecan lactone and hydroxy acid in phase I and pharmacological studies of topotecan.[25, 26] Although the dose of topotecan correlated with percent myelosuppression in a sigmoid Emax model, they failed to demonstrate a significant relationship between the AUC for topotecan lactone and the mean parcentage decrease in absolute neutrophil count (ANC) in a linear or non-linear model. We recently observed a significant relationship between the AUC for total CPT-11 and AUC for CPT-11 lactone, and between the AUC for total SN-38 and AUC for SN-38 lactone.[27] Although a significant relationship in terms of pharmacodynamics was demonstrated by the pharmacokinetic parameters of total CPT-11 and SN-38 in the present study, further investigation is necessary to identify the clinical role of the lactones of CPT-11 and SN-38. Recently, Rothenberg *et al.* reported the result of a phase I and pharmacokinetic trial of CPT-11 conducted in the U.S.[28] Although they analyzed CPT-11 lactone as well as SN-38 lactone, no better correlation was observed by using the pharmacokinetic parameters of the lactones as compared with total drug concentration. Rowinsky *et al.* also reported a phase I and pharmacologic study of this agent.[29] Their pharmacodynamic modeling revealed a correlation between AUC of total SN-38 and % decrease in absolute neutrophil count using the sigmoid Emax model, but they also failed to demonstrate the significance of measuring lactones for pharmacodynamic modeling. One of the major reasons why they obtained a different result from that of our current study seems to be that they used a different dose and administration schedule of CPT-11 from our trial (intermittent high dose). They did not subject the pharmacodynamic model to multivariate analysis.

Only two patients achieved partial response in this study. Although most of the patients had previously been treated, the response rate was disappointing. CPT-11 was demonstrated to be non-cross resistant with vincristine, melphalan, VP-16 and topotecan.[30] The clinical response of previously treated non-small cell carcinoma of the lung (NSCLC) was minimal, even though this agent is one of the most effective anticancer drugs for previously untreated NSCLC. Further investigation is necessary to elucidate the mechanism of CPT resistance. Recent studies have suggested promising antitumor activities of combination regimens including CPT-11.[31–33] The clinical significance of CPT-11 as a standard chemotherapeutic treatment should be carefully analyzed very soon.

One of the most important objectives of the present study was to see whether we could predict the patient population who would experience severe side effects

before administration of CPT-11. The AUC of SN-38, AUC of CPT-11 and ICG value were related to episodes of diarrhea and both AUC of CPT-11 and performance status were significant factors for %ΔWBC in the multivariate analysis. However, AUCs of CPT-11 and SN-38 can be analyzed only after drug administration. If a limited sampling model that predicts AUCs of CPT-11 and SN-38 were available, prediction of side effects for the second administration of CPT-11 would be possible. The present analysis suggests that if CPT-11 is administered to patients with poor performance status or at an old age, severe leukopenia can be expected. Although ICG has a significant relationship with the episodes of diarrhea, interpretation is difficult at present, because increased ICG value is weakly related to elevated AUC of SN-38 and decreased ICG value is a significant variable for diarrhea. These findings indicate that we do not have an effective predictive approach for the incidence of diarrhea in patients given CPT-11 treatment. A recent paper reported that high-dose loperamide is an effective measure for CPT-11-induced diarrhea.[34] Improvement of supportive care is also important for the safe administration of CPT-11.

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