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A Limited Sampling Model for Estimating Pharmacokinetics of CPT-11 and Its Metabolite SN-38

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The objective of this study was to develop a limited sampling model (LSM) to estimate the area under the curve (AUC) of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) and that of 7-ethyl-10-hydroxycamptothecin (SN-38) as predictive pharmacokinetic variables for leukopenia and episodes of diarrhea induced by CPT-11 administration. The model was developed with a training set consisting of pharmacokinetic studies in 36 patients who received a 90-min i.v. infusion of CPT-11 at a dose of 100 mg/m^2. A multiple regression analysis of CPT-11 or SN-38 concentrations observed at each time point in the training set was used to predict the AUC of CPT-11 or SN-38. The final sampling models using only two time points were:

$$AUC_{CPT\text{-}11} = 3.7891 * C2.5 + 14.0479 * C13.5 + 1.5463$$

$$AUC_{SN\text{-}38} = 0.5319 * C2.5 + 19.1468 * C13.5 + 72.7349$$

where C2.5 and C13.5 are the plasma concentration of CPT-11 (μg/ml) or SN-38 (ng/ml) at 2.5 and 13.5 h after the initiation of CPT-11 infusion, respectively. The models were validated prospectively on a separate test data set of 12 patients receiving the same dose of CPT-11 investigated in a previous study. Validation of the final LSM on the test data set gave values of root mean square error (RMSE) of 12.72% and 5.97% for the AUC of CPT-11 and that of SN-38, respectively. The model can be used to monitor the AUCs of both CPT-11 and SN-38 for the early prediction of toxicities and to establish a pharmacokinetically based dose modification strategy for safe administration of CPT-11.

Key words: CPT-11 — SN-38 — Limited sampling model — Pharmacokinetics — AUC

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) was developed in Japan as a derivative of camptothecin (CPT), which was obtained from the Chinese tree *Camptotheca accuminata,* to improve the therapeutic response as well as to decrease the side effects.[1)] CPT-11 has demonstrated anticancer activity in phase II studies on various kinds of solid tumors.[2–6)] However, the major toxicities in patients administered CPT-11 are myelosuppression and gastrointestinal toxicity, especially leukopenia and diarrhea, which are sometimes life-threatening. Our previous study showed that we could not predict side effects before treatment on the basis of the patient's characteristics, but we concluded that the large interpatient variability of the degree of leukopenia and diarrhea is due to a large plasma pharmacokinetic variation in CPT-11 or its metabolite 7-ethyl-10-hydroxycamptothecin (SN-38).[7)] The area under the concentration-time curve (AUC) of SN-38, the AUC of CPT-11 and the indocyanine green test (ICG) value were related to episodes of diarrhea, and the AUC of CPT-11 and performance status were significantly related to the percent decrease of white blood cell (WBC) in multivariate analysis. This finding indicates that SN-38 and CPT-11 are both active as regards pharmacodynamics. It would be useful if we could predict the AUCs of both CPT-11 and SN-38 easily from the results of the initial CPT-11 administration, not only for the prediction of side effects, but also for the establishment of an appropriate dose modification strategy.

Frequent blood sampling is inconvenient, unpleasant for the patient and costly, so that it is difficult to conduct pharmacologically guided drug administration or dose modification in a clinical setting. One promising approach to overcome the problems is the use of a limited sampling model (LSM), from which reliable estimates of total AUC can be made based on analysis of plasma drug concentrations at a minimal number (usually 2 or 3) of time points. LSM using stepwise multiple linear regression has been applied to vinblastine,[8)] amonafide,[9)] cyclophosphamide[10)] and etoposide.[11)]

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The objective of this study was to develop an LSM for the pharmacokinetics of CPT-11 and SN-38, based on the data sets of our previous two independent pharmacological studies conducted at the National Cancer Center Hospital and the National Cancer Hospital East, and to validate the model.

MATERIALS AND METHODS

Patients Two separate data sets were analyzed in this study. The first data set was from the pharmacokinetic and pharmacodynamic study conducted at the National Cancer Center Hospital between April 1991 to March 1992 on 36 patients, whose pharmacological data were used as a training set for the LSM development.[7] The second data sets was from the study investigating the pharmacological correlation between total drug concentrations and lactones of CPT-11 and SN-38 conducted at the National Cancer Center Hospital East between September 1992 and July 1993, and this was used as the test set.[12] The model validation was performed using the test set data (twelve patients). The eligibility criteria in the two studies were identical. All patients included in the training set and test set 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. The 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 a psychiatric disorder or neurologic disease, or were pregnant or lactating, or (5) were HTLV-III-positive or HBSag-positive. Both protocols were approved by the Institutional Review Board of the National Cancer Center. Written informed consent was obtained from all patients according to the institutional guidelines.

Treatment plan CPT-11 was 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 of 100 mg/m^2 of CPT-11 was administered by intravenous drip infusion over 90 min using an electric infusion pump (Termo, Tokyo). CPT-11 administration was repeated in the same patient once a week for six consecutive weeks. After a two-week rest, the patients received the same course of treatment until disease progression was documented or intolerable side effects were observed.

Pharmacokinetic studies Blood samples were collected in heparinized tubes before infusion, at 30, 60 and 90 min after the start of the infusion, and at 5, 15, 30, 60, 120, 240, 360, 480, 720 and 1440 min after the end of the infusion in the training set. Blood sampling in the test set was performed before infusion, at 45, and 90 min after the start of the infusion, and at 15, 30, 60, 120, 240, 480, 720, and 1440 min after the end of the infusion. The concentrations of both CPT-11 and SN-38 were measured using a reverse-phase high-performance liquid chromatography (HPLC) technique modified from the reported method.[13] 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. Each plasma sample was applied under nitrogen gas pressure to a C18 cassette of an advanced automated sample processor (AASP) (Analytichem International, Harbor City, CA); the cassette had been wetted with methanol and water before application, followed by rinsing with 1.5 ml of water. An HPLC system (Shimadzu, Kyoto) was linked to the AASP, which acted as an auto-sampler. A C18 reversed-phase column, ODS-80TM (250×4.6 mm I.D.) (Tosoh Co., Tokyo), with an ODS 120-T guard column (15×3.2 mm ID) (Tosoh Co.) was used for separation. 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, respectively. 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, at 380 nm and 540 nm for SN-38. The detection limits of CPT-11 and SN-38 were 0.15 μg/ml and 3 ng/ml, respectively. Because our previous analysis demonstrated a good pharmacokinetic correlation between lactone and total drug concentration of CPT-11 and SN-38, and the inter-patient variation of % lactones of both CPT-11 and SN-38 was small,[12] the LSM was constructed from the data sets of total CPT-11 or total SN-38 concentration. Pharmacokinetic parameters of both CPT-11 and SN-38 were determined by 2-compartmental and non-compartmental models, respectively, using the computer program

MULTI.[14] The AUC from the initiation of the infusion to 24 h after finishing the infusion was calculated by the trapezoidal method.

LSM development and evaluation Using the training data set, a limited sampling strategy was developed. Separate univariate analysis was performed for the concentrations at each time point (independent variable) versus the AUCs of CPT-11 and SN-38 (dependent variables), and a limited sampling strategy was developed by stepwise forward multiple regression. Missing data (3%) were excluded from the analysis. The final strategy developed was validated prospectively with the test data set, correlating the predicted and observed AUC. For initial model validation, the predicted AUC (AUC prd) was correlated with the observed AUC (AUC obs) on the test data set. The bias and the precision of the model were measured, respectively, by calculating the mean predictive error (MPE), mean squared predictive error (MSE) and root mean square prediction error (RMSE) and its percentage (RMSE%) according to the following formulas[15]:

$$MPE = S(AUC\ prd - AUC\ obs)/n$$
$$MSE = S(AUC\ prd - AUC\ obs)^2/n$$
$$RMSE = (MSE)^{1/2}$$

where n is the number of data sets. The RMSE%, the adjusted R^2 statistic and Akaike's information criterion[16] were used to select the final optimal LSM, because they take into consideration the degree of freedom of the model. All analyses were performed using the computer programs SYSTAT and Excel.

Table I. Characteristics of Patients

	Training set[7]	Test set[12]
No. of patients	36	12
Sex (M/F)	28/8	7/5
Median age, years	60	56
(range)	29–75	43–69
Median performance status	1	1
Previous therapy		
Operation	26	5
CT	16	7
RT	5	2
CT+RT	11	2
None	4	3
Diagnosis		
Lung (NSCLC)	16	3
Lung (SCLC)	2	1
Breast	0	2
Colon	9	2
Head & neck	4	1
Uterus	2	0
Pancreas	0	1
Others	3	2

Abbreviations: CT, chemotherapy; RT, radiotherapy; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

RESULTS

Thirty-six patients were entered in a previously reported pharmacokinetic/pharmacodynamic study at the National Cancer Center Hospital.[7] This cohort was used as the training data set (Table I). Another twelve patients were treated with the same dose and schedule of CPT-11 at the National Cancer Center Hospital East.

Table II. Univariate Correlation of CPT-11 Concentration at Each Time Point with the AUC

Time (h)	n	Mean (ng/ml)	SD	r
0.50	35	756.08	182.39	0.296
1.00	36	1064.73	317.66	0.382
1.50	36	1318.10	368.56	0.344
1.58	36	986.42	257.72	0.517
1.75	36	870.05	222.82	0.549
2.00	35	799.45	217.79	0.560
2.50	34	720.52	209.88	0.603
3.50	36	557.37	171.47	0.580
4.50	35	423.43	136.14	0.649
5.50	36	351.65	110.73	0.723
7.50	36	233.26	55.82	0.821
9.50	26	199.15	62.93	0.858
13.50	36	149.08	36.08	0.706
25.50	36	149.08	197.40	0.304

n, Number of samples. SD, Standard deviation.

Table III. Univariate Correlation of SN-38 Concentration at Each Time Point with the AUC

Time (h)	n	Mean (ng/ml)	SD	r
0.50	36	11.08	4.36	0.528
1.00	36	17.04	6.44	0.680
1.50	36	21.80	8.78	0.691
1.58	36	22.90	9.70	0.688
1.75	36	23.34	9.86	0.747
2.00	35	23.78	10.74	0.741
2.50	34	22.59	11.49	0.801
3.50	35	18.94	10.40	0.852
4.50	34	15.04	8.75	0.829
5.50	36	13.17	7.46	0.774
7.50	35	10.31	5.99	0.842
9.50	26	7.30	3.30	0.841
13.50	31	7.85	4.15	0.914
25.50	36	4.75	2.26	0.622

n, Number of samples. SD, Standard deviation.

The data set of the latter 12 patients was prospectively evaluated as the test data set for the validity of the limited sampling model derived from the training set (Table I). Although there was a difference in disease distribution between the two cohorts, all of the patients had good performance status with normal major organ function. There was a large interpatient pharmacokinetic variability in the concentration of CPT-11 (Table II) and SN-38 (Table III) at each of the 14 points in the training data set. Similar interpatient variability was observed in the AUC of CPT-11 as well as that of SN-38 (Fig. 1). The AUC of CPT-11 and that of SN-38 ranged from 4.14 μg h/ml to 12.05 μg h/ml and from 97.00 ng h/ml to 348.27 ng h/ml, respectively.

Initially, the concentration of CPT-11 or SN-38 at each time point was correlated by linear least-squares regression versus the AUC (Tables II and III). At 13.5 h, there was an excellent correlation between SN-38 concentration and the overall AUC of SN-38 ($r=0.914$) (Table III). On the other hand, the plasma concentration of CPT-11 at time 13.5 h had only a moderate correlation with the AUC of CPT-11 ($r=0.706$) (Table II).

Subsequently, the plasma concentrations of CPT-11 or SN-38 at all sampling points were subjected to a stepwise forward multiple linear regression analysis (Table IV). Multivariate analysis was performed independently between CPT-11 and SN-38. The most informative sampling point was 13.5 h. Then five different time points,

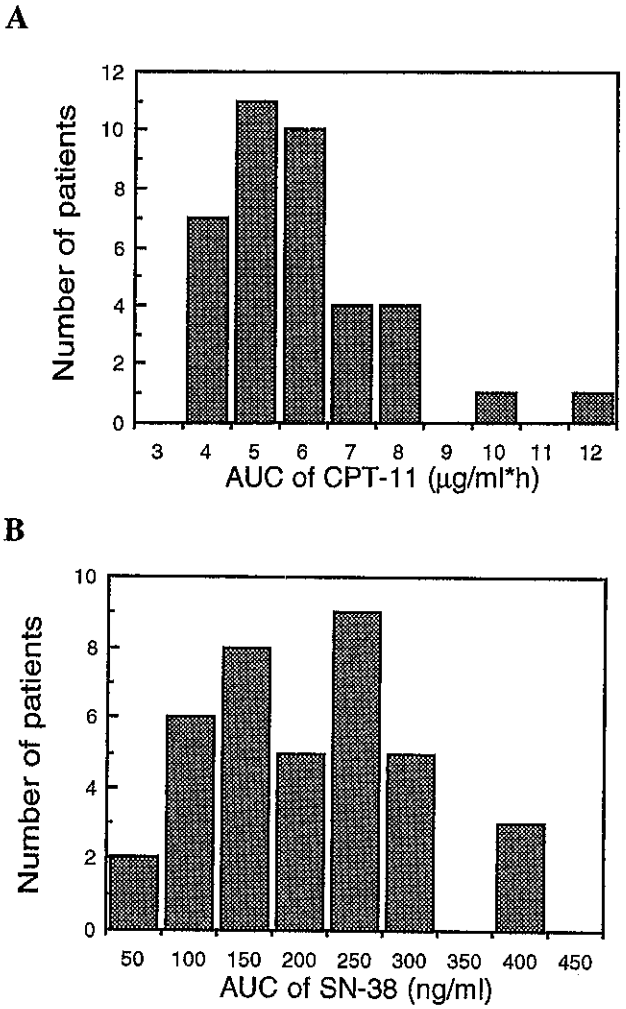

Fig. 1. Distribution of AUCs of CPT-11 (A) and SN-38 (B) among the 38 patients in the training set.

Table IV. Multivariate Correlation of CPT-11 and SN-38 Concentrations with the AUCs where $AUC=A*C_a+B*C_b+Intercept$

a (h)	b (h)	AUC_{CPT-11} r	AUC_{SN-38} r
2.0	13.5	0.8883	0.9144
2.5	13.5	0.9001	0.9142
3.5	13.5	0.8710	0.9288
4.5	13.5	0.8492	0.9182
5.5	13.5	0.8804	0.9176

C_a and C_b represent the concentrations of CPT-11 or SN-38 at time points a and b, respectively.

Table V. Stepwise Forward Multiple Regression Development of the Limited Sampling Strategy in Training Set

Sampling strategy	r
Model I	
$AUC_{CPT-11}=3.7891*C2.5+14.0479*C13.5+1.5463$	0.900
$AUC_{SN-38}=0.5319*C2.5+19.1468*C13.5+72.7349$	0.914
Model II	
$AUC_{CPT-11}=4.2707*C3.5+14.1030*C13.5+1.8963$	0.871
$AUC_{SN-38}=2.4933*C3.5+15.1795*C13.5+69.0480$	0.928

AUC_{CPT-11}, AUC of CPT-11 (μg/ml*h); AUC_{SN-38}, AUC of SN-38 (ng/ml*h); C2.5, C13.5, the plasma concentration of CPT-11 (μg/ml) or SN-38 (ng/ml) at 2.5 and 13.5 h after the first dose, respectively.

Table VI. Validation of the Limited Sampling Model in Test Set

Model	R^2	*P*	AIC	MPE	RMSE	RMSE%
Model I						
CPT-11	0.839	<0.001	3.46	−0.27	0.69	12.72
SN-38	0.653	0.001	12.37	3.24	11.96	5.97
Model II						
CPT-11	0.892	<0.001	3.06	0.24	0.55	10.05
SN-38	0.445	0.011	12.84	8.28	21.30	10.64

R^2, adjusted squared multiple R; AIC, Akaike's information criterion; MPE, mean predictive error; RMSE, root mean square prediction error; RMSE%, percent root mean square prediction error.

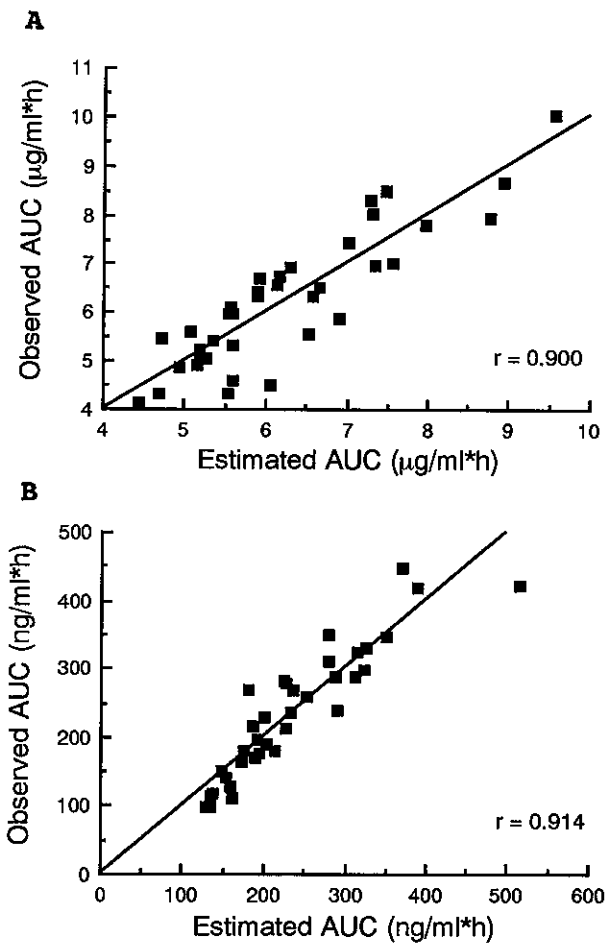

Fig. 2. The AUCs of CPT-11 (A) and SN-38 (B) estimated and observed among the 38 patients in the training set.

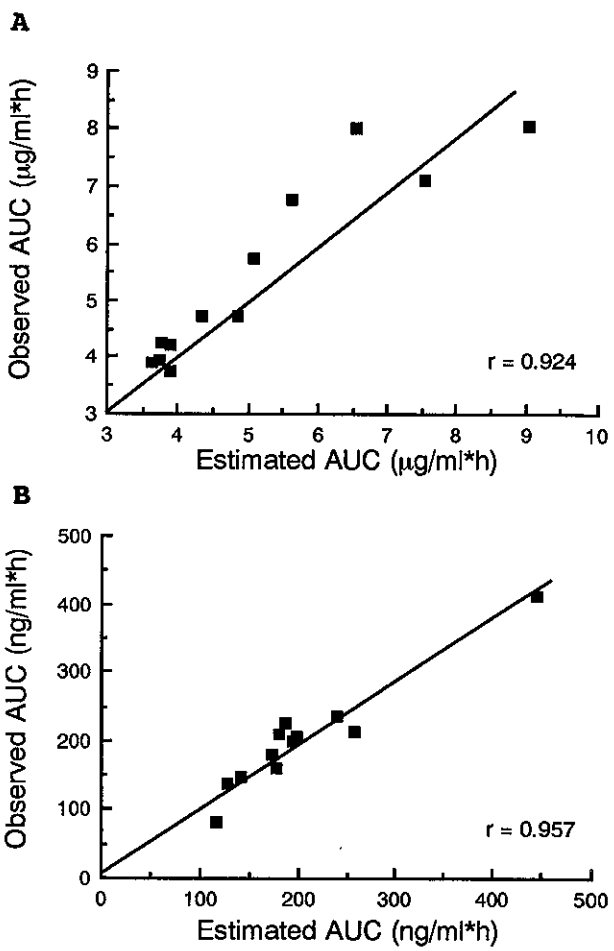

Fig. 3. The AUCs of CPT-11 (A) and SN-38 (B) estimated and observed in the test set.

2.0 h, 2.5 h, 3.5 h, 4.5 h and 5.5 h, were compared to determine the second most informative point. Finally two independent sampling models were proposed with two different time sets, 2.5 h and 13.5 h (Model I), and 3.5 h and 13.5 h (Model II) (Table V).

The two proposed models were prospectively evaluated in the test set composed of 12 patients. The predictability of AUC of CPT-11 is superior in Model II than Model I on the basis of AIC and RMSE%, although the difference is minimal. On the other hand, Model I has better

predictability than Model II for the AUC of SN-38, which is thought to be the major active metabolite and a predictive variable for episodes of diarrhea, which is a serious side effect induced by CPT-11 (Table VI). Because the plasma concentrations at 2.5 h and 3.5 h are almost equivalent for the prediction of AUC from the pharmacological standpoint (Tables II and III), a two-variable strategy and not three-variable strategy was selected as a final model, and we selected Model I as the final LSM:

$$AUC_{CPT\text{-}11} = 3.7891 * C2.5 + 14.0479 * C13.5 + 1.5463$$
$$AUC_{SN\text{-}38} = 0.5319 * C2.5 + 19.1468 * C13.5 + 72.7349$$

where C2.5 and C13.5 are the plasma concentrations of CPT-11 or SN-38 at 2.5 and 13.5 h after the first dose, respectively. Fig. 2 shows the relationship between the estimated AUC and observed AUC of CPT-11 or SN-38 by using this model in the training set. This two-variable model was moderately predictive in estimating the AUC of CPT-11 or AUC of SN-38 in the 12 courses of CPT-11 treatment that represented the test set (Fig. 3).

DISCUSSION

Although CPT-11 is one of the most promising anticancer agents in the treatment of solid tumors, this agent can cause severe side effects, especially leukopenia and diarrhea. The prediction and clinical management of those side effects remain difficult. In addition, a dose modification strategy for patients who experience a profound adverse effect is not yet established.

There has been increasing interest by medical oncologists in the relationship between the pharmacokinetics and pharmacodynamics of anticancer agents which are potentially harmful to normal organs.[17–19] The concept of LSM has been established in the fields of oncological pharmacology and cancer chemotherapy. In the present analysis, we established an LSM to predict the AUC of CPT-11 and that of SN-38 for the following reasons; (1) pharmacokinetic parameters are important tools not only to predict pharmacodynamics, especially side effects, of anticancer agents, but also to establish a scientifically optimal drug administration dose and schedule, (2) the AUC of CPT-11 and that of SN-38 are prognostic variables which correlated with leukopenia and episodes of diarrhea in our previous analysis, (3) a small number of blood sampling points is preferable for both patients and physicians and (4) an LSM would be useful for conducting large-scale clinical studies.

We used a stepwise multiple regression model to predict both the AUC of CPT-11 and that of SN-38, because CPT-11 is metabolized by carboxylesterase in the liver to SN-38 and both CPT-11 and SN-38 are considered to have anticancer activity (SN-38 is more potent than CPT-11). Our model could predict the AUCs with acceptable precision and the accuracy value for AIC and RMSE% obtained with this model seem to be satisfactory. However, the clinical significance of the present LSM is still unclear, because we demonstrated only good predictability of AUCs using this model and we did not show any predictability for side effects induced by CPT-11 administration, partly because of the small number of patients in the test set. Most of the reports on LSM of anticancer drugs have described good predictability of pharmacokinetic parameters, including the AUC of the drug. However, the ultimate utility of this strategy remains to be explored. We are now preparing to examine prospectively whether this LSM has clinical significance to predict and to manage CPT-11-related side effects in a large-scale study, and only such an approach can evaluate the usefulness of LSM in cancer chemotherapy. In addition, the concept of population pharmacokinetics has recently been applied to an anticancer agent to develop an LSM. Some of the authors also attempted Bayesian estimation of CPT-11 pharmacokinetics based on another cohort of patients.[20] However, this population model seems to be incomplete, because the model obtained by Bayesian estimation can predict only the AUC of CPT-11 and not the AUC of SN-38. In addition, the clinical significance of monitoring the AUC of CPT-11 with this model is unclear. This approach needs further evaluation.

The pharmacokinetics and pharmacodynamics of CPT-11 are complex, and we have only limited experience and knowledge of this agent in the clinical setting. Much more effort is needed to establish the most effective administration schedule of this unique agent.

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