Limited Sampling Model for the Area under the Concentration *versus* Time Curve of Irinotecan and Its Application to a Multicentric Phase II Trial[1]

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ABSTRACT

We previously established a limited sampling model (LSM) for the area under the concentration *versus* time curve (AUC) of irinotecan (CPT-11). Using this LSM, we performed a pharmacokinetic-pharmacodynamic analysis of CPT-11 in a multicentric Phase II study for non-small cell lung cancer. Ten institutes participated in this study, 36 patients were registered, and 30 patients were evaluable for the pharmacokinetic-pharmacodynamic analysis. CPT-11 and etoposide were administered daily for three consecutive days, both at a dose of 60 mg/m^2. Blood samples were obtained 4 and 8 h after infusion on days 1 and 3. When using the LSM, there is a significant possible source of error in the timing of these selected points. In this study, however, the sample timing error was small. Mean timing errors were 1.0–4.0 min at each point. The estimated CPT-11 AUCs were:

	Day 1	Day 2	Day 1 + 3
Mean ± SD (mg·h/liter)	3.76 ± 0.68	4.10 ± 0.86	7.86 ± 1.43
Range	2.01–5.03	2.29–5.72	4.30–10.68
Max/min	2.50	2.45	2.48

High interpatient variability was observed in the AUC. The CPT-11 AUC correlated positively with the grade of emesis ($P = 0.003$) and the percent decreases in WBC count ($P = 0.001$) and absolute neutrophil count ($P = 0.0006$), but it did not correlate with the grade of diarrhea or response.

We concluded that the LSM was useful in estimating individual pharmacokinetic parameters in multicentric trials.

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INTRODUCTION

Investigation of pharmacokinetic and pharmacodynamic relationships necessitates several troublesome processes. One major obstacle to such studies is the inconvenience and high cost involved in measuring individual pharmacokinetic parameters, which requires multiple blood sampling. A possible approach to solving this problem would be a LSM.[3] Thus, LSMs have been developed for many anticancer agents (1–6) and have been proposed as tools to facilitate pharmacological studies. However, thus far, there are no reports of PK/PD analyses using LSMs in large numbers of patients or institutions.

Irinotecan (CPT-11) is a novel and promising anticancer agent that has demonstrated significant antitumor activity against various kinds of tumors (7–11). However, treatment with CPT-11 has been associated with various toxicities, including myelosuppression, gastrointestinal toxicity, and especially neutropenia and diarrhea, which were sometimes life-threatening.

Because CPT-11 exhibited wide pharmacokinetic variability and because it had been suggested that there was a good correlation between the AUCs of CPT-11 and SN-38 (an active metabolite of CPT-11) and the induction of dose-limiting toxicities, we previously attempted to establish a LSM for estimating the AUC of CPT-11 and SN-38. Although the LSM for the CPT-11 AUC was proven to be highly predictive, large interpatient variability in the pharmacokinetics of SN-38 prevented us from developing a LSM for SN-38 AUC (12). Because the AUCs for both SN-38 and CPT-11 correlated with toxicities, we proposed that the investigation of the CPT-11 AUC and pharmacodynamic relationship necessitated large-scale studies.

Here, we report the results of a PK/PD analysis using the LSM of CPT-11 in a multicenter Phase II study in which CPT-11 was combined with etoposide for non-small cell lung cancer (13). The aims of this study were to examine the feasibility of a pharmacological study using a LSM within a multicentric trial and to assess the impact of the AUC of CPT-11 on pharmacodynamic parameters when it is combined with etoposide.

PATIENTS AND METHODS

Patients. Patient eligibility criteria for this study included: histologically or cytologically diagnosed non-small cell lung cancer; stage IV disease; age under 75 years; Eastern Cooperative Oncology Group performance status 0 or 1; no prior

[3] The abbreviations used are: LSM, limited sampling model; PK/PD, pharmacokinetic-pharmacodynamic; AUC, area under the concentration *versus* time curve; G-CSF, granulocyte colony-stimulating factor; ANC, absolute neutrophil count; JCOG, Japan Clinical Oncology Group.

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Table 1 Evaluation of sampling time error

	Day 1		Day 3	
	4 h	8 h	4 h	8 h
AMST[a] ± SD (min)	2.8 ± 7.5	4.0 ± 6.1	1.0 ± 2.2	2.1 ± 3.9
RMST (min)	1.7	3.1	0.4	1.6
Range (min)	−10–33	−5–20	−3–10	−3–15

[a] AMST, absolute sampling error; RMST, relative sampling error.

Table 2 The CPT-11 AUCs on days 1 and 3 calculated by this LSM

	Day 1	Day 3	Days 1 + 3
Mean ± SD (mg · h/liter)	3.76 ± 0.68	4.10 ± 0.86	7.86 ± 1.43
Range (mg · h/liter)	2.01–5.03	2.29–5.72	4.30–10.68
Max/min	2.50	2.45	2.48

Table 3 Toxicity in the first course by JCOG grade

	Grade (n = 30)			
	1	2	3	4
Leukopenia	8	2	4	2
Neutropenia	7	4	5	4
Nausea/vomiting	14	6	0	0
Diarrhea	12	9	2	1

chemotherapy or thoracic radiation; adequate bone marrow function (WBC count ≥ 4000/mm^3; hemoglobin ≥ 9.0 g/dl; platelets ≥ 100,000/mm^3), renal function (serum creatinine ≤ 1.5 mg/dl; creatinine clearance ≥ 60 ml/min), and hepatic function (total bilirubin ≤ 1.5 mg/dl; transaminases ≤ 2 × upper normal limits); life expectancy of at least 12 weeks; and written informed consent. All patients were required to have measurable or assessable tumors. The study was approved by the Institutional Review Boards of each institute. The participating institutions were as follows: National Cancer Center; National Cancer Center East; Niigata Cancer Center; National Sapporo Hospital; Cancer Institute Hospital; Hokkaido University School of Medicine; Asahikawa Medical College; Institute of Development, Aging and Cancer, Tohoku University; Showa University School of Medicine; and School of Medicine, Kanazawa University.

Treatment Protocol. Sixty mg/m^2 etoposide were dissolved in 250 ml of 5% glucose and administered i.v. over 60 min. Sixty mg/m^2 CPT-11 dissolved in 250 ml of 5% glucose were administered i.v. over 90 min just after the etoposide. Both CPT-11 and etoposide were given daily for 3 consecutive days. As antiemetic therapy, granisetron (3 mg) and dexamethasone (8 mg) were administered as a single 30-min infusion on days 1, 2, and 3; this therapy was completed before the infusion of etoposide. All patients received recombinant human G-CSF (50 μg/m^2 by daily s.c. injection from day 4 to day 17). Injection of recombinant human G-CSF was stopped if the ANC was greater than 5000/mm^3 after day 8 or greater than 2000/mm^3 after day 11. Patients continued to receive this treatment every 3–4 weeks until the disease showed progression or intolerable toxicity occurred.

Pharmacokinetic Studies and Limited Sampling Procedure. Blood samples (5 ml) were collected into heparinized tubes 4 and 8 h after the end of the CPT-11 infusion on both days 1 and 3. The blood was centrifuged immediately, and the plasma thus obtained was stored at −80°C until analysis. Plasma levels of CPT-11 were determined using a modification of the high-performance liquid chromatography method reported by Kaneda *et al.* (14). The detection limit for CPT-11 was 10 ng/ml. The laboratory intraassay coefficient of variation was 4–7%, whereas the interassay coefficient of variation ranged from 5 to 8%.

The formulas of the LSM that we developed previously for estimating CPT-11 AUC were:

$$\text{Day 1: CPT-11 AUC} = 5.09\,C4 + 16.48\,C8 + 1.05 \text{ (model 1)}$$

and

$$\text{Day 3: CPT-11 AUC} = 9.83\,C4 + 6.36\,C8 + 1.27 \text{ (model 2)}$$

where C4 and C8 are the plasma concentrations of CPT-11 (mg/liter) 4 and 8 h, respectively, after the end of the CPT-11 infusion. The precision of these models was assessed by calculating the percentage of the root mean squared error, and bias was assessed by calculating the percentage of the mean predictive error. These values were 3.0% and −1.4% for model 1 and 3.1% and 6.9% for model 2.

We used the Wilcoxon signed-ranks test to examine the accumulation between the each day's CPT-11 AUC.

Evaluation of Response, Toxicity, and Sampling Time. Tumor response was evaluated according to WHO criteria (15). Complete response was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response was defined as a reduction of at least 50% in the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks, with no appearance of new lesions or progression of any existing lesions. Disease progression was defined as an increase of at least 25% in tumor area or the appearance of new lesions. All other outcomes were classified as no change. Toxicities were evaluated according to JCOG criteria (16). For WBC counts, ANCs, and platelets, the percent decrease between the nadir and the pretreatment value were used to evaluate the degree of toxicity.

Because there is a significant possible source of error in the timing of blood sampling in this LSM, the exact finishing time of the CPT-11 infusion and sampling time were to be recorded so that the precision of the blood sampling time could be evaluated. Absolute mean sampling time error and its SD were defined as an absolute value of the difference between the planned and actual sampling times. Because it is clear whether a positive error is early or late, relative mean sampling time error was calculated by subtracting the planned actual sampling time from actual sampling time.

Pharmacodynamic Analysis. To determine whether a quantitative relationship exists between the AUC of CPT-11 and the magnitude of leukopenia and neutropenia, scatterplots of the percentage decrease in WBC counts and ANCs in the first course as a function of the CPT-11 AUC were made. These relationship were fitted to sigmoidal maximum effect (E_{max})

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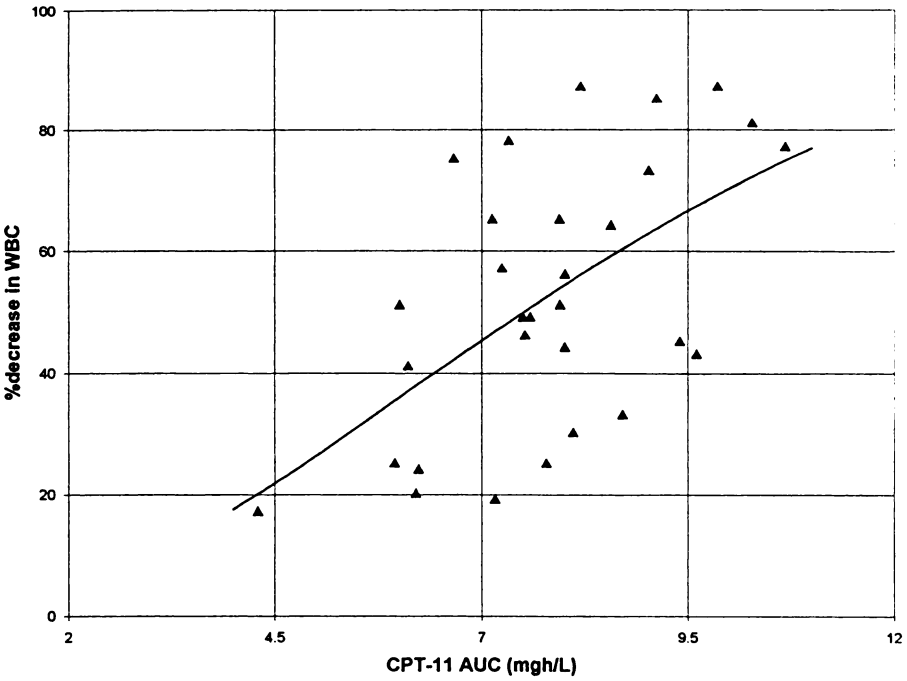

Fig. 1 Correlation between the percentage decrease in the WBC count and the CPT-11 AUC on days 1 and 3. Solid line is fit using a sigmoid E_{max} model defined as: % change in WBC $= E_{max}(AUC)^r/[(AUC_{50})^r + AUC^r]$, where $r = 6.17$, $AUC_{50} = 6.78$, and $E_{max} = 83.5$.

models by using the computer program WinNonlin and defined as:

% change in WBC counts or ANCs

$$= E_{max}(AUC)^r/[(AUC_{50})^r + AUC^r],$$

where r is a parameter describing the shape or sigmoidicity of the curve and AUC_{50} is the AUC that results in 50% of E_{max}.

The relationship between the CPT-11 AUC and response or the toxicity grade for diarrhea and nausea/vomiting were evaluated using single-factor ANOVA.

RESULTS

Between October 1993 and March 1994, 63 patients were entered into the Phase II study of CPT-11 combined with etoposide at 14 institutes, and 36 patients (57%) at 10 institutes (71%) were registered in this pharmacological study. However, six patients were excluded because of missing sampling data or damage sample during transport. Thus, 30 patients were evaluable. All patients were graded as PS 1. Twenty patients had adenocarcinoma, 5 had squamous cell carcinoma, and 5 had other types of carcinoma. Twenty-four patients had received no prior treatment.

Sampling Time Assessment. Although slight errors in sampling time did not markedly affect the precision of the LSM, large deviations from the protocol could invalidate its usefulness. Table 1 shows the evaluation of the precision of the sampling times. A total of 120 samples were collected. The absolute mean sampling time errors of day 1 C4, day 1 C8, day 3 C4, and day 3 C8 were 2.8, 4.0, 1.0 and 2.1 min, respectively, and SDs were small (7.5, 6.1, 2.2 and 3.9 min, respectively). A two-compartment model was fitted to the concentration-time curve of CPT-11 and the mean pharmacokinetic parameters used in our previous Phase I study of CPT-11 in combination with etoposide were: clearance, 14.1 liters/h/m^2; central compartment volume of distribution, 31.8 liters/m^2; and intercompartmental rate constants (K_{12} and K_{21}), 1.1 $^{h\ -1}$ and 0.4 $^{h\ -1}$ (17). A 5% change in the plasma concentration level at C4 and C8 was obtained with a sampling time error of approximately 10 min when we calculated using those parameters. A sampling time error of more than 10 min occurred for eight samples (7%), but there was no sampling time error of more than 10 min at both C4 and C8 in the same patient. Therefore, we calculated the AUC using all blood samples.

Pharmacokinetic Variability. The mean CPT-11 AUCs on day 1, day 3, and day 1 + day 3 calculated by LSM were 3.76, 4.10, and 7.86 mg·h/liter, respectively. The SDs were large, and the ratio of maximum AUC/minimum AUC was about 2.5, as shown in Table 2. The CPT-11 AUC was cumulative at the dose of 60 mg/m^2 administered i.v. for 90 min everyday for 3 consecutive days because there was significant difference between the CPT-11 AUC on day 1 and that on day 3 ($P = 0.0035$, Table 2). Considerable interpatient variability was noted in the AUCs on days 1 and 3.

Pharmacodynamics. All patients were assessable for toxicity. Leukopenia, neutropenia, and gastrointestinal toxicities were the main toxicities. Grade 3 or 4 leukopenia and neutropenia were observed in 6 (20%) and 9 (30%) patients, respectively, during the first course. Only two patients experienced grade 3 or 4 diarrhea. Other toxicities were mild and well tolerated (Table 3). Twenty-eight patients had measurable or evaluable lesions, allowing assessment of the clinical response. Six patients achieved partial response, 16 had no change, and 4 showed disease progression. The relationship between the

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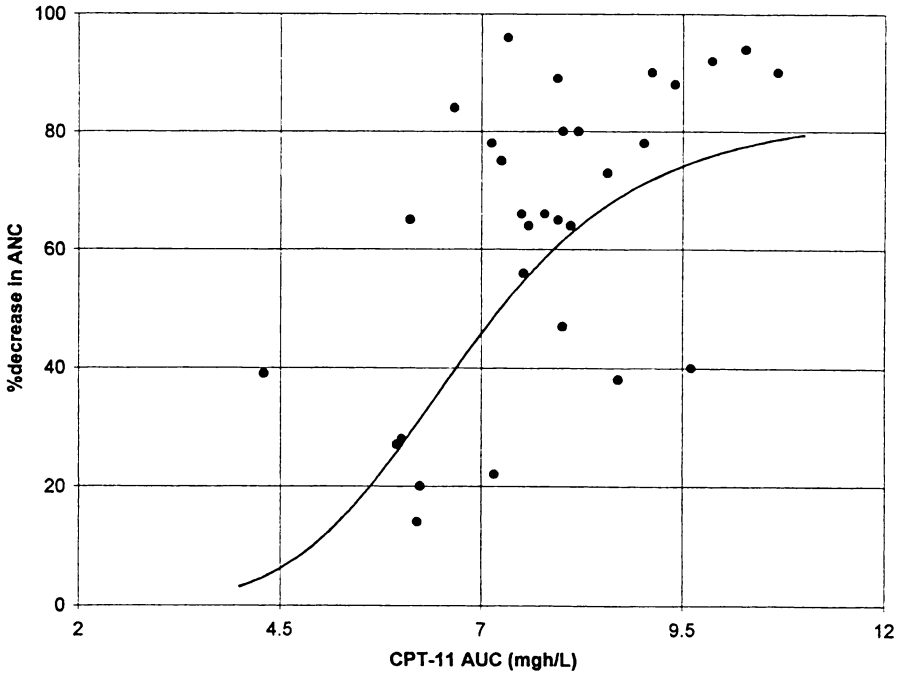

Fig. 2 Correlation between the percentage decrease in the ANC and the CPT-11 AUC on days 1 and 3. Solid line is fit using a sigmoid E_{max} model defined as: % change in ANC = $E_{max}(AUC)^r/[(AUC_{50})^r + AUC^r]$, where r = 2.20, AUC_{50} = 9.33, and E_{max} = 130.6.

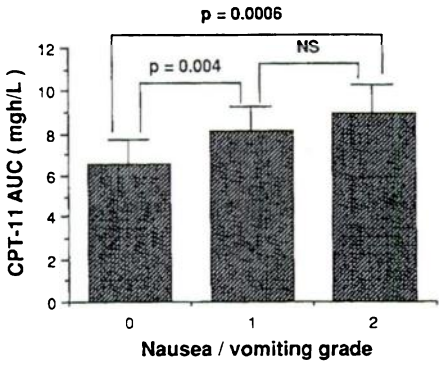

Fig. 3 Correlation between the grade of nausea/vomiting (JCOG toxicity criteria) and the CPT-11 AUC.

Table 4 PK/PD relationships

	P[a]					
	% decrease			Toxicity grade		
	WBC count	ANC	Plate	Diarrhea	Nausea/ vomiting	Response
AUC	0.001 [0.57]	<0.001 [0.59]	0.401 [0.16]	0.674	0.003	0.169

[a] Numbers in brackets indicate correlation relationships.

CPT-11 AUC and either the toxicity grade during the first course or response as pharmacodynamic effects was analyzed. The CPT-11 AUC correlated significantly with the percent decrease in WBCs and with the percent decrease in neutrophils (Figs. 1 and 2; Table 4). CPT-11 AUC also correlated significantly with the grade of nausea/vomiting (Fig. 3), but did not correlate with either the grade of diarrhea or response (Table 4).

DISCUSSION

To expand our knowledge of the pharmacodynamics of anticancer chemotherapy, methods must be developed for obtaining pharmacokinetic information from large numbers of patients. It has previously been suggested that LSM may be a useful method of obtaining such information because, for many drugs, only two or three samples are required to obtain acceptable estimates of the pharmacokinetic parameters. However, only a few studies have investigated the usefulness of a LSM in estimating AUCs in large numbers of patients in multicenter trials (18, 19). In the present study, we evaluated the utility of the limited sampling strategy for a novel anticancer agent, CPT-11, in multicentric Phase II study.

The biggest problem with LSM developed with stepwise forward regression is that the sampling points are fixed. Therefore, sampling time markedly affects the precision of the LSM. If samples are not obtained in strict accordance with the protocol, the value estimated from the LSM will be inaccurate. However, no reports have thus far referred to the evaluation of sampling times in multicenter trials. In the current study, the mean sampling time error was very small, about 2 min, and sampling time errors of more than 10 min occurred in only eight samples (7%). When we calculated plasma concentrations using the population pharmacokinetic parameters, sampling time errors of 10 min at C4 and C8 induced a 5% change in the plasma concentration, and therefore, all evaluable samples could be used in the LSM. Therefore, we suggest that pharmacokinetic studies using the LSM method could be useful in multicentric trials.

Of the 36 patients entered into this trial, 6 (20%) were

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excluded due to sampling mistakes. For example, in three patients, only two samples were collected. It would be desirable to control such mistakes to within 10%. In multicenter trials, institutes that are not interested in pharmacokinetic studies are included. In such institutes, it is difficult to collect plasma samples at a fixed time. We, therefore, require an alternative method that is flexible concerning sampling times and the number of samples. One approach to solve this problem would be the application of Bayesian method (20). The Bayesian algorithm integrates the information provided by a limited number of available samples with prior information about population pharmacokinetic parameter values, to allow estimation of parameter values for the individual patient. This method may allow some flexibility with regard to the sampling time.

Although CPT-11 has shown promising antitumor effects *in vitro* and *in vivo*, preclinical studies have suggested that most of its antitumor activity may be attributable to its active metabolite, SN-38. To examine the overall pharmacodynamics of CPT-11, it is, therefore, necessary to investigate the pharmacokinetics of SN-38 as well as those of CPT-11. Unfortunately, we were unable to develop a LSM for estimation of the SN-38 AUC because of large interpatient variability, resulting from the secondary peak in its plasma profile due to enterohepatic circulation. However, we considered information regarding the relationship between the CPT-11 AUC and its pharmacodynamics to be important as well. Although the antitumor activity of SN-38 was 100-1000 times stronger than that of CPT-11 *in vitro*, the plasma concentration of CPT-11 was shown to be 100 times higher than that of SN-38. This observation suggested that both SN-38 and CPT-11 are important for the pharmacodynamic effects such as antitumor activity and the toxicities. In fact, significant correlation between the CPT-11 AUC and toxicities has been shown in many Phase I studies of CPT-11.

Significant PK/PD relationships were observed in this patient population. The CPT-11 AUC correlated significantly with the intensity of leukopenia, neutropenia, and nausea/vomiting. Diarrhea did not correlate with the CPT-11 AUC. There was also no correlation between response and the CPT-11 AUC. This result agrees well with those of other studies (21, 22). However, these pharmacodynamic data are confounded by the administration of other agents such as etoposide or G-GSF, which would certainly influence the degree of myelosuppression, nausea, and vomiting. Thus, we consider that another investigation is needed to examine the relationship between the pharmacokinetics of CPT-11 and/or etoposide and pharmacodynamics such as toxicity or response without G-CSF because in this study: we haven't examined the pharmacokinetics of SN-38 and etoposide; the myelosuppression observed had been influenced by the G-CSF; the numbers of patients were too small to examine response adequately; and in another study, responses were observed with a high dose of CPT-11, which indicates that the AUC of CPT-11 and/or SN-38 is likely to be related to its anticancer effect (22).

In conclusion, we showed the usefulness of LSM in a multicentric trial. The blood sampling in LSM could be performed punctually, even in a multicentric trial. From an ethical and practical point of view, when performing pharmacological studies in large numbers of patients, a limiting sampling procedure including a Bayesian method for estimating individual pharmacokinetic parameters should be developed. We suggest, however, that we must not only develop the LSM but also conduct pharmacological studies using the LSM in large numbers of patients.

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