Cancer Chemother Pharmacol (2001) 48: 481–487
DOI 10.1007/s002800100355

ORIGINAL ARTICLE

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Phase I/II and pharmacologic study of irinotecan and carboplatin for patients with lung cancer

Received: 15 December 2000 / Accepted: 15 June 2001 / Published online: 21 September 2001

Abstract *Purpose*: To determine the maximum tolerated dose (MTD) of irinotecan combined with carboplatin, to evaluate its efficacy and toxicity for patients with lung cancer, and to examine its pharmacokinetics and pharmacodynamics. *Methods*: The dose of irinotecan was escalated from 40 mg/m^2 per week in increments of 10 mg/m^2. Carboplatin was fixed at 300 mg/m^2. Multivariate regression models with an interaction term were used to evaluate synergistic pharmacodynamic interactions. *Results*: The MTD and recommended dose of irinotecan were 60 and 50 mg/m^2, respectively. Dose-limiting toxicities were grade 4 neutropenia and grade 3 or 4 diarrhea. In phase II studies, response rates were 81.3% (95% confidence interval 61.8–100%) in 16 patients with small-cell lung cancer and 22.2% (2.7–41.8%) in 18 patients with non-small-cell lung cancer. Two patients (6%) experienced grade 4 neutropenia, thrombocytopenia, and grade 3 diarrhea. The area under the plasma concentration versus time curve (AUC) of carboplatin ranged from 2.87 to 9.31 mg·min/ml, with a median of 4.66 mg·min/ml. In pharmacodynamic analyses, the log-transformed surviving fraction in platelet count (SFp) showed a significant association with the AUC of carboplatin ($P = 0.010$), while that in neutrophil count (SFn) was not significantly correlated with any pharmacokinetic parameter. The interaction term was not significant in either case. *Conclusions*: These results indicate that AUC-based dosing of carboplatin is still rational in combination chemotherapy. A more sensitive method for predicting life-threatening toxicities is needed, however, because traditional pharmacokinetic parameters were not adequate tools for identifying patients at high risk of severe neutropenia and diarrhea. This combination regimen has only modest activity, and further studies are necessary to evaluate a different dose schedule.

Keywords Carboplatin · Irinotecan · Pharmacokinetics · Pharmacodynamics · Lung cancer

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Introduction

Irinotecan (CPT-11) is a topoisomerase I inhibitor showing greater antitumor activity and less toxicity than its parent compound camptothecin [21]. Irinotecan and its

major metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), have strong antitumor activities against various human malignancies including small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) [12, 23]. Irinotecan combined with cisplatin shows high response rates of 84% and 52% in SCLC and NSCLC, respectively [20, 26], and demonstrates a significant survival benefit for patients with extensive SCLC and stage IV NSCLC [27, 29]. Carboplatin is an analog of cisplatin, which produces less renal, neurologic, and gastrointestinal toxicities [3]. Because of the advantage of easier administration and an antitumor activity comparable with that of cisplatin, carboplatin is now widely used as a practical substitute for cisplatin in SCLC and NSCLC [18, 37].

The major dose-limiting toxicities (DLT) associated with irinotecan therapy are neutropenia and diarrhea, which may be life-threatening when the two toxicities are severe and occur coincidentally [11, 20, 26, 31]. Pharmacologic studies have shown that the areas under the plasma concentration versus time curve (AUC) of irinotecan and SN-38 might be correlated with the severity of leukopenia and neutropenia [4, 5, 30, 33]. The severity of diarrhea might be associated with the AUC or the peak plasma concentrations of SN-38 [5, 19]. In addition, Gupta et al. have suggested a correlation between the severity of diarrhea and a biliary index score, the index being the product of the relative AUC ratio of SN-38 to SN-38 glucuronide and the AUC of irinotecan [13, 14].

The major toxicity of carboplatin is hematologic, especially thrombocytopenia [9], and the AUC of unbound platinum has been shown to be correlated with the degree of hematologic toxicity when used as monotherapy [16]. The dose of carboplatin can be individualized to achieve a particular AUC using several dosing formulae [3, 6]. Among them, the most widely accepted is the Calvert formula which is based on the linear correlation of carboplatin clearance with glomerular filtration rate (GFR) [3]. Thus, AUC-based dosing of carboplatin is often used in combination chemotherapy [11, 31], even though little attention has been paid to possible pharmacokinetic/pharmacodynamic interaction with coadministered drugs.

In the present study, we performed a phase I/II trial of irinotecan and carboplatin on chemotherapy-naive patients with lung cancer. The objectives of the study were to determine the maximum tolerated dose (MTD) of this combination regimen, to evaluate its efficacy and toxicity, and to elucidate pharmacologic profiles of these drugs including an examination of pharmacokinetic/pharmacodynamic interaction using multivariate analysis.

Patients and methods

Eligibility criteria

Patients were enrolled in the study if they met the following criteria: (1) histologic or cytologic confirmation of lung cancer; (2) stage IV disease or stage III disease not amenable to concurrent chemoradiotherapy; (3) no prior chemotherapy and radiotherapy; (4) life expectancy at least 8 weeks; (5) age not more than 75 years; (6) performance status ≤ 2 on the World Health Organization (WHO) scale [39]; (7) adequate bone marrow function (leukocyte count $\geq 4000/\mu l$, neutrophil count $\geq 2000/\mu l$, platelet count $\geq 100{,}000/\mu l$), adequate hepatic function (bilirubin level $\leq$ 1.5 mg/dl, transaminase level not more than twice the upper limit of normal), and adequate renal function (serum creatinine level ≤ 1.5 mg/dl); (8) no concurrent malignancy; (9) no medical complications which prevented compliance with the protocol; and (10) no history of drug allergy. Patients with postoperative relapse or non-symptomatic brain metastasis were eligible. In the phase II studies, measurable lesions were also required. This study was approved by the Institutional Review Board at each participating institution, and written informed consent was obtained from all patients.

Evaluation

All patients underwent a complete medical history and physical examination, chest radiography, bone scintiscanning, computed tomography of the brain, chest, and abdomen, and fiberoptic bronchoscopy. Staging was done according to the TNM system [28]. Pretreatment evaluation included the following laboratory tests: complete differential blood cell count, serum electrolytes, total protein, albumin, total bilirubin, transaminases, alkaline phosphatase, lactate dehydrogenase, serum creatinine, urea nitrogen, and urinalysis. During the study, a complete blood cell count was obtained at least twice per week, and the other laboratory tests, and chest radiography were repeated weekly. Tumor responses were evaluated according to WHO criteria [39]. Toxicity was graded using the Japan Clinical Oncology Group grading system [38]. Patients were considered to be evaluable for response and toxicity if they had received at least one cycle of chemotherapy.

Treatment schedule

Irinotecan was dissolved in 250 ml 5% glucose solution and was given as a 90-min intravenous infusion. Subsequently, carboplatin dissolved in 500 ml saline was infused over 90 min. Irinotecan was planned to be administered on days 1, 8, and 15, and carboplatin was administered on day 1. If the patient experienced either hematologic toxicity greater than grade 1 or diarrhea greater than grade 0, irinotecan administration was withheld until recovery. The protocol recommended intensive use of loperamide as indicated by Gupta et al. [13] for patients who experienced diarrhea greater than grade 1, although the final decision was left to the oncologist in charge. In the event that the leukocyte count was less than $2000/\mu l$ or the neutrophil count less than $1000/\mu l$, granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously until recovery. Chemotherapy was repeated every 4 weeks.

Study design

Phase I study

At level 1, the irinotecan dose was set at 40 mg/m^2. At the subsequent levels, the irinotecan dose was increased in increments of 10 mg/m^2 and intrapatient dose escalation was not performed. The dose of carboplatin was fixed at 300 mg/m^2. At least three patients were to be entered at each dose level, and when any of them developed a DLT, three additional patients were entered. The DLT was defined as either hematologic toxicity of grade 4, or non-hematologic toxicity reaching grade 3 other than alopecia and nausea/vomiting. The MTD was defined as the dose level producing DLT in one-third or more of the patients. The dose level below the MTD was defined as the recommended dose for phase II studies.

Phase II studies

The total number of patients required for the phase II studies in SCLC and NSCLC were calculated separately, based on a two-stage minimax design [36]. We set response rates of 80% and 40% as target activity levels and chose 60% and 20% as the lowest response rates of interest for SCLC and NSCLC, respectively. In the first step, at least eight responses among 13 patients with SCLC and four among 18 patients with NSCLC were required for this combination to be considered worthy of further evaluation. Accrual of patients was not interrupted during the interim analysis.

Pharmacokinetic analysis

Pharmacokinetic study was performed on day 1 of the first course. Blood samples for a pharmacokinetic analysis of irinotecan were obtained at the end of irinotecan infusion, and 0.25, 0.5, 1, 2, 4, 8, and 24 h thereafter. The concentrations of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) were measured using high-performance liquid chromatography [17]. Blood samples for measurement of the ultrafiltered platinum were obtained at the end of the carboplatin infusion, and 0.25, 0.5, 1, 2.5, 4, 6.5, 22.5 h thereafter. Flameless atomic absorption spectrometry was used to measure platinum levels [22]. The carboplatin levels were calculated based on the platinum/carboplatin molar ratio. The AUC was obtained by the trapezoidal method with extrapolation to infinity using WINNONLIN ver 1.1 software (Scientific Consulting, Apex, N.C.). The biliary index was calculated as follows [13]:

$$\text{biliary index } (\text{ng}\cdot\text{h/ml}) = \frac{\text{AUC of irinotecan } (\text{ng}\cdot\text{h/ml}) \times \text{AUC of SN}-38(\text{ng}\cdot\text{h/ml})}{\text{AUC of SN}-38 \text{ glucuronide } (\text{ng}\cdot\text{h/ml})}$$

Because GFR was not measured in the present study, the observed AUC of carboplatin was compared using a paired *t*-test with that retrospectively calculated from the Calvert formula [3] using the Cockcroft-Gault equation [7] instead of GFR.

Pharmacodynamic analysis

The relationship between hematologic toxicities and pharmacokinetic parameters such as the biliary index, and the AUCs of carboplatin, irinotecan, SN-38, and SN-38 glucuronide were analyzed using a univariate linear regression model. The surviving fraction in neutrophil counts and in platelet counts were log-transformed and tested in the model:

$$\log-\text{transformed surviving fraction (SF)} = \log_{10}\frac{\text{nadir blood cell count}}{\text{pretreatment blood cell count}}$$

Because the biliary index, and the AUCs of irinotecan and SN-38 glucuronide were not significant in any univariate analysis, they were not included in subsequent multivariate analyses. Thus, a multivariate linear regression analysis was performed to determine whether the log-transformed surviving fraction was significantly associated with the AUCs of carboplatin and SN-38, and the interaction term between the two variables. Variables included in the model were selected in a forward stepwise procedure. The full model was as follows:

$$\text{SF} = \alpha + \beta_1 \times \text{AUC}_{\text{carboplatin}} + \beta_2 \times \text{AUC}_{\text{SN}-38} + \beta_3 \times \text{AUC}_{\text{carboplatin}} \times \text{AUC}_{\text{SN}-38}$$

Where $\text{AUC}_{\text{carboplatin}}\times\text{AUC}_{\text{SN-38}}$ denotes an interaction term to evaluate whether there was any pharmacodynamic interaction between the two drugs, α denotes an intercept, and β_x denotes a coefficient [34]. A logistic regression model was used to investigate the relationships between the pharmacokinetic variables and the proportion of patients who experienced diarrhea greater than grade 1, and between the pharmacokinetic variables and response rates. Statistical analyses were performed using JMP ver 3.0.2 software (SAS Institute, Cary, N.C.).

Results

From March 1995 to April 1997, a total of 44 patients were entered onto this phase I/II trial (Table 1). One patient with bulky stage IIIA NSCLC was considered eligible because the disease was judged to be not amenable to either surgery or concurrent chemoradiotherapy.

Dose escalation results

Table 2 summarizes the results of dose escalation. At levels 1 (40 mg/m^2 per week of irinotecan) and 2 (50 mg/m^2 per week), no patient experienced DLT (Table 2). One patient at level 3 (60 mg/m^2 per week) developed grade 4 hematologic toxicities (leukopenia, neutropenia, and thrombocytopenia), grade 3 diarrhea, and grade 4 liver and renal toxicities. The fourth patient

Table 1 Patient characteristics

	Phase I	Phase II	
		SCLC	NSCLC
No. of patients	10	16	18
Gender			
Male	8	13	16
Female	2	3	2
Age (years)			
Median	61.5	67	64
Range	52–74	34–72	34–74
Performance status, 0/1/2	3/6/1	12/3/1	5/13/0
SCLC, limited/extensive disease	1/2	14/2	
NSCLC, stage IIIA/IIIB/IV	1/4/2		0/8/10
Serum creatinine (mg/dl) (mean ± SD)	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.1
Body surface area (m^2) (mean ± SD)	1.57 ± 0.09	1.47 ± 0.17	1.49 ± 0.18

Table 2 Toxicities (grades 3/4, Japan Clinical Oncology Group) in phase I study (– no grade entity)

	Dose level		
	1	2	3
Dose of irinotecan (mg/m^2)	40	50	60
No. of patients	3	3	4
Leukopenia	1/0	0/0	0/2
Neutropenia	2/0	1/0	1/2
Thrombocytopenia	0/0	1/0	2/1
Anemia	2/–	1/–	1/–
Diarrhea	0/0	0/0	1/1
Abnormal liver function	0/0	0/0	0/1
Abnormal renal function	0/0	0/0	0/1

entered at level 3 experienced grade 4 leukopenia and neutropenia, grade 2 thrombocytopenia, and grade 4 diarrhea. Therefore, the accrual of additional patients at level 3 was stopped and we judged the dose level to be the MTD. The recommended dose for the phase II study was irinotecan 50 mg/m^2 on days 1, 8, 15 and carboplatin 300 mg/m^2 on day 1. In two separate phase II studies of SCLC and for NSCLC, 16 and 18 patients were included, respectively (Table 1).

Toxicity

In the evaluation of toxicity in the phase II trials, the results from 16 patients with SCLC and 18 with NSCLC were combined for analysis. A total of 95 courses of the treatment were delivered, and the median number of treatment courses was two (range one to six). Patients with SCLC received a median of four courses compared with two courses among NSCLC patients ($P = 0.032$). The hematologic and non-hematologic toxicities across all courses are shown in Table 3. In the first course of chemotherapy, two patients experienced severe hematologic toxicities (grade 4 leukopenia, neutropenia, and thrombocytopenia) accompanied by grade 3 diarrhea. In these patients and two other patients who experienced DLT in the phase I study, severe toxicities occurred after the administration of irinotecan on day 8. All the four patients received G-CSF only after development of grade 4 neutropenia because of a precipitous fall in their neutrophil count.

Table 3 Toxicities (grades 2/3/4, Japan Clinical Oncology Group) in phase II studies (– no grade entity)

No. of patients	34
Total number of courses	95
Hematologic	
Leukopenia	32/8/3
Neutropenia	34/2/1
Anemia	32/16/–
Thrombocytopenia	14/8/7
Non-hematologic	
Nausea/vomiting	7/3/0
Diarrhea	2/3/0
Fever	5/0/0
Nephrotoxicity	1/0/0

Response

Among 16 patients with SCLC, 14 had limited disease (LD) and 2 had extensive disease (ED). In patients with LD, all but one who developed brain metastasis during the treatment, received thoracic radiotherapy after the two courses of chemotherapy. Two complete responses (14.3%) and nine partial responses (64.3%) were observed at the end of the second course of chemotherapy in patients with LD. Two patients with ED also achieved partial responses. Although a response rate of 84.6% (11 of 13 patients) was observed at the interim analysis, the response rate in patients with LD did not reach 80% and therefore we judged this combination as unpromising and stopped the phase II study in SCLC.

In the phase II study for NSCLC, 4 out of 18 patients achieved a partial response. The response rate of 22.2% (95% confidence interval 2.7–41.8%) suggested borderline activity against NSCLC and the phase II study for NSCLC was also stopped.

Pharmacokinetics

Blood sampling was not performed in eight patients because of refusal in one and technical problem in seven. As a result, the pharmacokinetic study was performed on 36 patients. The results of the pharmacokinetic analyses are shown in Table 4. The AUCs of irinotecan in two patients at level 1 (40 mg/m^2 of irinotecan) were 4.39 and 6.73 μg·h/ml, and those of SN-38 were 222 and 494 ng·h/ml, and in two patients at level 3 (60 mg/m^2 of irinotecan) were 4.04 and 3.72 μg·h/ml, 339 and 437 ng·h/ml, respectively. In 32 patients receiving a 50 mg/m^2 dose, the AUCs of irinotecan, SN-38, and SN-38 glucuronide had ranges of 3.5-, 10.5-, and 10.5-fold, respectively. In 36 patients the metabolic ratio of SN-38, calculated as AUC of SN-38/AUC of SN-38 glucuronide, varied from 0.04 to 2.02 with a median of 0.38 and the biliary index also had an extremely wide range (78.2-fold).

The fixed dose of 300 mg/m^2 resulted in a wide range of carboplatin AUC (Table 4). The observed carboplatin clearance (Table 4) was lower than the estimated clearance determined from the Calvert formula using the Cockcroft-Gault equation as a substitute for GFR

Table 4 Pharmacokinetic parameters. Values are medians (range); 36 patients

Parameter	Irinotecan	SN-38	SN-38 glucuronide	Carboplatin
$T_{1/2}$ (h)	13.4 (7.3–24.2)	22.0 (3.5–56.4)	14.7 (4.8–136.2)	3.2 (1.5–9.4)
C_{max}	0.63 (0.51–0.97) μg/ml	17.0 (6.9–27.5) ng/ml	–	27.9 (16.2–34.6) μg/ml
AUC	5.00 (2.42–8.49) μg·h/ml[a]	260 (63–660) ng·h/ml[a]	570 (190–1991) ng·h/ml[a]	4.66 (2.87–9.31) mg·min/ml
CL	14.39 (8.25–28.97) l/h/m^2	–	–	93.2 (53.5–173.8) ml/min
Biliary index (ng·h/ml)[b]	–	–	1713 (175–13,695)	–

[a]Calculated from 32 patients treated at dose level 2 (50 mg/m^2 of irinotecan)
[b]$AUC_{irinotecan} \times AUC_{SN\text{-}38}/AUC_{SN\text{-}38\ glucuronide}$

(median 111.4 ml/min, range 74.7–161.3 ml/min, $P=0.038$).

Pharmacodynamics

Of the four patients who experienced severe toxicities in this phase I/II study, one patient refused blood sampling. In the first course of chemotherapy, 19 patients received the planned dose of irinotecan, 14 did not receive irinotecan on either day 8 or day 15, and 3 received irinotecan on day 1 only. In univariate analyses, the log-transformed surviving fraction in neutrophil counts (SFn) was not significantly correlated with either the AUC of SN-38 ($r=0.25$, $P=0.136$; Fig. 1A) or the AUC of carboplatin ($r=0.16$, $P=0.342$). In contrast, the log-transformed surviving fraction in platelet count (SFp) was correlated with the AUC of SN-38 ($r=0.36$, $P=0.030$) and the AUC of carboplatin ($r=0.50$, $P=0.002$; Fig. 1B). The risk of diarrhea greater than grade 1 was not significantly correlated with the AUC of SN-38 ($r=0.29$, $P=0.109$). The AUCs of irinotecan and SN-38 glucuronide, and the biliary index were not correlated with hematologic or non-hematologic toxicities.

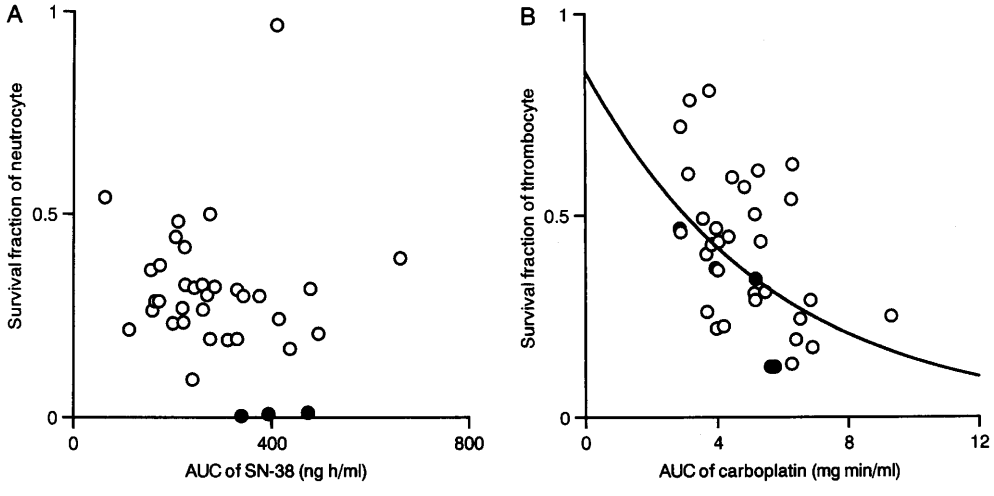
Multivariate linear regression analysis revealed no significant correlation between any of the pharmacokinetic parameters and SFn, although the AUC of SN-38 was selected in a stepwise procedure ($P=0.136$). On the other hand, multivariate analysis revealed a significant association between the AUC of carboplatin and SFp (coefficient –0.0656, $P=0.010$). The interaction term was not selected in either analysis, suggesting the absence of a synergistic pharmacodynamic interaction in this combination chemotherapy. After dividing the 36 patients into 19 who received irinotecan as planned and 17 who did not receive at least one dose, we reanalyzed the data and confirmed that the AUC of SN-38 and that of carboplatin were selected in stepwise procedure in both populations. The small number in each population, however, prevented the finding of statistical significance in the final model. In the multivariate logistic regression analysis for diarrhea, only the AUC of SN-38 remained in the model; the AUC of carboplatin and the interaction term were not selected in the stepwise procedure.

To investigate the relationships between antitumor response and the pharmacokinetic variables, multivariate logistic regression analyses were performed separately in patients with SCLC and NSCLC. No significant association was found in either analysis.

Fig. 1 **A** Relationship between surviving fraction of neutrophils and AUC of SN-38 (*closed circle* 3 patients who experienced diarrhea reaching grade 3 in the first course of chemotherapy, *open circles* 33 patients who did not experience diarrhea reaching grade 3 in the first course of chemotherapy). **B** Relationship between surviving fraction of platelets and AUC of carboplatin (*closed circles* 3 patients who experienced diarrhea reaching grade 3 in the first course of chemotherapy, *open circles* 33 patients who did not experience diarrhea reaching grade 3 in the first course of chemotherapy). The regression equation is: $\log_{10}(\text{surviving fraction of platelets}) = -0.0670-0.0077 \times \text{AUC}_{\text{carboplatin}}(\text{mg} \cdot \text{min/ml})$

Discussion

The MTD in this study was irinotecan 60 mg/m^2 on days 1, 8, 15 and carboplatin 300 mg/m^2 on day 1. Fukuda et al. have also reported the same dose of irinotecan as the MTD combined with a target carboplatin AUC of 5 mg·min/ml [11]. The DLTs in their study were neutropenia, thrombocytopenia, and diarrhea, including one patient who concomitantly experienced these toxicities and died of renal failure. Okamoto et al. conducted a phase I trial of irinotecan combined with a target carboplatin AUC of 5 mg·min/ml, with recombinant human granulocyte colony-stimulating factor support [31]. Although the incidence of neutropenia was decreased in their study, dose escalation was stopped at 70 mg/m^2 because of severe diarrhea. These authors stated that the combination of irinotecan and AUC-based carboplatin appears to be active in SCLC and NSCLC. We do not consider the dose used in the pre-



sent phase II trials suboptimal because the median AUC of carboplatin was 4.66 mg·min/ml, which is comparable to the target AUC in their studies. Nevertheless, this combination chemotherapy in this dose schedule had only borderline activity against SCLC and NSCLC. Our results might be partly explained by the conventional method of carboplatin dose calculation based on body surface area, since other investigators have found that AUC-based dosing can improve the therapeutic index of carboplatin in retrospective analyses [35].

In this study, total body clearance of irinotecan and the AUC of SN-38 divided by irinotecan dose (in milligrams per meters squared) were similar to those in patients treated with irinotecan alone or irinotecan combined with cisplatin [14, 24, 25, 32]. Previous investigators have also shown that the administration sequence of irinotecan and cisplatin has no influence on the pharmacokinetics of the two drugs [8]. Comparison with historical data, however, is an insufficient method to rule out pharmacokinetic interaction, and crossover designed pharmacokinetic studies are necessary for precise evaluation. We found that the measured AUC of carboplatin was significantly lower in the present study than that retrospectively calculated, which was also seen in a previous study of carboplatin monotherapy [2]. This discrepancy can be explained by the systematic overestimation of carboplatin clearance by the Calvert formula when the creatinine level is determined using the enzymatic method [1]. Since the serum creatinine levels were determined using this method in the present study, we consider that there is no clinically meaningful pharmacokinetic interaction between carboplatin and irinotecan.

In clinical trials of combination chemotherapy, pharmacodynamic analysis has rarely been performed because of its difficulty. Although Egorin et al. have proposed the generalized sigmoid E_{max} models to evaluate a pharmacodynamic relationship in combination chemotherapy, the precise mechanism of antitumor activity of each drug should be known if these models are to be used [10]. We used multivariate regression models which incorporated an interaction term and thus enabled pharmacodynamic interaction to be evaluated [34]. Although no synergistic pharmacodynamic interaction was confirmed in this study, at least an additive effect appeared to exist. In fact, a regression curve for the relationship between SFn and the AUC of SN-38 showed an intercept value of 0.43, which could be explained by the influence of carboplatin. Previous investigators have also reported that neutropenia in combination chemotherapy is more severe than would be expected from the sigmoid E_{max} model fitted to historical data [15].

In conclusion, we conducted a phase I/II trial of irinotecan and carboplatin. Pharmacologic analyses suggested the absence of a synergistic interaction in pharmacodynamics, although an additive effect seemed to exist. Because traditional pharmacokinetic parameters are not always adequate tools to identify patients at high risk of severe neutropenia and diarrhea, a more sensitive method is required for predicting these life-threatening toxicities. Abandonment of conventional carboplatin dosing according to body surface area would be appropriate in further studies of this combination regimen.

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