Table 2. Number of patients with each toxicity

	Grade			
	1	2	3	4
Leukopenia	0	1	1	0
Neutropenia	1	1	1	0
Anemia	0	2	0	0
Thrombocytopenia	0	0	0	0
Alopecia	0	4	–	–
Neuropathy	4	0	0	0
Arthralgia	2	0	0	0
Myalgia	1	1	0	0

One patient achieved a complete response after 18 cycles of paclitaxel, two patients achieved partial responses after 18 cycles of treatment, and one patient had disease progression after 6 cycles of treatment (Table 1). The PFS of the four patients ranged from 1.5 to 12 months. The PFSs were 1.5 months in the patient whose disease progressed and 8 months in the patient whose disease achieved a complete response. The PFSs for the two patients who had partial responses were 6.5 and 12 months.

All patients were assessed for toxicity, and no patients discontinued or skipped administration of paclitaxel because of toxicity. Toxicity was evaluated according to the NCI-CTC, version 2. Toxicities are listed in Table 2. Two patients experienced grade 2 or 3 leukopenia, three experienced grade 1, 2, or 3 neutropenia, and two experienced grade 2 anemia. No patients experienced thrombocytopenia. All of the patients experienced grade 2 alopecia. Peripheral neuropathy was within grade 1 for all patients. Grade 1 arthralgia occurred in two patients and grade 1 or 2 myalgia in two patients. All of the patients were able to have paclitaxel administered at the outpatient clinic.

Discussion

Weekly paclitaxel has been reported as effective salvage chemotherapy for ovarian carcinoma.[10-12] Markman et al.[10] conducted a phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. They treated 52 patients with weekly paclitaxel (80 mg/m^2; 1-h infusion) and reported that it was generally well tolerated. Of a total of 248 cycles, only 13 (5%) were modified (dose reduction or treatment delay) because of side effects. Therapy was discontinued in 5 patients because of toxicity (4 because of peripheral neuropathy, and 1 because of painful fingernail beds). Because of these reports of minimal toxicity in patients with ovarian carcinoma, weekly paclitaxel is thought to be a reasonable treatment for patients with advanced or recurrent endometrial carcinoma. Because it is not currently possible to provide curative therapy to patients with advanced or recurrent endometrial carcinoma, the role of chemotherapy for these patients remains palliative. It is, therefore, important that patients do not suffer from severe toxicity during treatment, and that the impact of treatment on patients' QOL is minimized.

In our case series of weekly paclitaxel for CAP-resistant advanced or recurrent endometrial carcinoma, none of the four patients suffered from severe toxicity requiring hospitalization or treatment discontinuation. Furthermore, all the patients were able to have treatment in an outpatient setting.

The effectiveness of paclitaxel for endometrial carcinoma has recently become evident. The response rate of paclitaxel for endometrial carcinoma has been reported as 36% to 46% in three trials.[2,4,13] Paclitaxel should therefore also be beneficial in CAP-resistant advanced or recurrent endometrial carcinoma. Indeed, three of our four patients had some response to paclitaxel. Weekly administration of paclitaxel may also be an improved method for sustained cumulative exposure and dose-dense drug delivery. Preclinical data have suggested that the duration of exposure is an important factor in the cytotoxic activity of paclitaxel.[14] In patients with metastatic breast cancer who have undergone prolonged (96-h) infusions of paclitaxel, duration of exposure has been found to be important for the clinical activity of the drug. However, a 96-h continuous infusion of paclitaxel is inconvenient for both clinics and patients. Extended cumulative exposures can also be achieved with frequent, repetitive drug administrations; for example, with a weekly schedule. Weekly dosing of paclitaxel has been demonstrated to be well-tolerated and feasible. Weekly administration of paclitaxel is dose-intense, but also yields a favorable toxicity profile. Cellular cytokinetic principles imply that frequent drug exposure affords less opportunity for the emergence and regrowth of drug-resistant cell clones. Thus, weekly paclitaxel therapy may be an improved method for sustained cumulative exposure and dose-dense drug delivery.[15]

We suggest that weekly administration of paclitaxel may be a feasible chemotherapy treatment for CAP-resistant advanced or recurrent endometrial carcinoma. However, we treated only a small number of patients; therefore, future clinical trials are needed to further evaluate the effectiveness and toxicity of this treatment.

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A Phase I Study and Pharmacologic Evaluation of Irinotecan and Carboplatin for Patients with Advanced Ovarian Carcinoma who Previously Received Platinum-Containing Chemotherapy

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BACKGROUND. The objectives of the current study were to determine the maximum tolerated dose (MTD) of irinotecan and carboplatin in combination, to evaluate the efficacy and toxicity of the combination in patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy, and to examine the pharmacokinetics and pharmacodynamics of both drugs by using the Chatelut formula.

METHODS. Patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy were treated with a combination of irinotecan and carboplatin. Carboplatin was administered as a 60-minute intravenous infusion on Day 1 and was followed by irinotecan, which was administered as a 90-minute intravenous infusion on Days 1, 8, and 15. Six dose levels of irinotecan (in mg/m^2)/carboplatin (mg · mL/min) were planned: 50 mg/m^2/4 mg · mL/minute, 60 mg/m^2/4 mg · mL/minute, 50 mg/m^2/5 mg · mL/minute, 60 mg/m^2/5 mg · mL/minute, 50 mg/m^2/6 mg · mL/minute, and 60 mg/m^2/6 mg · mL/minute. The carboplatin dosage was calculated by using the Chatelut formula. Treatment was repeated at 28-day intervals.

RESULTS. In total, 19 patients in cohorts of 3 to 5 patients received irinotecan and carboplatin at 5 dose levels. The dose-limiting toxicities were Grade 4 neutropenia and Grade 4 thrombocytopenia. The MTD of the irinotecan/carboplatin combination was 60 mg/m^2/5 · mg mL/minute. Partial responses were observed at higher dose levels. Pharmacologic studies demonstrated that administration of the dosage estimated with the Chatelut formula instead of the Chatelut formula with adjustment for serum creatinine resulted in a slightly excessive dose of carboplatin.

CONCLUSIONS. The recommended dose for the Phase II study was irinotecan 60 mg/m^2 on Days 1, 8, and 15 with carboplatin 5 mg/mL · minute on Day 1 repeated every 4 weeks. *Cancer* **2005;104:1204–12.** © *2005 American Cancer Society.*

KEYWORDS: irinotecan, carboplatin, ovarian carcinoma, pharmacokinetics, Chatelut formula.

An objective response is achieved in approximately 60–80% of women with advanced ovarian carcinoma who are treated with platinum plus taxane combination chemotherapy.[1,2] Nonetheless, recurrence rates remain high even with current treatments, and most women with advanced ovarian carcinoma ultimately die of their disease. Thus, it is important not only to establish effective second-line chemotherapies but to use new drugs with no cross-resistance in first-line chemotherapy to avoid expression of drug-resistant clones in the early treatment period.

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Irinotecan (CPT-11) is a plant alkaloid extract from *Camptotheca acuminate* and a potent inhibitor of DNA topoisomerase I. It exhibits excellent antitumor activity not only against experimental models of a broad spectrum of tumors but against drug-resistant tumor cell lines. No cross-resistance has been found between CPT-11 and carboplatin, and a synergistic effect has been observed when CPT-11 has been used in combination with carboplatin in preclinical studies.[3–5] Moreover, it was demonstrated recently that CPT-11 is an active agent in patients with platinum-resistant ovarian carcinoma.[6]

Carboplatin is an analogue of cisplatin with less nonhematologic toxicity, and leukopenia and thrombocytopenia are its dose-limiting toxicities (DLTs).[7,8] The area under the plasma concentration-versus-time curve (AUC) of carboplatin correlates well with the extent of myelosuppression as well as with the response rate in patients with ovarian carcinoma,[9] and the dose of carboplatin can be individualized to achieve a particular AUC by using several formulae.[10,11] The most widely accepted is the Calvert formula, which is based on the linear correlation between carboplatin clearance and the glomerular filtration rate.[10] However, because the effect of the possible pharmacokinetic interaction with coadministered drugs on carboplatin clearance is unknown, the most practical formula for routine clinical use remains a matter of controversy.[12–17] The objectives of the current study were: 1) to determine the maximum tolerated dose (MTD) and the recommended dose of CPT-11 and carboplatin in combination for patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy, 2) to investigate the pharmacokinetics and pharmacodynamics of the combination, and 3) to evaluate the utility of the serum creatinine adjustment model for the Chatelut formula by using the creatinine peroxidase-antiperoxidase (PAP) method developed in a previous study in Japanese patients.[18]

MATERIALS AND METHODS

Patient Selection

Patients were enrolled in the study if they fulfilled the following eligibility criteria: 1) histologically proven ovarian carcinoma; 2) prior platinum-containing chemotherapy, whether in platinum-sensitive or platinum-resistant patients[19]; 3) life expectancy $\geq$ 3 months; 4) age 15 years or older but younger than 75 years; 5) an Eastern Cooperative Oncology Group performance status $<$ 2; 6) adequate bone marrow and organ function (leukocytes $\geq$ 4000/μL, neutrophils $\geq$ 2000/μL, platelets $\geq$ 100,000/μL, total bilirubin $\geq$ 1.5 mg/dL, serum transaminase levels not more than 2.5 times the upper limit of normal, serum creatinine $\geq$ 1.5 mg/dL); 7) having measurable lesions was not required; and 8) written informed consent. This study was approved by the Institutional Review Board of the National Cancer Center Hospital.

Patients who had active infection, bowel obstruction, interstitial pneumonitis, severe heart disease, or a past history of hypersensitivity to antitumor drugs were excluded from the study. Patients who had pleural effusion or ascites that required drainage, brain metastasis, or active concomitant malignancy also were excluded.

Treatment Plan and Dose-Escalation Procedure

Carboplatin dissolved in 250 mL of saline or 5% glucose solution was infused over 60 minutes; subsequently, CPT-11 dissolved in 500 mL saline or 5% glucose solution was given as a 90-minute intravenous infusion. Administration of CPT-11 was planned for Days 1, 8, and 15, and administration of carboplatin was planned on Day 1 at a dose targeting a specific AUC, as determined by the Chatelut formula: dose (mg) = AUC $\cdot$ [0.134 $\cdot$ weight + (218 $\cdot$ weight $\cdot$ (1-0.00457 $\cdot$ age) $\cdot$ (1-0.314 $\cdot$ gender)/serum creatinine expressed in micromolar concentration)], with weight expressed in kilograms, age in years, and gender equal to 0 for male and 1 for female.[11] Serum creatinine was measured by the PAP method with the Serotec CRE-L kit (Serotec Company, Sapporo, Japan). CPT-11 was withdrawn on Days 8 and 15 if the leukocyte count was $<$ 3000/μL, the platelet count was $<$ 100,000/μL, or diarrhea was $\geq$ Grade 1. This chemotherapy regimen was repeated every 4 weeks. Granisetron was used routinely as an antiemetic on Days 1, 8, and 15. Prophylactic granulocyte-colony stimulating factors were not used routinely.

The starting dose of CPT-11 and carboplatin was 50 mg/m^2 and AUC 4. Dose escalation with six different dose levels was planned, and at least three patients were entered at each dose level. No interpatient dose escalation was performed.

DLT and MTD

Severe or life-threatening (Grade 3 or 4) nonhematologic toxicity, with the exception of nausea and emesis, was considered dose limiting. A leukocyte count $<$ 1000/μL or a neutrophil count $<$ 500/μL that lasted $>$ 3 days or a platelet count $<$ 25,000/μL of any duration also were considered dose limiting. The dose was escalated to the next level when none of the three patients experienced DLT in the first cycle. If one of the three patients experienced DLT in the first cycle, then three additional patients were entered at that dose level. The MTD was defined as one dose level

below the dose that induced DLT in three of six patients during the first cycle.

Assessment of Treatment

We used World Health Organization (WHO) criteria to assess the response to treatment of patients who had measurable lesions.[20] Measurable lesions were evaluated radiographically. Pleural effusion, ascites, and bone metastases were not considered measurable sites. Patients without measurable lesions were classified as not evaluable.

CA-125 response was defined as a 50% reduction in the CA-125 level below the baseline value that persisted for ≥ 4 weeks. The CA-125 response was assessed and reported separately from the response of patients with measurable disease.[21] Toxicity was evaluated according to the Japan Clinical Oncology Group Grading system.[22]

Pharmacologic Analysis

CPT and carboplatin were infused in 1 arm of each patient, and blood samples for the pharmacokinetic study were taken from each patient's other arm on Day 1 of the first course. Blood samples (1 mL) for pharmacokinetic analysis of CPT-11 were obtained before the chemotherapy; at the end of the CPT-11 infusion; and 5 minutes, 15 minutes, and 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours after the end of the infusion. The concentrations of CPT-11 and its metabolites (SN-38 and SN-38 glucuronide [SN-38G]) were measured by a modified, reverse-phase, high-performance liquid chromatography method.[23] Blood samples (2 mL) for measurement of carboplatin were obtained before chemotherapy; at the end of the infusion; and 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 10 hours, and 24 hours after the end of the infusion. After immediate centrifugation, the plasma was transferred to an Amicon Centrifree tube (Amicon, Inc., Beverly, MA), and the ultrafiltrates of the plasma were stored at − 20 °C until measurement of the plasma-free platinum concentration by flameless atomic absorption spectrometry.[24] The carboplatin level was calculated based on the platinum/carboplatin molar ratio. The AUC was obtained by the trapezoidal method with extrapolation to infinity using WINNONLIN version 1.1 software (Scientific Consulting, Apex, NC). The biliary index was calculated based on the method described in a previous report.[25]

In the pharmacodynamic study, we evaluated the correlations between pharmacokinetic parameters and observed hematologic toxicities in the first course. Hematologic toxicity was calculated according to the following formula: percentage decrease = 100 × (count before treatment − nadir count)/(count before treatment), and it was related to the AUC according to a sigmoid E_{max} model as follows: Effect (%) = $100 \times E_{max}(AUC)^{\kappa}/(AUC_{50})^{\kappa} + AUC^{\kappa}$. Nonlinear least-squares regression performed with WINNONLIN was used to estimate the AUC that produce 50% of the maximum effect (AUC_{50}) and the sigmoidicity coefficient (κ).

To evaluate for adjustment serum creatinine by adding 0.2 mg/dL,[18] we compared the observed carboplatin clearance with carboplatin clearance calculated with the Chatelut formula using PAP methods with or without the adjustment model. The accuracy of the estimate was measured by calculating the mean predictive error (MPE) and the root mean square error (RMSE).[26]

TABLE 1
Patient Characteristics

Characteristic	No. of patients
No. of patients entered	19
Median age in yrs (range)	58 (40–63)
Performance status	
0	6
1	13
Histology	
Serous	15
Mucinous	1
Endometrioid	1
Clear cell	1
Unclassified	1
No. of previous regimens	
1	10
2	6
3	2
4	1
Platinum-free interval	
< 3 mos	10
3–6 mos	3
≥ 6 mos	6
Disease sites	
Pelvic tumor	7
Liver metastasis	3
Lymph node metastasis	3
Ascites	5
Pleural effusion	3
Other	2
Median 24-hr creatinine clearance mL/min (range)	65.9 (16.9–98.8)

RESULTS

Patient Characteristics

In total, 19 patients were enrolled on this trial between August 1996 and July 1999, and all patients previously has received platinum-containing chemotherapy. The patient characteristics are listed in Table 1. Their median age was 58 years (range, 40–63 yrs), and the performance status was 0 in 6 patients and 1 in 13

TABLE 2
Dose-Escalation Schedule and Actual Doses Given to Patients

Level	Dose		No. of patients	Total no. of courses	CPT-11 dose intensity (mg/m²/wk) delivered/projected	CPT-11 percentage dose delivered[a]
	CBDCA (AUC)	CPT-11 (mg/m²)				
1	4	50	3	7	30/38	81
2	4	60	3	8	26/45	64
3	5	50	3	7	29/38	80
4	5	60	5	23	25/45	60
5	6	50	5	25	21/38	58

CBDCA: the observed area under the concentration curve (AUC) for carboplatin; CPT-11: irinotecan.
[a] Actually delivered CPT-11 dose as a percentage of the planned dose.

TABLE 3
Major Toxicities Stratified by Dose Levels (70 courses)

	Toxicity grade															
	Leukopenia		Neutropenia		Anemia		Platelets		Nausea/emesis				Diarrhea			
Level	3	4	3	4	3	4	3	4	1	2	3	4	1	2	3	4
1	0	0	1	0	1	0	0	0	2	1	0	0	0	0	0	0
2	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
3	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0
4	1	0	0	1	3	0	4	0	0	2	0	0	0	1	0	0
5	1	1	2	2[a]	2	0	1	3	2	1	1	0	2	1	0	0

Platelets: thrombocytopenia.
[a] Two patients experienced Grade 3 febrile neutropenia.

patients. Nine patients had received one or more chemotherapy regimens before this study. In total, 70 courses of the regimen used in this study were administered through 5 dose levels, and all patients were assessable for toxicity (Table 2). The median number of courses was 4 (range, 1–7 courses). One-half of the patients (58.2%) in this study actually received CPT-11 on Day 8, but only 31.3% of patients received CPT-11 on Day 15. CPT-11 was withdrawn on Day 8 or Day 15 on 72 occasions, because of thrombocytopenia in 49% of episodes and because of leukopenia in 31% of episodes. However, on 9 occasions, the thrombocyte count was $> 75{,}000/\mu L$; and, on 17 occasions, the leukocyte count was $> 2000/\mu L$. Dose intensity and the percentage of the CPT-11 dose administered that was delivered at each dose level are shown in Table 2.

Recommended Dose Level

None of the 3 patients at Dose Levels 1, 2, 3, and 4 experienced DLTs. Because 1 of the 3 patients at Dose Level 5 experienced DLT (neutropenia and thrombocytopenia), an additional 3 patients were enrolled. Two of those patients developed DLT (neutropenia and thrombocytopenia); therefore, it was concluded that Dose Level 4 was the MTD and the recommended dose.

Toxicity

Leukopenia and neutropenia were the DLTs associated with this combination chemotherapy. Major toxicities stratified by dose levels are shown in Table 3. At Dose Level 5, 2 patients required platelet infusion and developed febrile neutropenia that required intravenous antibiotics. No anemia that required blood transfusion was observed in any treatment cycle at any level. Gastrointestinal toxicities, such as nausea, emesis, diarrhea, and appetite loss, were prominent. CPT-11 caused diarrhea, but it was mild (Grade 1–2). No treatment-related deaths occurred in the current study.

Responses

Ten patients had measurable lesions, and they were assessed for responses according to WHO criteria (2 patients at Dose Level 1, 2 patients at Dose Level 2, 1 patient at Dose Level 3, 3 patients at Dose Level 4, and

TABLE 4
Objective Response and CA-125 Response

Level	No. of patients	Response				No. of CA-125 responses[a]
		PR	NC	PD	NE	
1	3	0	2	0	1	1
2	3	0	2	0	1	0
3	3	0	0	1	2	0
4	5	3	0	0	2	2
5	5	2	1	0	2	3

PR: partial response; NC: no change; PD: progressive disease; NE: not evaluable.
[a] The number of CA-125 responses means number of patients who achieved a 50% reduction in CA-125 level compared with the baseline level, which that must have persisted for ≥ 4 weeks.

3 patients at Dose Level 5). An objective response was observed in 5 patients: a partial response was seen at Dose Level 4 in 3 patients, and a partial response was seen at Dose Level 5 in 2 patients. The platinum-free interval was < 3 months in 2 of the 3 patients who achieved a partial response at Dose Level 4. CA-125 responses were observed in 6 patients (Table 4). The median time to disease progression in this study was 6.1 months (range, 0.93–19.4 mos), and the median survival was 16.2 months (range, 2.5–51.9 mos).

Pharmacologic Study of CPT-11 and CBDCA

The pharmacokinetic study was performed in only 13 patients, because the other 6 patients refused blood sampling for the pharmacokinetic analysis. A summary of the pharmacokinetic parameters of CPT-11, SN-38, and SN-38G is shown in Table 5. The concentrations of CPT-11 and SN-38 versus the time curve at each dose are shown in Figures 1 and 2, respectively. The metabolic ratios of SN-38 and the biliary indexes calculated as the AUC of CPT-11 and the AUC of SN-38/AUC of SN-38G[25] were similar at both dose levels.

A summary of the pharmacokinetic parameters of carboplatin is shown in Table 5. The measured AUCs of carboplatin were higher than the estimated AUCs (Fig. 3). The observed carboplatin clearance and the carboplatin clearance calculated using the Chatelut formula were 74.1 ± 24.6 mL/minute (range, 31.8–120.0 mL/min) and 93.7 ± 29.2 mL/minute (range 37.0–138.9 mL/min), respectively. The accuracy of the estimation evaluated on the basis of the MPE and the RMSE was 22.8% and 31.3%, respectively, using the Chatelut formula without the adjustment model and − 1.1% and 17%, respectively, on the basis of calculations with the adjustment model (Fig. 4).

The pharmacodynamic analysis was undertaken to evaluate the correlations between pharmacokinetic parameters and hematologic toxicity in the first course. The correlation between the SN-38 AUC and the percentage decrease in neutrophil count is shown in Figure 5 (r = 0.292), and the AUC_{50} of SN-38 was 36.0 ng/hour/mL, with κ estimated at 0.38. The correlation between the carboplatin AUC and the percentage decrease in thrombocyte is shown in Figure 6 (r = 0.514), and the AUC_{50} of carboplatin was 2.76 mg · min/mL, with κ estimated at 2.80.

DISCUSSION

Based on the results of the current study, the combination of CPT-11 and carboplatin was feasible for patients who previously received platinum-containing chemotherapy, and it was concluded that the recommended dose for the Phase II study in patients with advanced ovarian carcinoma was CPT-11 60 mg/m^2 on Days 1, 8, and 15 combined with carboplatin AUC 5 on Day 1. To our knowledge, this is the first report of combination therapy with carboplatin and CPT-11 in patients with ovarian carcinoma.

In Phase I trials in previously untreated patients with lung carcinoma, the recommended dose of this regimen was CPT-11 50 mg/m^2 on Days 1, 8, and 15 and carboplatin AUC 5 mg/mL · minute on Day 1, and the DLTs were neutropenia, thrombocytopenia, and diarrhea.[27,28] Although the recommended CPT-11 dose in the current study was higher than in those studies, the main DLTs were neutropenia and thrombocytopenia, as expected, and no severe nonhematologic toxicities, such as diarrhea, were observed. We believe that the reasons for this may be that the dose intensity of CPT-11 (mg/m^2 per week) and the percentage of the dose delivered in our study were lower than in the other studies. The difference of the dose intensity is attributable to the fact that our criteria for administration on Days 8 and 15 were stricter than those used in the previous studies[17,27,28] and to the difference in the number of patients in a previously untreated or heavily treated setting.

Although the sequence of administration of CPT-11 and carboplatin in the current study was different from the sequence used in the patients with lung carcinoma, the pharmacokinetic parameters of CPT-11 and SN-38 were almost the same as those in the patients with lung carcinoma who were treated with CPT-11 (50 mg/m^2 on Days 1, 8, and 15) followed by a fixed dose of carboplatin (300 mg/m^2 on Day 1).[28] The sequence of the drug administration in a previous study did not affect the pharmacodynamics or kinetics in the combination of CPT-11 and cisplatin.[29] Therefore, the drug sequence administration may have no major influence on the pharmacokinetic parameters in the combination of CPT-11 and carboplatin.

TABLE 5
Summary of Pharmacokinetic Parameters[a]

Pharmacokinetic parameter	No. of patients	Cmax	$AUC^{0\rightarrow\infty}$	CL	$T_{1/2}$	Biliary index[b]
CPT-11		μ/mL	μg·hr/ml	L/m² hr	Hr	
50 mg/m²	8	0.69 ± 0.06	3.32 ± 0.25	13.21 ± 1.32	8.03 ± 0.75	—
60 mg/m²	5	1.14 ± 0.10	4.79 ± 0.44	13.00 ± 1.32	8.35 ± 1.05	—
SN-38		ng/mL	ng·hr/ml		Hr	
50 mg/m²	8	22.86 ± 2.6	225.6 ± 40.3	—	10.51 ± 1.98	—
60 mg/m²	5	28.27 ± 4.5	283.9 ± 62.7	—	11.67 ± 2.41	—
SN-38G		ng/mL	ng·hr/ml		Hr	ng·hr/ml
50 mg/m²	8	29.8 ± 3.1	464.7 ± 70.4	—	12.06 ± 1.50	1692.8 ± 843.7
60 mg/m²	5	45.6 ± 12.5	1040.2 ± 416.8	—	16.05 ± 1.41	1652.2 ± 511.4
CBDCA		mg/mL	mg·min/ml	mL/min	Hr	
AUC 4	6	13.97 ± 4.1	4.95 ± 0.99	77.7 ± 27.53	4.25 ± 0.74	—
AUC 5	4	16.4 ± 3.3	5.59 ± 0.48	77.99 ± 30.73	4.17 ± 1.23	—
AUC 6	3	21.7 ± 2.5	7.94 ± 1.88	80.69 ± 24.83	4.18 ± 0.37	—

Cmax: maximum plasma concentrations; AUC: area under the concentration curve; CL: clearance; $T_{1/2}$: elimination half-life; CPT-11: irinotecan; SN-38: 7-ethyl-10-hydoxycamptothecin; SN38G: SN-38-glucronide; CBDCA: the observed AUC of carboplatin.

[a] Data shown are the mean ± standard deviation in 13 patients.

[b] "Biliary index (ng·hr/ml)" was calculated as $AUC_{CPT-11} \times AUC_{SN-38}/AUC_{SN-38G}$.

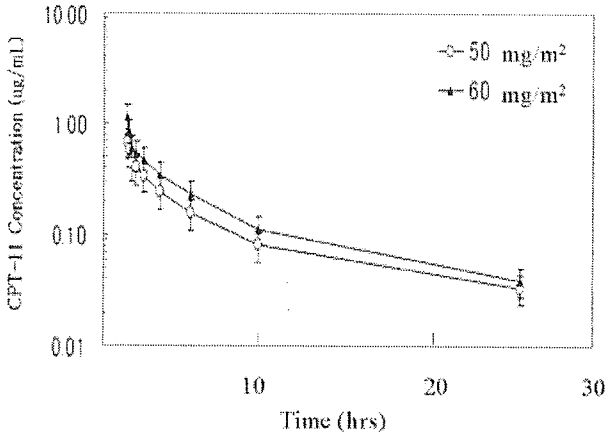

FIGURE 1. The concentrations of irinotecan (CPT-11) versus the time curve are illustrated for patients who received doses of 50 mg/m² and 60 mg/m² (n = 13 patients).

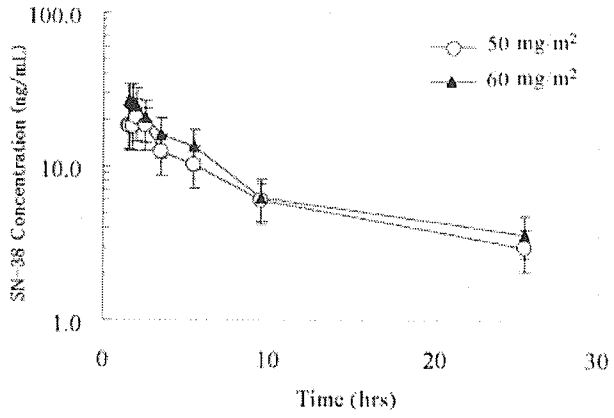

FIGURE 2. The concentrations of SN-38 versus the time curve are illustrated for patients who received in doses of 50 mg/m² and 60 mg/m² (n = 13 patients).

Although we used the Chatelut formula in the current study, several formulas are available to calculate the dose of carboplatin. The Calvert formula requires measurement of the glomerular filtration rate with a radioisotope, but creatinine clearance rates estimated by the Cockcroft–Gault or Jelliffe formula or actually measured, 24-hour creatinine clearance have been used widely instead. Several studies have compared the performance of the Chatelut formula and the Calvert formula by using several methods,[14–16] but the performance of each formula remains a matter of controversy, because previous studies have reported differences according to race, gender, method of calculating creatinine clearance, and unknown pharmacokinetic interactions between drugs in combination.[12–17] Fukuda et al. reported that a Phase I study of CPT-11 and carboplatin in 11 previously untreated Japanese patients with solid malignancies showed a significant correlation between measured carboplatin clearance and carboplatin clearance estimated by the Chatelut formula, and those authors recommended using the formula.[18] However, several clinical pharmacologic studies have shown that carboplatin clearance calculated by the Chatelut formula was higher than measured clearance and clearance calculated by the Calvert formula.[12–14] Furthermore, it has been reported that the adjusted serum creatinine value is

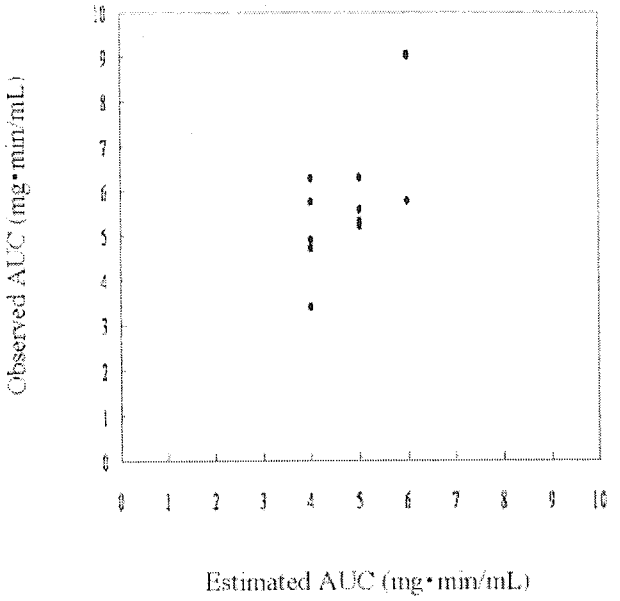

FIGURE 3. This chart illustrates the correlation between the observed area under the plasma concentration-versus-time curve (AUCs) of carboplatin (CBDCA) and the estimated AUC.

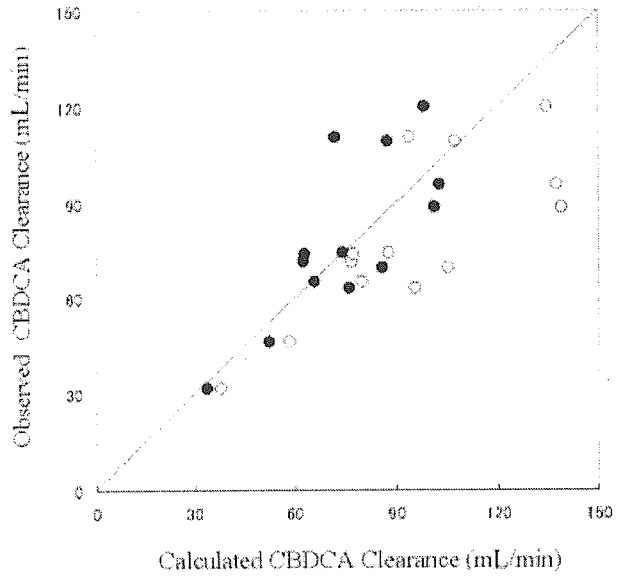

FIGURE 4. This chart illustrates the correlation between observed carboplatin (CBDCA) clearance and CBDCA clearance calculated with the Chatelut formula (open circles) and with the Chatelut formula adjusted for serum creatinine (solid circle) (see Dooley et al., 2002[17]). The line of identity (solid line) is shown. The bias and precision of each formula are expressed by the mean prediction error and the root mean square error (see Kaneda et al., 1990[24]).

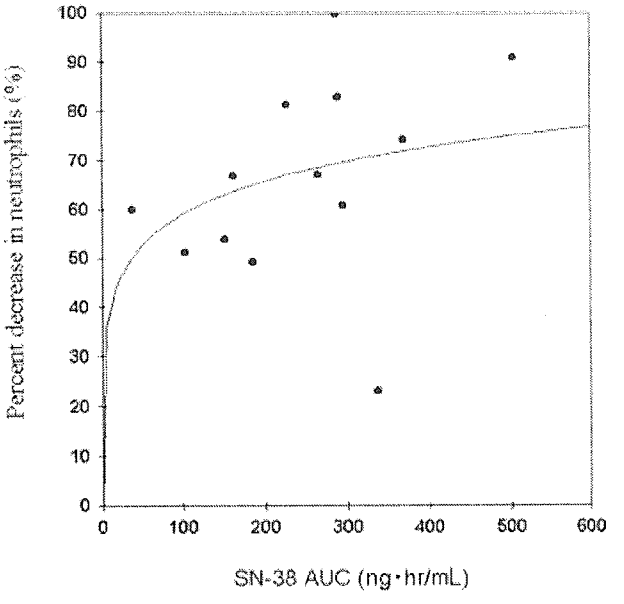

FIGURE 5. This chart illustrates the correlation between the SN-38 area under the plasma concentration-versus-time curve (AUC) and the percentage decrease in neutrophil count in Course 1 based on the sigmoid E_{max} model.

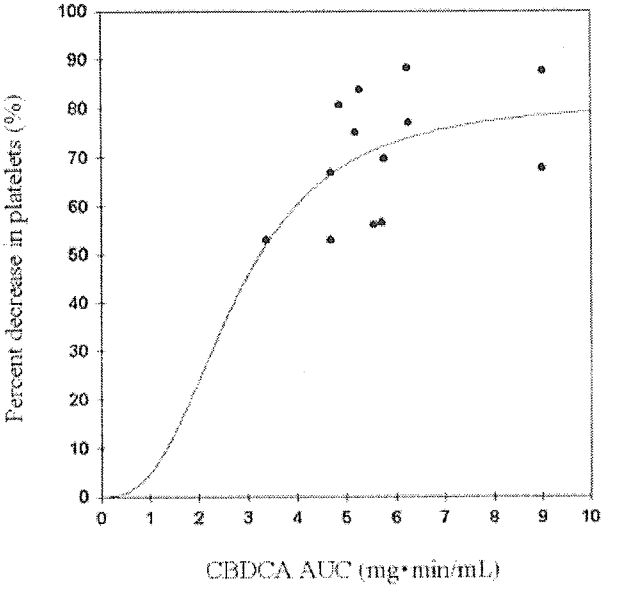

FIGURE 6. This chart illustrates the correlation between the carboplatin (CBDCA) area under the plasma concentration-versus-time curve (AUC) and the percentage decrease in platelet count in Course 1 based on the sigmoid E_{max} model.

appropriate for calculating the proper carboplatin clearance in Japanese patients.[18] Similar to previous reports, our study showed that the calculated carboplatin clearance values were higher than the measured values, and the accuracy of estimation by using the Chatelut formula improved when adjusted serum creatinine values were used.

In recent years, it has been demonstrated that paclitaxel is highly effective for ovarian carcinoma, and paclitaxel plus platinum combination chemotherapy now is accepted widely as a standard regimen for the first-line treatment for advanced ovarian carcinoma.[1,2] CPT-11 is a topoisomerase I inhibitor that has unique antitumor action. In a Phase II trial, CPT-11 and cisplatin combination chemotherapy yielded a high response rate of 76% in previously untreated patients with advanced ovarian carcinoma.[30] CPT-11 and cisplatin also yielded an overall response rate of 40% in patients who were treated previously with platinum-containing chemotherapy and a response rate of 30% in platinum-resistant patients.[31] Kigawa et al. reported a high response rate (60%) to second-line CPT-11 and cisplatin combination chemotherapy among patients who were treated previously cisplatin, and there was no difference in the proportion of patients who had platinum-sensitive or platinum-resistant tumors between responders and nonresponders.[32] Although the current study was performed in a Phase I trial setting, it is noteworthy that half of the patients with measurable lesions achieved responses. A previous study reported that the CPT-11 response rate was 17%, even among patients with platinum-resistant tumors.[7] Thus, our regimen may be effective both in patients with platinum-sensitive disease and in patients with platinum-resistant disease who previously received paclitaxel plus platinum combination chemotherapy.

In conclusion, the recommended doses of CPT-11 and carboplatin in combination are 60 mg/m^2 and an AUC of 5 mg/mL · minute according to the Chatelut formula, respectively, and this regimen may be effective in patients with ovarian carcinoma who previously received platinum-containing chemotherapy. The results of the pharmacologic analysis in this study suggest that the carboplatin clearance rates calculated with the Chatelut formula are higher than the actually measured carboplatin clearance and that adjustment for serum creatinine may be useful in calculating the proper dose.

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