A Phase I Clinical and Pharmacologic Study of a Carboplatin and Irinotecan Regimen Combined with Recombinant Human Granulocyte-Colony Stimulating Factor in the Treatment of Patients with Advanced Nonsmall Cell Lung Carcinoma

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Supported in part by Bristol Myers Squibb Co., Ltd., and Yakult Co., Ltd., Tokyo, Japan.

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Received July 28, 1997; revision received December 1, 1997; accepted December 1, 1997.

BACKGROUND. This Phase I study was designed to determine the toxicity and efficacy of a carboplatin and irinotecan (CPT-11) regimen with recombinant human granulocyte colony-stimulating factor (rhG-CSF) support for patients with advanced nonsmall cell lung carcinoma.

METHODS. Treatment consisted of carboplatin administered intravenously (i.v.) on Day 1 plus CPT-11 i.v. on Days 1, 8, and 15. The carboplatin dose was calculated using Calvert's formula, where the target area under the plasma concentration versus the time curve (AUC) was 5 or 6 mg · min/mL. rhG-CSF (2 μg/kg) was administered daily, except on Days 1, 8, and 15, until the leukocyte count exceeded 20,000/mm^3 (10,000/mm^3 after Day 16). Cycles were repeated every 4 weeks. Groups entered the trial at escalating CPT-11 and carboplatin dose levels of 60 mg/m^2 and 5 mg · min/mL, 70/5 and 60/6.

RESULTS. Twenty-one patients were enrolled in this study, of whom 20 were assessable for toxicity and therapeutic efficacy. Two of 6 patients experienced Grade 4 diarrhea at the 70/5 dose level, suggesting that this was the maximum tolerated dose (MTD). However, the 60/6 dose level was included because toxicities were very mild at the 60/5 dose level. At the 60/6 dose level, 1 of 6 patients experienced severe, life-threatening toxicity. Therefore, subsequent dose escalation was stopped and the study terminated. There were 7 responses (35%) among the 20 patients. At the 60/6 dose level (n = 5), the observed carboplatin AUC after aiming for a target AUC of 6 was 5.9 $\pm$ 0.9 mg · min/mL, as expected, although the AUCs of both CPT-11 and its active metabolite, SN-38, were lower than expected.

CONCLUSIONS. The recommended doses for Phase II studies are 60 mg/m^2 of CPT-11 and a target AUC of 5 mg · min/mL for carboplatin, plus rhG-CSF. The combination of AUC-based carboplatin and CPT-11 with rhG-CSF support appears to be an active regimen in the treatment of patients with NSCLC. ***Cancer* 1998;82: 2166–72.** © *1998 American Cancer Society.*

KEYWORDS: carboplatin, irinotecan (CPT-11), rhG-CSF, Calvert's formula, Phase I study, pharmacologic study.

Irinotecan (CPT-11), a new derivative of camptothecin, has been found to have clinical activity against leukemia, lymphoma,[1] small cell lung carcinoma (SCLC),[2] nonsmall cell lung carcinoma (NSCLC),[3] colorectal carcinoma,[4] and gynecologic cancer.[5] Its major active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), is also active against these tumors.[6] The dose-limiting toxicities (DLTs) of CPT-11

are diarrhea and leukopenia.[1–5] CPT-11 in combination with cisplatin has been found to be active against NSCLC, with response rates in the range of 31–54%.[7–9] Carboplatin is an analog of cisplatin but produces less nonhematologic toxicity.[10] It is active against NSCLC and its DLTs are thrombocytopenia and leukopenia. The area under the plasma concentration versus the time curve (AUC) of carboplatin correlates well with the degree of myelosuppression, especially thrombocytopenia, and with the response rates of patients with ovarian carcinoma.[11,12] Carboplatin is a unique antineoplastic agent, for which the desired AUC can be controlled on the basis of individual renal function, and dosing can be individualized using Calvert's formula: Dose (mg/body) = AUC · (glomerular filtration rate [GFR] + 25).[13] AUC-based dosing of carboplatin is a reasonable strategy for ensuring constant drug exposure, reducing the risk of unnecessary toxicity, and possibly improving the response rate.[14] With the availability of recombinant human granulocyte-colony stimulating factor (rhG-CSF), it has become possible to reduce the severity and duration of the leukopenia induced by combined chemotherapy. The use of rhG-CSF allows higher doses of CPT-11 and carboplatin to be used without incurring significant myelosuppression. Furthermore, carboplatin shows no cross-resistance with CPT-11,[15] and a synergistic effect has been observed with combined carboplatin and CPT-11 in preclinical studies.[16] When compared with other chemotherapy regimens by a cooperative group study, carboplatin was associated with a modest improvement in the 1-year survival rate of patients with advanced NSCLC.[17] Therefore, we conducted a Phase I study of combined CPT-11 and carboplatin with rhG-CSF support for advanced NSCLC. The objectives of the study were 1) to determine the optimal doses of CPT-11 and carboplatin when used in combination with rhG-CSF support, 2) to detect and quantify the clinical toxicities of this combination, 3) to assess its therapeutic activity in patients with advanced NSCLC, and 4) to investigate the pharmacokinetics of carboplatin, CPT-11, and its metabolite, SN-38.

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically confirmed advanced NSCLC were eligible for this Phase I study. Eligibility criteria included an expected survival of ≥3 months, age <75 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, measurable or evaluable lesions, no chemotherapy or radiotherapy within 4 weeks of entering this study, no previous platinum-based chemotherapy, adequate hematologic function (a leukocyte count of ≥4,000/mm^3, a platelet count of ≥10 × 10^4/mm^3, and hemoglobin ≥10.0 g/dL), renal function (serum creatinine ≤1.5 mg/dL and creatinine clearance [Ccr] ≥60 mL/min), and hepatic function (total serum bilirubin <1.5 mg/dL, and glutamic oxaloacetic transaminase and glutamic pyruvic transaminase less than twice the upper limit of the normal range). Patients who had experienced postoperative recurrence and those who had received radiotherapy to metastatic sites were eligible for the current study. Written informed consent was obtained from all patients.

Dose Escalation Procedure

The starting dose of CPT-11 was 60 mg/m^2 administered intravenously (i.v.) on Days 1, 8, and 15, increasing in 10 mg/m^2 steps. The starting dose of CPT-11 was based on that used in another Phase I study of the combination of CPT-11 and cisplatin with rhG-CSF support.[8] CPT-11 was infused i.v. in 250 mL 5% glucose over 90 minutes. Carboplatin was administered by 60-minute infusion after the CPT-11 infusion on Day 1, with the dose targeted to a specific AUC as described by Calvert et al.[13] The dose was determined by multiplying the targeted AUC by the sum of the glomerular filtration rate (GFR) plus 25. The 24-hour creatinine clearance was substituted for GFR. The starting target AUC of carboplatin was 5 mg · min/mL, increasing in 1 mg · min/mL steps. The starting target AUC was based on the finding that an AUC of 5 mg · min/mL was the minimum value producing tumor response with manageable toxicity in ovarian carcinoma.[11] Both drugs were administered using an electric infusion pump. RhG-CSF 2 μg/kg was administered daily by subcutaneous injection, except on Days 1, 8, and 15, until the leukocyte count exceeded 20,000/mm^3. If the leukocyte count exceeded 10,000/mm^3 after Day 16, rhG-CSF administration was stopped until the leukocyte count decreased to less than 3000/mm^3. Thirty minutes before CPT-11 administration, patients received antiemetic therapy consisting of dexamethasone 8 mg and granisetron 40 μg/kg by i.v. injection. For CPT-11–induced diarrhea, routine doses of loperamide or codeine phosphate were administered to patients receiving Step 1 and 2 chemotherapy, and high dose loperamide treatment, as described by Abigerges et al.,[18] was administered to Step 3 patients. High dose loperamide treatment given was as follows: at the first diarrheal episode, the patient took 2 mg loperamide every 2 hours. The patient was allowed to stop loperamide only after a 12-hour diarrhea free interval, after the last diarrheal episode. Subsequent courses of chemotherapy were initiated when the leukocyte count was ≥4000/mm^3 and the platelet count was ≥100,000/mm^3 after Day 28. If the leuko-

TABLE 1
Dose-Escalation Schedule and Actual Treatment Given to Patients: CPT-11 and CBDCA plus rhG-CSF

Step	Dose of CPT-11 (mg/m^2)	AUC of CBDCA (mg · min/mL)	No. of patients	Total no. of courses	Delivered DI of CPT-11/ projected DI of CPT-11	%[a]
1	60	5	8	21	44.3/45.0	98.4
2	70	5	6	15	47.8/52.5	91.1
3	60	6	6	12	40.4/45.0	89.8

DI: dose intensity (mg/m^2/wk); CBDCA: carboplatin; rhG-CSF: recombinant human granulocyte-colony stimulating factor; AUC: area under the plasma concentration versus the time curve.
[a] Percentage of the CPT-11 dose actually delivered, vs. the planned dose at each dose level, is represented.

cyte or platelet counts had not returned to normal levels or diarrhea had not disappeared by Day 1 of the next course of chemotherapy, both drugs were withheld until full recovery. If more than 6 weeks passed from the time of the last treatment before these criteria were satisfied, the patient was removed from the study.

Dose adjustments were made for both carboplatin and CPT-11 based on toxicity. Patients who experienced Grade 4 leukopenia or diarrhea Grade 3 or higher had their CPT-11 dose reduced by 25% for the next cycle. Patients who experienced thrombocytopenia Grade 3 or higher had their target AUC of carboplatin reduced by 20% for the next cycle. CPT-11 was withdrawn if the leukocyte count was less than 3000/mm^3, the platelet count was less than 75,000/mm^3, or diarrhea Grade 2 or higher occurred on Days 8 and 15.

Three dose levels were chosen (Table 1). At least 6 patients were included at each dose level, and the regimen was repeated every 28 days. No intrapatient dose escalation was initiated.

Evaluation

Tumor responses were evaluated according to World Health Organization criteria.[19] Complete response (CR) was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response (PR) was defined as a ≥50% reduction in the sum of the products of the 2 greatest perpendicular dimensions of all indicator lesions or a reduction of ≥50% in assessable disease for at least 4 weeks, with no appearance of new lesions or progression of any existing lesions. Progressive disease (PD) was defined as a ≥25% increase in the tumor area or the appearance of new lesions. All other outcomes were classified as no change (NC). Toxicities were evaluated according to ECOG common toxicity criteria. The maximum tolerated dose was defined as the dose causing Grade 3–4 nonhematologic toxicity (except nausea and vomiting) in at least one-third of the initial cycles and/or Grade 3–4 hematologic toxicity in at least two-thirds of the initial cycles.[8]

Pharmacokinetic Analysis

Pharmacokinetic analysis of carboplatin was performed on Day 1 of chemotherapy. Blood samples were collected into heparinized tubes 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after the i.v. administration of carboplatin over 60 minutes. The plasma free platinum concentration was measured using flameless atomic absorption spectrophotometry, as described previously.[20] The lower limit of sensitivity of the assay for free platinum was 10 ng/mL. The postinfusional plasma concentration versus time data were fitted in monoexponential equations.[21,22] The exact AUC for free platinum was calculated using standard equations.[22,23] Pharmacokinetic analysis of CPT-11 was performed on Day 8 of chemotherapy. Blood samples were collected into heparinized tubes before CPT-11 infusion; 0.5, 1, and 1.5 hours after the start of the infusion; and 5, 15, and 30 minutes and 1, 2, 4, 8, 12, and 24 hours after completion of the infusion. The blood was centrifuged immediately, and the plasma thus obtained was stored at −20 °C until analysis. Plasma levels of CPT-11 and SN-38 were determined by high performance liquid chromatography.[6] The lower limit of determination was 5 ng/mL for CPT-11 and 0.75 ng/mL for SN-38.

RESULTS

Between May 1994 and May 1996, 21 patients were registered for the study, and all received chemotherapy. Patient characteristics are listed in Table 2. There were 3 women and 18 men, with a median age of 64 (range, 34–74) years and a median 24-hour Ccr of 95 (range, 63–131) mL/min. Nineteen patients (90%) had an ECOG performance status score of 0–1. One patient had Stage IIIA, 5 Stage IIIB, and 15 Stage IV disease. The predominant histology was adenocarcinoma (52%). Nine patients had received prior therapy; two had received chemotherapy (paclitaxel) and seven had undergone surgery. The number of patients and courses per dose level are listed in Table 1. One patient was ineligible for analysis because rhG-CSF was

TABLE 2
Patient Characteristics

Characteristics	No. of patients
Total no. of patients	21
No. assessable	20
Gender	
Male	18
Female	3
Age, yrs	
Median	64
Range	34–74
Performance status[a]	
0	3
1	16
2	2
Stage	
IIIA	1
IIIB	5
IV	15
Histology	
Adenocarcinoma	11
Squamous cell carcinoma	5
Large cell carcinoma	3
Adenosquamous carcinoma	2
No. with no prior therapy	12
No. with prior therapy	9
Operation	7
Chemotherapy by paclitaxel	2
24-hr creatinine clearance, mL/min	
Median	95
Range	63–131

[a] Eastern Cooperative Oncology Group.

not administered due to a protocol violation during the first course of chemotherapy. Twenty patients were therefore assessable for toxicity and received 1–4 courses (median, 2; total, 48). Twelve patients (60%) received 2 courses and 6 (30%) received 3–4 courses.

Toxicity

Hematologic and nonhematologic toxicities are listed in Table 3. At Step 2, 2 of 6 patients experienced Grade 4 diarrhea, and this dose level was therefore considered to be the MTD according to our criteria. However, because toxicities during Step 1 therapy were generally mild, dose escalation to Step 3 was optionally performed. One patient who was registered at Step 3 experienced simultaneous Grade 4 leukopenia, thrombocytopenia, and diarrhea on Day 7 of the first course of chemotherapy, so the administration of CPT-11 scheduled for Days 8 and 15 was cancelled. Furthermore, this patient developed severe pneumonia with prolonged neutropenia and needed mechanical ventilation for 1 week. Although the patient was rescued by intensive care, these toxicities were defined as intractable, severe, life-threatening toxicities related to treatment, and subsequently the dose-escalation study was discontinued. In all 20 evaluable patients, hematologic toxicities were generally mild except in the 1 patient receiving Step 3 therapy. Nonhematologic toxicities, except for diarrhea, were also mild in all steps. Transient Grade 2 or 3 liver dysfunction was observed in 2 patients (10%) and Grade 2 or 3 alopecia was observed in 13 patients (65%). No renal insufficiency of Grade $\geq$2 was observed. There were no treatment-related deaths. Finally, we concluded that the recommended dose for further studies was Step 1. Details of the percentage of the scheduled CPT-11 dose actually delivered at each dose level are listed in Table 1. The percentage of the scheduled dose actually administered was relatively high at all three dose levels.

Response and Survival

There was no clear correlation between the dose of either CPT-11 or carboplatin and the response to treatment, with a PR occurring in 3 of 8 patients (38%) at Step1, 2 of 6 patients (33%) at Step 2, and 2 of 6 patients (33%) at Step 3. Of the 20 evaluable patients, objective responses were observed in 7 (35%). Eight patients showed NC, and five experienced PD. Of the 7 responders, the median time required to reach remission was 25 (range, 15–40) days, and the median response duration was 158 (range, 66–613) days. The median survival time for all 21 patients registered was 8.0 months.

Pharmacokinetics

Pharmacokinetic analysis was performed only in patients receiving Step 3 therapy. Five of seven patients at Step 3 agreed to participate in pharmacokinetic blood testing. Pharmacokinetic analysis was not permitted in two patients, one with severe life-threatening toxicity and another with a partial response. Table 4 shows the correlations between pharmacokinetic parameters, toxicity, and response in Step 3 patients. The observed carboplatin AUC, after aiming for a target AUC of 6, was 5.9 $\pm$ 0.9 mg $\cdot$ min/mL, indicating no bias compared with the target value. The AUC and maximum plasma level (Cmax) of CPT-11 were 2.64 $\pm$ 0.66 μg $\cdot$ hr/mL and 0.74 $\pm$ 0.16 μg/mL, respectively. In contrast, variabilities among patients in the Cmax and AUC of SN-38 were very large. The AUC and Cmax of SN-38 were 29.9 $\pm$ 16.3 ng $\cdot$ hr/mL and 6.8 $\pm$ 2.5 ng/mL, respectively. Patient 4, who showed the highest carboplatin AUC, experienced Grade 3 thrombocytopenia, whereas Patient 2, who showed a high SN-38 AUC, experienced Grade 2 diarrhea. Only one

TABLE 3
Major Toxicities According to ECOG Common Toxicity Criteria

Step	Dose of CPT-11 (mg/m^2)	AUC of CBDCA (mg · min/mL)	No. of patients	Diarrhea			Vomiting			Leukocyte grade			Neutro			Hb			PLT		
				2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
1	60	5	8	1	0	0	5	1	0	2	0	0	2	1	0	3	1	0	0	2	0
2	70	5	6	1	0	2	3	2	0	0	0	0	1	0	0	2	1	0	0	1	0
3	60	6	6	0	0	1	2	0	0	2	0	1	1	1	1	2	3	0	2	1	1

ECOG: Eastern Cooperative Oncology Group; AUC: area under the plasma concentration versus the time curve; CBDCA: carboplatin; Neutro: neutrophils; Hb: hemoglobin; PLT: platelets.

TABLE 4
Correlations between Pharmacokinetic Parameters, Toxicity, and Response in Step 3 Treatment[a]

Patient	CBDCA AUC (mg · min/mL)	CPT-11 AUC (μg · hr/mL)	CPT-11 Cmax (μg/mL)	CPT-11 $T_{1/2}$ (hrs)	SN-38 AUC (ng · hr/mL)	SN-38 Cmax (ng/mL)	SN-38 $T_{1/2}$ (hrs)	ECOG common toxicity grade: Leukocytes	ECOG common toxicity grade: PLT	ECOG common toxicity grade: Diarrhea	Response
1	6.01	2.25	0.88	4.23	25.2	6	2.66	0	0	0	NC
2[b]	6.03	2.55	0.55	3.74	45.9	5	5.25	3	2	2	NE
3	5.14	2.73	0.73	3.04	22.8	7	2.03	0	0	1	NC
4	7.07	1.97	0.64	2.87	8.7	5	0.70	0	3	0	PD
5	5.08	3.69	0.92	2.90	46.6	11	2.15	1	2	1	PR
Mean	5.9	2.64	0.74	3.36	29.9	6.8	2.56				
SD	0.9	0.66	0.16	0.60	16.3	2.5	1.67				

CBDCA: carboplatin; AUC: area under the plasma concentration versus the time curve; ECOG: Eastern Cooperative Oncology Group; PLT: platelets; Cmax: peak plasma concentration; $T_{1/2}$: terminal half-life; NC: no change; NE: not evaluable; PD: progressive disease; PR: partial response; SD: standard deviation.

[a] Step 3: 60mg/m^2 CPT-11 and a target AUC of 6 mg · min/mL CBDCA.

[b] Protocol violation (granulocyte colony-stimulating factor) was not administered).

responder (Patient 5) showed high pharmacokinetic parameter values for both CPT-11 and SN-38.

DISCUSSION

The response rate to CPT-11 in patients with advanced NSCLC without previous chemotherapy has been reported to be 15–32%.[3,24] CPT-11 in combination with cisplatin has been found to be very active against NSCLC, with response rates in the range of 31–54%.[7–9] The DLTs in these studies were leukopenia and diarrhea. Carboplatin produces less nonhematologic toxicity than cisplatin, and its principal toxicity, unlike that of cisplatin, is thrombocytopenia. The carboplatin AUC is well predicted by Calvert's formula, based on individual renal function,[13] and correlates well with toxicity and tumor response in patients with ovarian carcinoma.[11,12,14] In other words, more acceptable toxicities and greater efficacy are to be expected when the carboplatin dose is AUC-based rather than body surface area (BSA)–based. Furthermore, the use of rhG-CSF is expected to allow higher doses of CPT-11 and carboplatin to be used without patients' incurring significant myelosuppression. Therefore, we conducted this Phase I study of CPT-11 and carboplatin with rhG-CSF support for advanced NSCLC.

In this study, hematologic toxicities were generally mild except in one patient receiving Step 3 therapy. Furthermore, as shown in Table 1, the percentage of the scheduled dose actually administered was relatively high at all three dose levels. These favorable results may be due to the prophylactic use of rhG-CSF and the AUC-based strategy of determining carboplatin dose. In this study, three patients experienced Grade 4 diarrhea. Although the optimal use of antidiarrheal drugs has not been established, Abigerges et al. recommended high dose loperamide therapy for CPT-11–induced diarrhea.[18] This antidiarrheal therapy was not used in either Step 1 or 2 therapy and was initially given at the Step 3 dose level. Had this antidiarrheal therapy been used at Step 2, it might have prevented the Grade 4 diarrhea experienced by 2 patients at this level, and a higher dose escalation might have been possible in this study. One patient who received Step 3 therapy experienced severe, life-threatening toxicity.

However, this patient was one of the two with an ECOG performance status score of 2 and may have therefore been a poor candidate for intensive chemotherapy.

Calvert et al. reported that AUC-based dosing of carboplatin resulted in more acceptable toxicity and greater efficacy against carboplatin-sensitive tumors than the BSA-based dosing strategy.[14] With this in mind, recent Phase II trials of paclitaxel and carboplatin for NSCLC have also used the AUC-based dosing strategy.[25,26]

Although dose adjustment based on the isotopic determination of GFR has been proposed, it has not been widely applied because an inconvenient, invasive, and expensive method is required to determine the GFR. Therefore, 24-hour Ccr was substituted for the GFR in this study. Several investigators have reported that when they used Calvert's formula, the 24-hour Ccr caused an overestimation of the GFR, resulting in overexposure,[27–29] whereas others have reported that use of the 24-hour Ccr caused an underestimation of the GFR, resulting in an AUC approximately 10–15% lower than the ideal.[30] However, as expected, the actual carboplatin AUC observed in this study after using Calvert's formula based on the 24-hour Ccr to calculate the dose was 5.9 ± 0.9 mg · min/mL, indicating no bias compared with the values predicted from the dosing formula. This result also suggested that carboplatin pharmacokinetics are not influenced by the prior administration of CPT-11.

In contrast, there were large variations among patients in both CPT-11 and SN-38 pharmacokinetics. There was a twofold difference in the CPT-11 AUC and a fivefold difference in the SN-38 AUC among 5 Step 3 patients. These results are consistent with those of previous studies.[31–33] It is noteworthy that, in our study, AUC and Cmax of both CPT-11 and SN-38 were lower than those seen in other studies. Masuda et al. reported that AUC and Cmax values after CPT-11 60 mg/m^2 i.v. (Days 1, 8, and 15) in combination with etoposide i.v. (Days 1–3) were 4.35 μg/mL · hr and 0.78 μg/mL, respectively.[34] Similarly, Masuda et al. reported that AUC and Cmax values after CPT-11 80 mg/m^2 i.v. (Days 1, 8, and 15) in combination with cisplatin i.v. (Day 1) were 7.29 μg/mL · hr and 1.08 μg/mL, respectively.[8] In these studies, pharmacokinetic analysis of CPT-11 was performed on Day 8, as in our study. Shinkai et al. reported that the AUC and Cmax of CPT-11 80 mg/m^2 i.v. (Days 1 and 8) in combination with cisplatin i.v. (Day 1) and vindesine i.v. (Days 1 and 8) were 6.79 μg/mL · hr and 1.09 μg/mL, respectively.[31] The pharmacokinetic analysis of CPT-11 was performed on Day 1. In our study, the elimination half-life (T1/2) of CPT-11 was 3.3 hours, which was approximately one-fourth of that in other reports. In other words, clearance of CPT-11 was greater when administered with carboplatin than with etoposide or cisplatin and vindesine, suggesting that there might be unknown drug–drug interactions between CPT-11 and other agents.

The response rate of 35% and the median survival time of 8.0 months in our study were encouraging, because patients with postoperative recurrence, a history of prior chemotherapy, and an ECOG performance status score of 2 were included. No dose-response correlation was apparent in this relatively small clinical study. For patients with ovarian carcinoma, the most appropriate carboplatin dose appears to range between an AUC of 5 and 7 mg/mL · min; higher doses are associated with greater toxicity, but there is no obvious improvement in their therapeutic efficacy.[11] The dose-response curve of carboplatin has been described as sigmoidal. If carboplatin is administered with other agents, its dose-response curve may shift to the left. Although it remains unknown whether a similar correlation exists in NSCLC, this may be the reason why no dose-response correlation was observed in our study.

In conclusion, the recommended dose for Phase II studies is 60 mg/m^2 CPT-11, and a target AUC of 5 mg · min/mL carboplatin, plus rhG-CSF. Carboplatin pharmacokinetics do not appear to be influenced by the prior administration of CPT-11. A combination of AUC-based carboplatin and CPT-11 with rhG-CSF support appear to be an active regimen in the treatment of patients with NSCLC. However, a prospective randomized comparison of carboplatin plus CPT-11 and an existing cisplatin-based regimen is warranted to determine the impact of this regimen on survival.

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