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Irinotecan (CPT-11) in combination with weekly administration of cisplatin (CDDP) for non-small-cell lung cancer

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Abstract *Purpose*: CPT-11 (60 mg/m^2 on days 1, 8 and 15) in combination with CDDP (80 mg/m^2 on day 1) has shown promising antitumor activity for non-small-cell lung cancer (NSCLC), but dose-limiting toxicities (DLT) are leukopenia and diarrhea, with a wide variation among patients. To estimate weekly CDDP administration in combination with CPT-11, a phase I study for patients with advanced NSCLC was conducted. *Methods*: Patients were treated with CPT-11 at a fixed dose of 60 mg/m^2 together with CDDP at 27 mg/m^2 (level 1, 6 patients), 33 mg/m^2 (level 2, 12 patients), and 40 mg/m^2 (level 3, 6 patients) with 1600 ml hydration on days 1, 8 and 15 over 4 weeks. During the treatment course, drug was not administered on the day it was due in the presence of leukopenia (<3000/ml) and/or diarrhea. *Results*: The planned administration was completed in 5 of 6 patients at level 1, 6 of 12 patients at level 2, and 2 of 6 patients at level 3. The most common toxicity observed was leukopenia (five patients with grade 3 and one patient with grade 4). Leukopenia was considered to be a DLT, and the maximum tolerated dose (MTD) was level 2. Although there were patients who suffered from diarrhea (four patients with higher than grade 2), diarrhea was judged not to be a DLT with this weekly regimen. Nausea and vomiting were mild. Pharmacokinetic analysis of free platinum from CDDP demonstrated that the area under the curve (AUC) from 33 mg/m^2 CDDP was 0.92 ± 0.29 μg/ml h. In 13 patients evaluated for response, the response rate was 54%. *Conclusion*: The value of weekly administration of CDDP in combination with CPT-11 was shown by (1) diarrhea not being dose-limiting, (2) mild nausea, (3) well-maintained AUC of free platinum, and (4) promising activity.

Key words Irinotecan · Cisplatin · Non-small-cell lung cancer · Pharmacokinetics · Weekly administration

Introduction

7-Ethyl-10-[10-4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin (irinotecan; CPT-11) is a semisynthetic derivative of camptothecin [8]. CPT-11 is strongly activated when metabolized to SN-38 by carboxylesterase [17]. SN-38 has a time-dependent cytotoxicity, and appears to be a potent inhibitor of topoisomerase I [5, 8]. CPT-11 has shown strong antitumor activity against a broad spectrum of experimental tumor models [2, 8], and has been found to be clinically active against tumors, including lymphoma, colorectal cancer and small-cell lung cancer (SCLC) [9, 12, 15]. As a single agent, CPT-11 at a dose of 100 mg/m^2 on days 1, 8, and 15 every 4 weeks has also been found to be active against and non-small-cell lung cancer (NSCLC) [3].

Cisplatin (CDDP), whose main action is alkylation, has shown marked synergism with CPT-11 and some lack of cross-resistance with it [2, 11]. CPT-11 (60 mg/m^2 on days 1, 8 and 15) in combination with a single administration of CDDP (80 mg/m^2 on day 1) has been reported to show promising antitumor activity against NSCLC [10]. However, dose-limiting toxicities (DLT) are leukopenia and severe diarrhea, and interpatient variability is considered to be a major deterrent to clinical use [10].

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Maximal synergistic effect has been observed by the simultaneous combination of CDDP and CPT-11 in vitro [11]. The metabolite of CPT-11, SN-38, can modulate the removal of platinum–DNA adducts [11]. Our experiments in vitro using cell lines of NSCLC have confirmed that the cytotoxicity of platinum compounds, including CDDP, is dependent on AUC (area under the concentration-time curve) [6, 7]. We have also estimated that the antitumor activity of CDDP is less weakened by divided administration than other platinum compounds such as carboplatin and nedaplatin [6]. In a clinical study of patients with NSCLC, weekly treatment with CDDP in combination with vindesine has been found to be as active as conventional treatment with a single administration of CDDP on day 1 with vindesine [18]. These findings indicate that CPT-11 can be used simultaneously with CDDP through weekly administration.

We conducted a phase I study to evaluate the combination of CPT-11 and CDDP in divided weekly administrations in patients with advanced NSCLC. The objectives of this study were (1) to determine the maximum tolerated dose (MTD) of CDDP administered weekly in combination with CPT-11 at a fixed dose of 60 mg/m^2, (2) to describe and quantify the clinical toxicities of the combination and to investigate means to overcome interpatient variability, (3) to estimate the AUC of CDDP, and (4) to obtain preliminary evidence of the therapeutic activity of this regimen in patients with advanced NSCLC. The AUC of CDDP and the therapeutic activity would prove the validity of weekly administration of CDDP in combination with CPT-11.

Patients and methods

Patient selection

Prior to their participation in the study, patients admitted to the International Medical Center of Japan and Nippon Medical School Main Hospital were examined to ensure that they met the following criteria: (1) histologic diagnosis of NSCLC; (2) stage III_B or IV disease; (3) no effects of prior treatment (more than 3 months after the previous treatment); (4) life expectancy of at least 8 weeks; (5) age <75 years; (6) performance status of 2 or better on the Eastern Cooperative Oncology Group (ECOG) scale; (7) adequate bone marrow function (leukocyte count >4000/ml, platelet count $>100\,000$/ml, hemoglobin concentration >9 g/dl), hepatic function (bilirubin <1.5 mg/dl, transaminases less than twice the upper limit of normal), and renal function (creatinine <1.5 mg/dl, creatinine clearance >40 ml/min); (8) no medical problems severe enough to prevent compliance with the study requirements; and (9) informed consent of the patient.

Dose-escalation procedure

The dose of CPT-11, which was given intravenously (i.v.), was fixed at 60 mg/m^2, the same as that used in the study by Masuda et al. [10], on days 1, 8 and 15, whereas the concurrent dose of CDDP was increased, with a starting dose of 27 mg/m^2 given i.v. This amount of CDDP resulted in a total dose of 81 mg/m^2 over 4 weeks, almost the same as that in the study by Masuda et al. [10]. Initially, CPT-11 was administered in 100 ml normal saline as a 60-min i.v. infusion, then CDDP was given during a 60-min period after CPT-11 administration. For emesis, 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist was given i.v. prior to the administration of CPT-11 and CDDP. To avoid CDDP-induced renal damage, patients were given 1600 ml of hydration i.v. on days 1, 8 and 15. During the course of treatment, the dose of CPT-11 and CDDP was withheld on the day it was due in the presence of leukopenia (<3000/ml) and/or diarrhea in excess of grade 1, again the same as in the study by Masuda et al. [10]. Granulocyte colony-stimulating factor (G-CSF) was administered when grade 3 leukopenia (<2000/ml) and/or neutropenia (<1000/ml) were observed. Patients with obvious evidence of disease progression were removed from the study.

The weekly dose of CDDP was escalated as follows: 27 mg/m$^2 \times 3$ (total dose 81 mg/m^2 over 4 weeks), 33 mg/m$^2 \times 3$ (total dose 99 mg/m^2 over 4 weeks), and 40 mg/m$^2 \times 3$ (total dose 120 mg/m^2 over 4 weeks). Intrapatient dose escalation was permitted.

Evaluation

To determine the stage of disease, patients were evaluated by physical examination, routine chest radiograph, whole-lung tomography, bone scintiscan, computed tomography of the head, chest and abdomen, and fiberoptic bronchoscopy. Staging procedures followed those of the tumor-node-metastasis system. Prior to the first course, each patient was subjected to a complete blood cell count (CBC) that included a differential and platelet count, serum chemistry for renal and hepatic functions, electrolyte analysis, and urinalysis. CBC, serum chemistry, electrolyte analysis, urinalysis, and chest radiographs were assessed at least once a week after the initial evaluation. After the completion of chemotherapy, each patient was restaged by all the tests used during the initial workup except for fiberoptic bronchoscopy. Tumor response was classified in accordance with World Health Organization criteria.

ECOG common toxicity criteria (CTC) were used to grade organ system damage. The MTD was defined as the dose that led to grade 3 or 4 nonhematologic toxicity (except nausea and vomiting) in one-third or more of the patients and/or grade 3 or 4 hematologic toxicity in two-thirds or more of the patients on the CTC scale included at that level after the first course (the same rule as in the study by Masuda et al. [10]). In light of the finding of Masuda et al. [10], we considered that the withholding of the planned doze on days 8 and/or 15 for leukopenia and/or diarrhea was a sufficient criterion for an assignment of more than grade 3 toxicity, and judged the MTD on this basis.

Pharmacokinetics

Heparinized blood samples (5 ml) for the pharmacokinetic study of CDDP were obtained before the infusion of CDDP, at the end of infusion, and at 30, 60, 120, and 240 min after the completion of infusion. The blood was centrifuged immediately. In order to estimate the AUC of non-protein-bound platinum (free Pt), 1 ml of plasma was centrifuged using an Amicon Centrifree 4104 (Amicon Corporation, Mass.) at 1980 g for 20 min. The concentration of free Pt in the supernatant was determined by flameless atomic absorption spectrometry. The pharmacokinetic parameters of free Pt were determined on the basis of a one-compartment model, using a computer program, PK for Macintosh ver 2.0 (Meiji Co., Tokyo). The AUC of free Pt was calculated using the trapezoidal rule.

Results

Between August 1994 and July 1996, 18 patients participated in the trial. The characteristics of this patient population are given in Table 1. Five patients were women and 13 were men; the mean age was 61 years

Table 1 Patient characteristics

Male/female	13/5
Age (years)	
Mean	61
Range	42–74
Stage	
III_B	4
IV	14
Performance status	
0	5
1	7
2	6
Pathology	
adenocarcinoma	15
squamous cell carcinoma	2
large cell carcinoma	1
Treatment history	
Previously treated	12
Previously untreated	6

(range 42 to 74 years). Four patients exhibited stage III_B disease and 14 stage IV disease; 15 had adenocarcinoma, 2 squamous cell carcinoma, and 1 large cell carcinoma. Of the 18 patients, 12 had been treated previously and 6 were untreated.

Toxicity and actual doses

Leukopenia was the major toxicity (Tables 2, 3). The leukocyte count nadir usually occurred around day 21 (Table 2). At dose level 1, one patient experienced grade 3 leukopenia. At dose level 2, two patients and one patient exhibited grades 3 and 4 leukopenia, respectively. Also, at this dose level, two and three patients experienced grade 2 leukopenia on days 8 and 15, respectively, necessitating the abandonment of the CDDP and CPT-11 treatment due on that day. At dose level 3, two patients exhibited grade 3 leukopenia. Also at dose level 3, only two patients received the full treatment on days 1, 8, and 15. Four patients experienced grade 2 leukopenia on day 8 or 15, forcing the cessation of CPT-11 with CDDP treatment on that day (Table 3). Figure 1 shows the relationship between the nadir WBC count and the ratio of WBC on day 8 to that on day 1. The nadir WBC count was significantly correlated with the ratio of WBC on day 8 to that on day 1 ($r = 0.603, P = 0.0081$).

Thrombocytopenia occurred less frequently than leukopenia and was less severe (Tables 2, 4). Thrombocytopenia higher than grade 2 was observed in two patients.

Diarrhea higher than grade 2 occurred in two patients at dose level 1. Grade 2 diarrhea occurred in two patients at dose level 2 (Tables 3, 4). However, no patients at dose level 3 experienced diarrhea. Of the four patients experiencing diarrhea, two had grade 3 leukopenia coincidentally. Although these patients required rapid, vigorous hydration with i.v. hyperalimentation (IVH), they recovered in from 7 to 12 days.

Table 2 Hematologic toxicity of CPT-11 combined with weekly cisplatin administration. Patients were treated with CPT-11 at a fixed dose of 60 mg/m^2 and CDDP at 27 mg/m^2 (level 1, six patients), 33 mg/m^2 (level 2, 12 patients), and 40 mg/m^2 (level 3, six patients) on days 1, 8 and 15

	Level 1 (n = 6)	Level 2 (n = 12)	Level 3 (n = 6)
WBC nadirs			
Count (/ml)			
Mean ± SD	3040 ± 1036	2428 ± 1150	2190 ± 577
Range	1400–4450	200–5000	1200–2820
Day of nadir			
Mean ± SD	22.5 ± 3.4	20.4 ± 5.2	20.2 ± 3.7
Range	17–26	8–25	15–26
Platelet nadirs			
Count ($\times 10^4$/ml)			
Mean ± SD	15.1 ± 7.8	14.2 ± 7.0	12.5 ± 4.8
Range	4.7–27.7	0.5–24.3	7.4–14.0
Day of nadir			
Mean ± SD	24.0 ± 2.4	20.9 ± 4.4	21.7 ± 4.8
Range	20–26	14–26	15–25

Table 3 Leukopenia and diarrhea [*Skip* number of patients not given the planned doze, *Grade*, *3*, *4*, *skip* number of patients who experienced grade 3 and 4 toxicity and were not given the planned dose (correct for overlap)]

	Level 1 (n = 6)	Level 2 (n = 12)	Level 3 (n = 6)
Leukopenia			
Grade 2	1	7	4
Grade 3	1	2	2
Grade 4	0	1	0
Skip	0	4	4
Grade 3, 4, skip	1	5	4
Diarrhea			
Grade 1	0	1	0
Grade 2	1	2	0
Grade 3	1	0	0
Grade 4	0	0	0
Skip	1	2	0
Grade 3, 4, skip	1	2	0

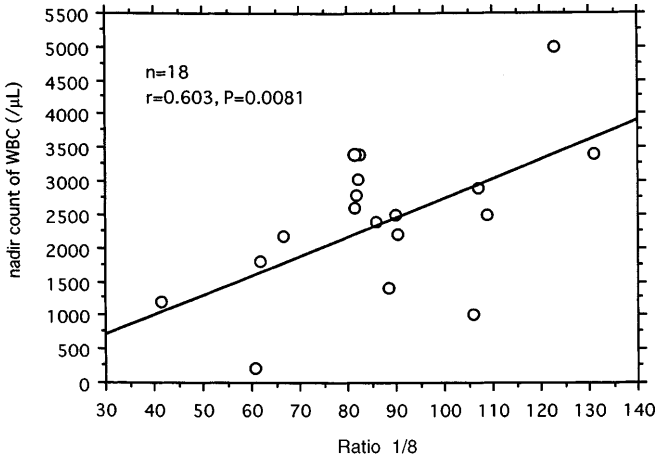

Fig. 1 Relationship between the nadir WBC count and percentage decrease in WBC for 8 days. Data at the time when each of the 18 patients had been given the first treatment of the study were analysed (*rate. 1/8* the ratio of WBC on day 8 to that on day 1)

Although no grade 3 nausea or vomiting was observed at any level, about one-third of the patients experienced grade 2 nausea (Table 4), indicating that nausea and vomiting were mild under this regimen. One patient had an elevated creatinine level of 2.0 mg/dl. No pulmonary toxicity related to drug administration was observed in this trial.

The doses of CDDP and CPT-11 actually delivered at each dose level are listed in Table 5. At level 1, five of six patients received the planned dose, and mean actual doses of 170 mg/m^2 of CPT-11 and 77 mg/m^2 of CDDP were delivered over 28 days. At level 2, 6 of 12 patients received the planned dose, and the mean actual doses of 145 mg/m^2 of CPT-11 and 80 mg/m^2 of CDDP were delivered in 28 days. However, only two of six patients were given the planned dose at dose level 3. The remaining four did not receive the planned dose because of grade 2 leukopenia on day 8 or 15. From the protocol described above, the MTD was judged to be level 2, at which 60 mg/m^2 of CPT-11 with 33 mg/m^2 of CDDP was given i.v. on days 1, 8 and 15 (Table 3). Leukopenia was considered to be a DLT, but diarrhea did not reach the severity of a DLT in this regimen.

In the one toxic death, the patient exhibited grade 4 myelotoxicity (leukopenia and thrombocytopenia) and grade 1 diarrhea, observed at dose level 2. The patient received 60 mg/m^2 CPT-11 and 33 mg/m^2 CDDP on days 1 and 8. Clinically, it appeared that death, which occurred on day 18 after the start of the chemotherapy, was from sepsis resulting from *Candida albicans* infection. Autopsy revealed pseudomembranous jejunoileitis with marked *Candida* infection. There was also *Candida albicans* colonization of the pharynx. It is considered that the reabsorption of CPT-11 and SN-38 by intestinal cells induced the severe damage to the epithelium of the small intestine resulting in a suitable environment for *Candida* growth causing sepsis.

Response

Of the 18 patients, 13 were assessed for response (Table 6), and of the 5 patients who could not be assessed for response, 1 died on day 18 and 4 exhibited no lesions that could be evaluated. Seven patients showed a partial response (PR), four showed no change, and two suffered disease progression. The response rates for adenocarcinoma and squamous cell carcinoma were 5 of 11 patients and 2 of 2 patients, respectively. A PR was obtained in 2 of 4 patients with stage III_B disease, and 5 of 9 with stage IV disease.

Table 4 Other toxicities at the different cisplatin dose levels (values are the numbers of patients with ECOG grade 2 or more)

	Level 1 (n = 6)	Level 2 (n = 12)	Level 3 (n = 6)
Thrombocytopenia	1	1	0
Anemia	2	5	3
Diarrhea	2	2	0
Nausea and vomiting	2	3	2
Alopecia	0	0	0
Abnormal liver function	0	0	0
Abnormal renal function	1	0	0

Table 5 Actual doses delivered (*weekly dose* CPT-11 at 60 mg/m^2 and CDDP at 27 mg/m^2 (level 1), 33 mg/m^2 (level 2) or 40 mg/m^2 (level 3))

	Level 1 (n = 6)	Level 2 (n = 12)	Level 3 (n = 6)
Number of patients receiving weekly dose			
Once a course	0	1	0
Twice a course	1	5	4
Three times a course	5	6	2
Actual dose			
CDDP (mg/m^2)	77	80	93
CPT-11 (mg/m^2)	170	145	140
Actual dose/planned dose	94%	81%	78%

Table 6 Response rate

	Complete response	Partial response	No change	Progressive disease	Not evaluable	Response rate
Previously untreated (n = 6)	0	3	1	2	0	3/6 (50%)
Previously treated (n = 12)	0	4	3	0	5	4/7 (57%)
Total (n = 18)	0	7	4	2	5	7/13 (54%)

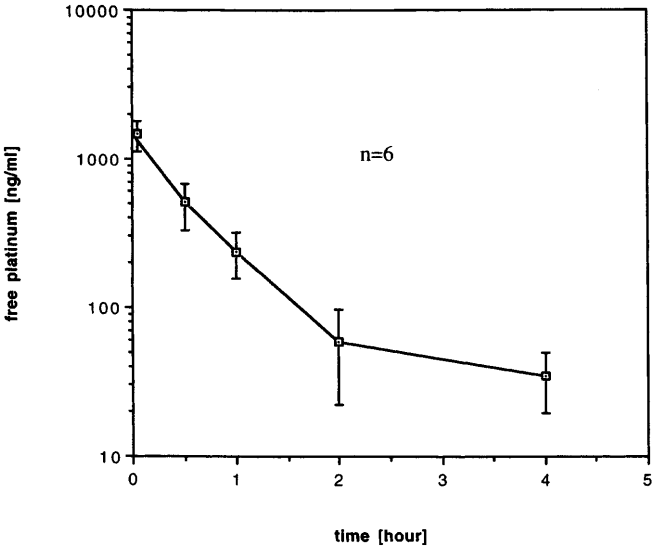

Fig. 2 Pharmacokinetics of CDDP administered by divided dose. The pharmacokinetic study was performed on day 1 at dose level 2. Plasma samples were obtained from six patients who were treated with 33 mg/m^2 of CDDP and 60 mg/m^2 of CPT-11

Pharmacokinetics

Plasma samples were obtained from six patients who were treated with 33 mg/m^2 CDDP and 60 mg/m^2 CPT-11 (level 2). The plasma concentration-time curves for the different doses of CDDP are shown in Fig. 2. The pharmacokinetic parameters derived from the plotted data were maximum concentration of free Pt (Cmax, 1.47 $\pm$ 0.34 mg/ml), half-life ($t_{1/2}$, 0.37 $\pm$ 0.05 h), and AUC of free Pt (0.92 $\pm$ 0.29 μg/ml h).

Discussion

It has been reported that both CDDP and CPT-11 cause mucosal damage to the mouse ileum and cecum [4, 16]. CDDP causes diarrhea by diffuse mucosal damage, and CPT-11 produces characteristic mucosal changes in the intestine by inducing apoptosis and cell differentiation [4]. Thus, the combined use of CDDP and CPT-11 is considered to enhance the adverse effects of CPT-11. If the dose of CDDP in combination with CPT-11 cause concern regarding CPT-11-induced diarrhea, a lower dose of CDDP combined with CPT-11 at the same time in a divided regimen may cause less toxicity than a single administration of higher dose of CDDP with CPT-11. The results of this phase I study confirmed that the DLT was leukopenia, the same as found with single CDDP administration combined with CPT-11. However, diarrhea with divided administration of CDDP was not regarded as a DLT, although there were patients who suffered from diarrhea with this divided administration of CDDP, with an incidence of 4% at grade 3 or 4. Although the number of patients was also relatively small in the study by Matsuda et al. [10], the corresponding incidence in that study was reported to be 11% after a single administration of CDDP at 80 mg/m^2.

The four patients whose day 8 to day 1 WBC ratio was less than 0.7, (i.e. a greater than 30% decrease of WBC on day 8 to that on day 1) could not be given the planned dose (Fig. 1). These patients received only two doses of CPT-11 of 60 mg/m^2 and CDDP of 33–40 mg/m^2. Furthermore, three of the four patients experienced leukopenia higher than grade 3. In the one patient who died from toxicity, there was a 39.3% decrease and grade 4 leukopenia. From these and the significant correlation between the WBC nadir and the ratio of WBC on day 8 to that on day 1 (Fig. 1), the percentage decrease could possibly be used to predict major toxicity of leukopenia with this combination of CPT-11 with weekly CDDP.

Nausea and vomiting during the weekly administration of CDDP with CPT-11 in combination with a 5-HT_3 receptor antagonist was mild, with an incidence at grade 3 or 4 of 0%, while the incidence has been reported to be 24% after a single administration of CDDP at 80 mg/m^2 [10]. On the day of treatment, 1600 ml of hydration was required, a procedure that can be completed in 5.5 h. Medication in outpatient clinics may also be possible.

The cytotoxicity of anticancer agents can be classified as time-dependent or AUC-dependent [13]. It has been demonstrated that the cytotoxic effect of CDDP is determined not by the blood concentration of the drug but by the AUC (concentration $\times$ time) of nonprotein-bound platinum (free platinum) [7]. Pharmacokinetic analysis in the present study demonstrated that the AUC of free platinum from 33 mg/m^2 CDDP was 0.92 $\pm$ 0.29 mg/ml h. In step 2, 11 of 12 patients were given twice or three times of 33 mg/m^2 CDDP with 60 mg/m^2 CPT-11 in 28 days (Table 5). In another study, three patients, who fulfilled the entry criteria for this study, were enrolled in another study and treated by a single administration of 80 mg/m^2 CDDP combined with CPT-11 60 mg/m^2. Pharmacokinetic analysis was also performed, and the AUC of free platinum from 80 mg/m^2 CDDP was found to be 1.80 $\pm$ 0.17 mg/ml h.

These results indicate a well-maintained AUC by this divided administration.

Clinical efficacy was demonstrated in 7 of 13 patients. Comparison with the response rates previously reported for other combinations in NSCLC indicates that this regimen appears promising [1, 14]. Of seven patients who had been given previous treatment(s) before this study, four had received conventional treatment with CDDP in combination with vindesine. Two of the four patients had a partial response, indicating that the weekly administration of CDDP with CPT-11 was still active after CDDP in combination with vindesine.

In conclusion, the MTD of this regimen was 60 mg/m^2 of CPT-11 and 33 mg/m^2 of CDDP on days 1, 8, and 15 over 4 weeks, and the DLT was leukopenia. The value of weekly administration of CDDP in combination with CPT-11 was shown by (1) diarrhea not being dose-limiting, (2) mild nausea, (3) the well-maintained AUC of free platinum, and (4) promising activity. It is considered that this weekly administration schedule is a viable alternative to the schedule containing a single administration of 80 mg/m^2 CDDP on days 1 and 60 mg/m^2 CPT-11 on days 1, 8, and 15. To confirm both response and side effects, we are now undertaking a phase II study of CPT-11 in combination with weekly administration of CDDP for NSCLC. In the phase II regimen, the doses of CPT-11 and CDDP are withheld on day 8 when the percentage decrease in WBC count on day 8 from that on day 1 is more than 30%.

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