Phase I Clinical Trial of Irinotecan (CPT-11), 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carboxyloxy-camptothecin, and Cisplatin in Combination with Fixed Dose of Vindesine in Advanced Non-Small Cell Lung Cancer


ABSTRACT

Irinotecan hydrochloride (CPT-11), a semisynthetic derivative of camptothecin, has been demonstrated to be active against solid tumors such as non-small cell lung cancer and colorectal cancer. Two combination phase I trials were undertaken to determine the maximum tolerated dose of CPT-11 in combination with cisplatin and vindesine in patients with advanced non-small cell lung cancer. All 46 patients (age 32–73 years) entered into these trials had a good performance status (Eastern Cooperative Oncology Group score, 0–1) and had received no prior chemotherapy or radiotherapy. In the first trial, 14 stage IV and 2 stage IIIb patients were studied; in the second trial 30 patients with stage IV disease were accrued. In the first trial, CPT-11 was given as a 90-min i.v. infusion on days 1 and 8 in combination with a fixed dose of cisplatin (100 mg/m², i.v., on day 1) and vindesine (3 mg/m², i.v., on days 1 and 8), every 4 weeks. The starting dose of CPT-11 was 25 mg/m², and the dose was increased in increments of 25 mg/m². In the second trial, the doses of either CPT-11 (days 1 and 8) or cisplatin (day 1) were escalated with a fixed dose of vindesine (same dose as the first study) given in a 4-week cycle. The starting doses of CPT-11 and cisplatin were 20 and 60 mg/m², respectively, and the dose of either CPT-11 or cisplatin was increased in increments of 20 mg/m². At least 3 patients were entered at each dose level in both trials. Use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor was not permitted in this trial. In the first trial, grade 4 granulocytopenia and grade ≥3 diarrhea were dose limiting at 50 mg/m² CPT-11, which represented the maximum tolerated dose. At the subsequent dose of CPT-11, 7 new patients were required at the 50% reduced dose level of 37.5 mg/m² on days 1 and 8. Nine patients were evaluable for response, and 4 of them achieved a partial response. In spite of a low dose of CPT-11 (25–37.5 mg/m²), the maximum concentration in plasma of CPT-11 (>0.4 µg/ml) reached >10-fold the in vitro concentration of CPT-11 required for 50% inhibition of growth. In the second trial, the dose-limiting toxicities were grade 4 granulocytopenia lasting for ≥7 days and grade ≥3 diarrhea. The maximum tolerated dose was 100 mg/m² of CPT-11 and 60 mg/m² of cisplatin in this regimen. The other severe toxicity was to the liver. Ten of 30 patients entered (10 of 22 patients assessable for response) achieved a partial response. Intractable diarrhea induced by CPT-11 was associated with the dose of cisplatin used in our trials and occurred coincidentally with granulocytopenia of grade 4. For future phase II trials, we recommend doses of CPT-11 of 37.5 and 80 mg/m² on days 1 and 8 combined with vindesine and either high-dose cisplatin (100 mg/m²) or low-dose cisplatin (60 mg/m²), respectively.

INTRODUCTION

Very few agents show activity against NSCLC. Only five drugs appear to have moderate activity against NSCLC: cisplatin, ifosfamide, mitomycin C, vindesine, and vinblastine (1, 2). Since the introduction of cisplatin-based chemotherapy, there are data showing that a variety of combination chemotherapy regimens such as cisplatin plus Vinca alkaloid (vindesine/vinblastine) or etoposide and mitomycin C plus Vinca alkaloid plus cisplatin produces a response in NSCLC in the range of 25–50% (3, 4). A recent randomized study showed that cisplatin-based combination chemotherapy produces a slight but significant improvement in survival (5, 6). However, the overall outcome for patients with advanced NSCLC remains poor (7–10). Clinical trials on NSCLC have been made difficult by the lack of effective drugs. Advances in treatment of this disease will be made only by discovering more active agents and successfully including such drugs in rational combination chemotherapy regimens.

CPT, obtained from the Chinese tree Camptotheca acuminate, is an alkaloid with a novel ring structure (11). Although CPT has shown promising antitumor activity in vitro (12, 13), and in vivo, its clinical activity was disappointing because of its low therapeutic efficacy and severe toxicity to the intestine, bladder, and bone marrow (14–17). To improve the therapeutic index of CPT, various derivatives of CPT have been semisynthesized, including CPT-11, a new water-soluble derivative, which has potent antitumor activity against several tumors in the murine system (18). SN-38, a metabolite of CPT-11, shows much stronger cytotoxicity than CPT-11 in vitro (19), and both CPT-11 and SN-38 may be responsible for the antitumor effect and side effects. A phase I clinical study of CPT-11 by single-dose i.v. administration every 4 weeks showed that the DLT of CPT-11 was myelosuppression and the MTD was 250 mg/m² (20). Camptothecin and its derivatives have demonstrated schedule-dependent antitumor activity and toxicity (15, 21). A phase I study of CPT-11 on a schedule of i.v. administration once weekly revealed that the MTD on this schedule was 100 mg/m² and the DLTs were myelosuppression (predominantly leukopenia), nausea and vomiting, and diarrhea (22). This schedule appears to allow a CPT-11 dose intensity which is double the dose intensity possible on a once-every-4-weeks schedule. The response rate of CPT-11 in patients with advanced NSCLC without prior chemotherapy has been reported to be 32% with i.v. administration on a schedule of 100 mg/m² weekly (23).

Cisplatin and vindesine are active as a single agent against NSCLC (1, 2). The combination of cisplatin and Vinca alkaloid currently is one of the active regimens for patients with advanced NSCLC (24–27). The abbreviations used are: NSCLC, non-small cell lung cancer; CPT, camptothecin; CPT-11, irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carboxyloxy-camptothecin; SN-38, 7-ethyl-10-hydroxy-camptothecin; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; C max, maximum concentration in plasma; AUC, the area under the plasma concentration versus time curve; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
PHASE I STUDY OF CPT-11, CISPLATIN, AND VINDESEINE IN NSCLC

26) and has been shown to prolong survival significantly compared with the best supportive care of patients with advanced NSCLC (5) and compared with radiation alone in patients with stage III NSCLC (6). In order to reinforce the therapeutic efficacy of this combination against advanced NSCLC, various agents have been combined with cisplatin and Vinca alkaloid (9, 27–29). However, there are no clear survival data to support the idea that a regimen using more than three drugs is superior to a regimen using two drugs.

CPT-11 appears to be one of the most promising novel anticancer agents (30). In preclinical studies, CPT showed no cross-resistance with cisplatin (31–33). To evaluate the potential therapeutic benefit of adding CPT-11 to vindesine plus cisplatin and to further assess the toxicity of CPT-11 in combination chemotherapy, we performed two phase I clinical studies in patients with metastatic NSCLC who had received no prior chemotherapy or radiotherapy. The purposes of these studies were (a) to determine the optimal doses of CPT-11 and cisplatin in combination with a fixed dose of vindesine, (b) to further assess the toxicity of CPT-11 in combination chemotherapy, and (c) to study the clinical pharmacology of CPT-11 and its metabolite, SN-38.

MATERIALS AND METHODS

Patient Population. Patients with histologically or cytologically confirmed advanced NSCLC were eligible for this phase I trial. None of the patients had received prior chemotherapy or radiotherapy. Other eligibility criteria included expected survival of ≥6 weeks, age <75 years, Eastern Cooperative Oncology Group performance score of 0–1, measurable lesions, no brain metastasis, adequate hematological function (WBC ≥ 4000/mm³, platelet count ≥ 100,000/mm³, hemoglobin ≥ 11 g/dl), renal function (serum creatinine ≤ 1.5 mg/dl, creatinine clearance > 60 ml/min), and hepatic function (total serum bilirubin < 1.5 mg/dl, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase less than twice the normal range, indocyanine green test ≤ 15%).

The protocols used were approved by the ethical committee of the National Cancer Center (Tokyo). Written informed consent was obtained in every case stating that the patient was aware of the investigational nature of this treatment regimen. Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent radionuclide bone scan, computerized tomography of the brain and thorax, and ultrasonography or computerized tomography of the abdomen. All patients were admitted to the National Cancer Center Hospital during this trial. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained weekly during this phase I trial. Tests of measurable disease parameters such as computerized tomography were repeated every 4 weeks. The patient characteristics are shown in Table 1.

Study Design and Treatment Plan. All patients were hospitalized for the combined treatment with CPT-11 plus vindesine plus cisplatin.

In the first study, the starting CPT-11 dose was 25 mg/m² on days 1 and 8 (50 mg/m²/course), and the dosage was increased in subsequent increments of 25 mg/m². The starting dose (50 mg/m²/course) was based on 1/10 (26.4 mg/m²) of the dose which was lethal to 10% of the mice tested or 1/3 (69.3 mg/m²) of the low toxic dose in the dog on the single-dose schedule (data on file at Daiichi Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd.). CPT-11 was kindly provided by Yakult Honsha (Tokyo, Japan), and Daiichi (Tokyo, Japan). Six patients were entered at the first level, seven patients were entered at the second level, and three patients were entered at the third level (Table 2). The dose of CPT-11 in 500 ml of normal saline or 5% glucose was infused i.v. over 90 min. Vindesine was given at a dose of 3 mg/m² as an i.v. bolus on days 1 and 8. Cisplatin was given i.v. at a dose of 100 mg/m² over 30 min after prehydration with 500 ml of normal saline following CPT-11 administration on day 1. Following administration of cisplatin, patients received mannitol (20%) i.v. at a rate of 50 ml/h over 6 h and 2000 ml of 5% glucose in 0.45% NaCl with 20 mEq K⁺/liter at a rate of 200 ml/h. To control cisplatin-induced emesis, patients received high-dose metoclopramide (2 mg/kg, i.v., every 2 h × 4) plus i.v. infusions of dexamethasone and promethazine. The course was repeated every 4 weeks.

In the second trial, a successive cohort of new patients with metastatic NSCLC was used to study interpatient dose escalation of CPT-11 (i.v. on days 1 and 8) and cisplatin (i.v. on day 1) with a fixed dose of vindesine (3 mg/m², i.v., on days 1 and 8), given every 4 weeks (if possible every 3 weeks). The starting doses of CPT-11 and cisplatin were 20 and 60 mg/m², respectively, and the dosage was escalated in subsequent alternate increments of 20 mg/m².

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Common toxicity</th>
<th>Dose (mg/m²)</th>
<th>No. of patients/</th>
<th>WBC (grade)</th>
<th>Granulocyte (grade)</th>
<th>Platelet (grade)</th>
<th>Diarrhea (grade)</th>
<th>Nausea/ vomiting (grade)</th>
<th>Liver (grade)</th>
<th>Kidney (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11</td>
<td>Cisplatin</td>
<td>no. of cycles/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>2/3</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>37.5</td>
<td>100</td>
<td>7/13/2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
<td>3/3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, numbers of patients with grade 4 granulocytopenia lasting ≥ 7 days.

2637
cyte and platelet counts decreased <2,000/mm³ and 50,000/mm³, respectively. The reason we decided to use granulocytopenia lasting ≥7 days as a dose-limiting factor is that we anticipated that this regimen would induce severe granulocytopenia and granulocytopenia would be manageable under the careful supervision provided by the hospital setting. Use of G-CSF or GM-CSF was not permitted in this trial. In addition, no prophylactic measures such as antibiotics were undertaken prior to occurrence of fever associated with granulocytopenia.

Toxicity was graded according to the common toxicity criteria (34). Patients were treated for at least two cycles of therapy unless disease progression or unacceptable toxicity was encountered or the patient's wishes intervened. No dosage modification was made on the basis of bone marrow toxicity. In the case of stable or progressive disease after two courses of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient. The criteria for response were as follows. Complete response was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response was defined as a ≥50% reduction in the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks and no appearance of new lesions or progression of any lesion. Disease progression was defined as a ≥25% increase in tumor area or the appearance of new lesions. All other circumstances were classified as stable disease.

Pharmacokinetics. In the first study the pharmacokinetics of CPT-11 and SN-38 were determined for the first three cohorts of patients treated at each dose level. CPT-11 was infused over a 90-min period. Blood samples (5 ml) were drawn into heparinized tubes before infusion; then at 30, 60, and 90 (end of CPT-11 infusion) min; and 5, 15, and 30 min and 1, 2, 3, 4, 5, 12, and 14 h after the end of the CPT-11 infusion. Samples (5 ml) were centrifuged immediately at 4°C, and then plasma was stored at −40°C until assayed. A previously described high-performance liquid chromatography technique (19) was used for CPT-11 and SN-38 measurements in plasma. The pharmacokinetic analysis was performed using a nonlinear estimation program, PC-Nonline (Statistical Consultants Inc, Lexington, KY). The AUC was calculated by using the trapezoidal method; the portion of the AUC after the final time point was calculated by dividing the final detectable CPT-11 or SN-38 concentration by the terminal disposition rate constant (35).

RESULTS

Sixteen patients were enrolled in the first trial from January 1990 to July 1990 and received 33 courses of the CPT-11-cisplatin-vindesine regimen. Thirty patients were entered into the second trial from July 1991 to April 1993 and received 68 courses of this regimen.

First Trial

Toxicity. The common toxicities (criterion grade ≥ 2) encountered during the first 8 weeks of treatment (first and second courses) in the first trial are summarized in Table 2. The dose-limiting toxicities on this schedule were granulocytopenia and diarrhea. All three patients treated at 50 mg/m² CPT-11 (100% increment) developed grade 3 (two patients) or 4 (one patient) diarrhea, and one of these three patients experienced granulocytopenia of grade 4 lasting 10 days. All three patients at this dose level (50 mg/m² CPT-11 on days 1 and 8) were removed from the study because of toxicity after one cycle of treatment. The subsequent dose of CPT-11 was decreased to 37.5 mg/m² on days 1 and 8 (50% increment). At the CPT-11 dose of 37.5 mg/m², all seven patients experienced granulocytopenia of grade 3 or 4. However, only one patient experienced granulocytopenia of grade 4 lasting ≥7 days associated with diarrhea of grade 3. Median duration of granulocytopenia of grade 4 was 4 days (range, 2–10 days). However, leukopenia or granulocytopenia did not result in any treatment delay at 25 or 37.5 mg/m² CPT-11. No life-threatening infections were observed as a result of granulocytopenia. Thrombocytopenia was generally mild, and only one patient at the CPT-11 dose level of 37.5 mg/m² experienced thrombocytopenia of grade 2. Anaemia of grade 3 was observed in two of six patients and five of seven patients at the CPT-11 dose levels of 25 and 37.5 mg/m², respectively.

Usually diarrhea was observed as frequent small amounts of caddy or watery stools from day 8 to day 16 after the start of treatment. It occurred coincidently with granulocytopenia of grade 4. No patients experienced tarry stool or grossly bloody diarrhea. One patient receiving 50 mg/m² CPT-11 who experienced diarrhea of grade 3 from day 9 to day 19 was examined by colonofiberscope on day 22, after treatment. Macroscopic examination revealed mild erosion at several points, and histological examination revealed colonic mucosa with superficial erosion. Another patient at the CPT-11 dose of 50 mg/m² who experienced diarrhea of grade ≥3 from day 6 to day 12 was examined with barium enema on day 11 after the start of treatment. No remarkable change was observed except for diverticulosis. Grade 3 elevation of transaminase occurred in one patient, but this might have been caused by vindesine because in this patient we observed similar evidence of liver dysfunction when vindesine and cisplatin were administered without CPT-11 following the current treatment. No renal insufficiency of grade ≥2 was observed. The MTD in the first phase I trial was 50 mg/m² CPT-11 on days 1 and 8 combined with high-dose cisplatin (100 mg/m²) and vindesine (Table 2).

Response to Treatment. Table 3 shows the therapeutic response in patients treated with this regimen in the first phase I trial. Five patients were nonassessable for response, because they were removed from the study after one cycle of treatment for the following reasons: one had diarrhea of grade 3 at the first level, one had liver dysfunction of grade 3 at the second level, and three had diarrhea of grade ≥3 and/or granulocytopenia of grade 4 lasting 7 days at the third level. Two patients with only diarrhea of grade 3 as the dose-limiting toxicity received the second course of treatment and were successfully treated without further dose-limiting toxicity.

No patient achieved a complete response. At the CPT-11 dose level of 25 mg/m², three of five assessable patients achieved partial responses. At the CPT-11 dose level of 37.5 mg/m², two of six assessable patients achieved partial responses. At the CPT-11 dose level of 50 mg/m², a >50% shrinkage of the tumor was observed in two patients after one cycle of treatment. Overall, five of the 16 patients entered (five of 11 assessable patients) achieved partial responses.

Second Trial

Toxicity. The toxicities of grade ≥2 observed during the first 8 weeks of treatment in the second trial are summarized in Table 4. Before the start of the second trial, the planned dose levels of CPT-11/cisplatin were 20/60, 40/60, 60/60, 60/80, 80/60, 80/80, and 100/80 mg/m². However, as listed in Table 4, a 60/80-mg/m² dose level of CPT-11/cisplatin was found to be intolerable. Therefore, subsequent dose escalation was modified. As also shown in Table 4, granulocytopenia of grade 4 was observed at each dose level; however, granulocytopenia of grade 4 lasting ≥7 days was observed at the 60/80-mg/m² dose level of CPT-11/cisplatin. The median duration of granulocytopenia of grade 4 was 3 days (range, 1–10 days). Ten patients experienced granulocytopenic fever of grade ≥2, and febrile neutropenia of grade 4 was observed in three patients. However, no patient developed life-threatening infection. Thrombocytopenia was

<table>
<thead>
<tr>
<th>Table 3 Therapeutic response in first phase I trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT-11</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>37.5</td>
</tr>
<tr>
<td>50</td>
</tr>
</tbody>
</table>

* CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, nonassessable.
Phase I trial was 100 mg/m² CPT-11 on days 1 and 8 combined with patient variation in the degree of granulocytopenia was noted at each was not observed. No pulmonary toxicity related to drug administration.

Diarrhea usually took the form of frequent small amounts of catty or watery stools, was observed from day 10 to day I trial (Table 5). The granulocyte count nadir (median, 428/μl; range, 242—966) and the median duration of granulocytopenia of <1000/μl was 7 days (range, 2—16 days). Although wide inter-patient variability in the degree of granulocytopenia was noted at each dose level, the severity of granulocytopenia tended to increase as the dose level increased. Diarrhea usually took the form of frequent small amounts of catty or watery stools, was observed from day 10 to day 16 after the start of treatment, and occurred coincidentally with granulocytopenia of grade 4. No patients experienced grossly bloody diarrhea.

With the combination of CPT-11, cisplatin, and vindesine, the MTDs of CPT-11 combined with either high-dose (100 mg/m²) or low-dose cisplatin (60 mg/m²) and vindesine did not increase with increasing doses of CPT-11. The MTD in the second phase I trial was 100 mg/m² CPT-11 on days 1 and 8 combined with low-dose cisplatin (60 mg/m²) and vindesine (Table 4).

Granulocytopenia and diarrhea were observed in the second phase I trial (Table 5). The granulocyte count nadir (median, 428/μl; range, 26—3477/μl) usually occurred at approximately day 14 (between days 8 and 17), and the median duration of granulocytopenia of <1000/μl was 7 days (range, 2—16 days). Although wide inter-patient variability in the degree of granulocytopenia was noted at each dose level, the severity of granulocytopenia tended to increase as the dose level increased. Diarrhea usually took the form of frequent small amounts of catty or watery stools, was observed from day 10 to day 16 after the start of treatment, and occurred coincidentally with granulocytopenia of grade 4. No patients experienced grossly bloody diarrhea.

The combination of CPT-11, cisplatin, and vindesine, the MTDs of CPT-11 combined with either high-dose (100 mg/m²) or low-dose cisplatin (60 mg/m²) and vindesine was 50 and 100 mg/m² on days 1 and 8, respectively. No further dose escalation was performed during these trials.

**Response to Treatment.** Table 6 shows the therapeutic responses of patients treated with this regimen in the second phase I trial. Eight patients were nonassessable for response. These patients were removed from study after one cycle of treatment for the following reasons: one had granulocytopenia of grade 4 lasting 7 days and one had diarrhea of grade 4 at the CPT-11/cisplatin dose level of 60/80 mg/m²; two had granulocytopenia of grade 4 lasting 7 days and diarrhea of grade ≥3 and one had liver dysfunction of grade 3 at the CPT-11/cisplatin dose level of 80/60 mg/m²; two had granulocytopenia of grade 4 lasting 7 days and diarrhea of grade ≥3 and one had liver dysfunction of grade 3 at the CPT-11/cisplatin dose level of 80/60 mg/m². One patient with only diarrhea of grade 3 as the dose-limiting toxicity received the second course of treatment and was successfully treated without further dose-limiting toxicity.

No patient achieved a complete response. Five of 11 patients entered from the first level to the fourth level achieved partial responses. Among the patients treated with CPT-11 (80 mg/m²) on days 1 and 8 and cisplatin (60 mg/m²) on day 1, four of eight assessable patients achieved partial responses. Overall, 10 of 30 patients entered (10 of 22 assessable patients) in the second phase I trial achieved partial responses. The median duration of response was 28 weeks (range, 10—54 weeks).

**Pharmacokinetics.** Pharmacokinetic data were obtained from six patients who were entered in the first phase I study and three patients who were entered in the second trial (Table 7). In the first trial, the C max of CPT-11 was observed 0 to 5 min after the end of CPT-11 infusion, and the range of the CPT-11 C max was 0.41—0.70 μg/ml. The C max of SN-38 was observed during 5—30 min after the end of CPT-11 infusion, and the range of the SN-38 C max was 11.7—23.5 ng/ml in patients treated with CPT-11 at doses of 25—37.5 mg/m². In the second trial, C max and AUC of CPT-11 increased in relation to the dose of CPT-11; however, interpatient variability of C max and AUC of SN-38 was very large. Cases 44 and 45 experienced intractable diarrhea.

### Table 5  Granulocytopenia and diarrhea in the second phase I trial

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>WBC (grade)</th>
<th>Granulocytes (grade)</th>
<th>Platelet (grade)</th>
<th>Diarrhea (grade)</th>
<th>Nausea/vomiting (grade)</th>
<th>Liver (grade)</th>
<th>Kidney (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11 + Cisplatin</td>
<td>20/60</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>40/60</td>
<td>60</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>60/80</td>
<td>80</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>80/60</td>
<td>100</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>100/60</td>
<td>110</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 4  Toxicity of second phase I trial

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients/</th>
<th>WBC (grade)</th>
<th>Granulocytes (grade)</th>
<th>Platelet (grade)</th>
<th>Diarrhea (grade)</th>
<th>Nausea/vomiting (grade)</th>
<th>Liver (grade)</th>
<th>Kidney (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11 + Cisplatin</td>
<td>20</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>≥3</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>≥3</td>
</tr>
<tr>
<td>80</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>≥3</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>≥3</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, numbers of patients with grade 4 granulocytopenia lasting ≥7 days.
DISCUSSION

CPT-11 is a promising new active agent against NSCLC. Dose-limiting toxicities were leukenopectasia and diarrhea in a phase II study (23). The current phase I study of CPT-11 in combination with cisplatin and a fixed dose of vindesine was conducted to determine the toxicity/morbidity of this regimen in the treatment of patients with metastatic NSCLC who had received no prior therapy.

The toxicities of this regimen were leukenopectasia and gastrointestinal toxicity, especially diarrhea. In the current studies, we defined an absolute granulocyte count of <500/mm^3 for 7 days or more as unacceptable toxicity. The duration of granulocytopenia might be reduced by using recombinant human G-CSF or GM-CSF. In the current studies without G-CSF and GM-CSF, however, granulocytopenia might be minimized using a hematopoietic growth factor such as G-CSF or GM-CSF in cases with granulocytopenia of grade 3. The criteria of dose-limiting toxicity and MTD used in the current studies were very similar to those used in recent phase I trials of new single agents such as taxotere or taxol (37—39), in which neutropenia was the major dose-limiting toxicity.

Although the dose intensity of cisplatin in the treatment of advanced non-small cell lung cancer has been debated, high-dose cisplatin has been used widely for this disease. The current study demonstrated important pharmacokinetic results for CPT-11 (37.5 mg/m², days 1 and 8) combined with high-dose cisplatin (100 mg/m²). The dose of 37.5 mg/m² CPT-11 appears to be quite low (one-fifth) compared with that (100 mg/m² weekly) in the previous phase I study of CPT-11 as a single agent (22). The pharmacokinetic data, however, showed that the C max of SN-38, the active metabolite of CPT-11, showed increase to 50% seen in in vitro studies (31, 32). Moreover, as shown in Table 7, the C max of CPT-11 (>0.4 μg/ml) reached >10-fold the concentration required to inhibit growth by 50% seen in in vitro studies (31, 32). Therefore, 37.5 mg/m² CPT-11 weekly combined with high-dose cisplatin appears to have therapeutic value.

Based on the assumption of a dose-effective relationship, however, CPT-11 could be combined with high-dose cisplatin (100 mg/m²) and vindesine at only 19% (37.5 mg/m² on days 1 and 8) of the dose intensity of 100 mg/m²weekly that could be achieved by a single agent (22). Therefore, we conducted a second phase II study of this regimen to focus primarily on the dose escalation of CPT-11. As a result, the dose of CPT-11 combined with low-dose cisplatin (60 mg/m²) and vindesine could be increased at 40% (80 mg/m² on days 1 and 8) of the dose intensity of the drug when it was given alone. This dose intensity of CPT-11 (40%) was very close to that of CPT-11 (45%) reported by Masuda et al. (40) in their phase I trial of the combination of CPT-11 and a modest dose of cisplatin (80 mg/m²), although the criteria for MTD were different in the two studies.

On the other hand, it is unclear which is important, the dose intensity of cisplatin or dose intensity of CPT-11, in the combination of cisplatin and CPT-11 in the management of patients with advanced NSCLC. In the current phase I studies, which regimen is active is unclear because of small number of patients; however, at the recommended dose, high-dose CPT-11 combined with low-dose cisplatin seems to be less toxic, especially gastrointestinal toxicity, received antibiotics for fever associated with granulocytopenia. However, in 10 of 12 patients delayed diarrhea occurred prior to the use of antibiotics. In one of two patients who received antibiotics for 5 to 7 days prior to the occurrence of severe delayed diarrhea, stool was examined for the presence of enterotoxin D-1 produced by Clostridium difficile. C. difficile, however, was not detected. The mechanism of diarrhea induced by CPT-11 is unclear. Sasaki et al. (36) reported that there was a positive correlation between the AUCs of CPT-11 and the percentage decrease in leucocyte cell count and that episodes of diarrhea were more closely correlated with the AUCs of SN-38 than those of CPT-11. More detailed basic and clinical research concerning the diarrhea induced by CPT-11 will be necessary to clarify this point.

In the current phase I studies of the combination of CPT-11, cisplatin, and vindesine, the recommended i.v. doses for a phase II trial of CPT-11 given on days 1 and 8 and combined with either high-dose cisplatin (100 mg/m²) or low-dose cisplatin (60 mg/m²) are 37.5 and 80 mg/m², respectively. Although the criteria for MTD in the current studies may be considered slightly aggressive relative to standard definitions of MTD (grade 3 to 4 toxicity in one-third or more of patients), they are based, in part, on the relatively reversible nature of granulocytopenia and on the paucity of granulocytopenic complications at these doses. And granulocytopenia may be minimized using a hematopoietic growth factor such as G-CSF or GM-CSF in cases with granulocytopenia of grade ≥3. The criteria of dose-limiting toxicity and MTD used in the current studies were very similar to those used in recent phase I trials of new single agents such as taxotere or taxol (37—39), in which neutropenia was the major dose-limiting toxicity.
compared to low-dose CPT-11 combined with high-dose cisplatin, probably with equal activity as shown in Tables 3 and 6, and the former regimen is easily administered to the patients with less vigorous hydration-diuresis.

In the current second phase I study, 10 of 30 patients entered (10 of 24 assessable patients) with metastatic NSCLC achieved partial responses. Although no patient achieved a complete response, the response data for this regimen appear to be encouraging (41). In the current phase I studies, however, it is unclear whether this regimen is any better than CPT-11 alone or cisplatin alone, and there is synergy for these agents observed in vitro studies (32). We are now proposing a phase II study of this regimen for ambulatory patients with metastatic NSCLC using 80 mg/m² CPT-11 (on days 1 and 8) combined with 60 mg/m² cisplatin (on day 1) and vindeine (3 mg/m² on days 1 and 8), every 4 weeks, as a multicenter cooperative trial on the basis of the following: (a) Gralla et al. (24) reported that the response rate of a combination of low-dose cisplatin (60 mg/m²) and vindeine against advanced NSCLC was 43%; (b) randomized trials comparing high-dose cisplatin (120 mg/m²) and low-dose cisplatin (60 mg/m²) in combination with vindeine (24) or etoposide (42) in advanced NSCLC failed to demonstrate a significant survival advantage with a high-dose regimen; (c) the dose intensity of CPT-11 combined with low-dose cisplatin (60 mg/m²) and vindeine may increase to double the dose intensity of the drug combined with high-dose cisplatin (100 mg/m²) and vindeine; and (d) gastrointestinal toxicities were less in patients treated with low-dose cisplatin (60 mg/m²) and 80 mg/m² CPT-11 than in those treated with high-dose cisplatin (100 mg/m²) and 37.5 mg/m² CPT-11.

ACKNOWLEDGMENTS

We thank Dr. John S. Lazo, Department of Pharmacology, University of Pittsburgh, for his valuable advice.

REFERENCES


Phase I Clinical Trial of Irinotecan (CPT-11), 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, and Cisplatin in Combination with Fixed Dose of Vindesine in Advanced Non-Small Cell Lung Cancer

Tetsu Shinkai, Hitoshi Arioka, Hiroshi Kunikane, et al.


Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/54/10/2636

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/54/10/2636. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.