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ORIGINAL ARTICLE

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A phase II study of irinotecan and infusional cisplatin with recombinant human granulocyte colony-stimulating factor support for advanced non-small-cell lung cancer

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Abstract *Purpose*: We administered chemotherapy consisting of a combination of 5-day continuous infusion of cisplatin (20 mg/m^2 per day) plus irinotecan (160 mg/m^2 per day, as a bolus, on day 1) with recombinant human granulocyte colony-stimulating factor (rG-CSF) support to previously untreated advanced non-small-cell lung cancer (NSCLC) patients, and evaluated the effectiveness and safety of this therapy. *Patients*: Enrolled in the study were 41 NSCLC patients. *Results*: Of the 41 patients, 24 achieved a partial response. The response rate was 58.5% (95% confidence interval, 42.2% to 74.8%), with a median response duration of 32.1 weeks. The median survival time was 44.8 weeks and the 1-year survival rate was 44%. A total of 100 courses of therapy were given. The major toxic effects were grade 3 or 4 diarrhea (23%), granulocytopenia (20%), thrombocytopenia (15%) and anemia (15%). There were no treatment-related deaths. *Conclusions*: Combination chemotherapy with irinotecan plus infusional cisplatin with rG-CSF support was well tolerated and effective in patients with advanced NSCLC.

Key words Phase II study · Non-small-cell lung cancer · Cisplatin · Irinotecan · rG-CSF

Introduction

Irinotecan hydrochloride (CPT-11), a semisynthetic derivative of camptothecin, shows strong tumor activity against a broad spectrum of tumors in vitro [5, 10]. CPT-11 has also been found to be active against Non-small-cell lung cancer (NSCLC) [3, 13], small-cell lung cancer [6], leukemia, lymphoma [14] and colorectal cancer [16, 19]. The response rate of NSCLC to CPT-11 of 32% is encouraging [3].

Cisplatin is not the most effective active single agent for advanced lung cancer worldwide. In addition, cisplatin is gaining widespread acceptance as one of the two or three agents used in combination chemotherapy [1, 17]. In previous study at our institute, cisplatin was given by 5-day continuous infusion as a single agent to 30 previously untreated patients with NSCLC, and a high response rate (40%) was obtained. A good clinical outcome has been obtained for infusional cisplatin, and although the total dose is larger than that for bolus administration, infusional cisplatin is associated with less severe emesis and renal toxicity [18], making infusional cisplatin an effective and safe treatment for NSCLC.

In in vitro studies, CPT-11 and cisplatin have shown synergistic action [4], and the two drugs have different action mechanisms with negligible overlap of principal toxicities. Therefore, combination therapy with CPT-11 and cisplatin is also used against advanced lung cancer [7–9, 20].

We have previously studied the combination of CPT-11 and infusional cisplatin in a clinical phase I trial [11, 12]. An encouraging response rate of 47%–55% was obtained in previously untreated NSCLC patients. We therefore carried out a phase II study of CPT-11 and infusional cisplatin with recombinant human granulocyte colony-stimulating factor (rG-CSF) support in previously untreated NSCLC patients, and evaluated the response and safety of this therapy.

Materials and methods

Patient population

The eligibility criteria for this phase II trial included histologically or cytologically confirmed advanced NSCLC, expected survival of 12 weeks or more, age ≤75 years, Eastern Cooperative Oncology Group performance status (PS) score of 0–2, measurable lesions, and adequate hematological function (WBC ≥ 4000/mm^3, platelet count

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100 000/mm^3, hemoglobin ≥10 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). None of the patients enrolled had received prior therapy. The protocols used were approved by the ethical committee of the Tochigi Cancer Center (Tochigi). Written informed consent was obtained from every patient 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 Tochigi Cancer Center Hospital during the trial. Complete blood count, biochemical tests and serum electrolytes were obtained three times a week, and urinalysis and chest roentgenograms were obtained weekly during this phase II trial. Tests of measurable disease parameters such as computerized tomography were repeated every 4 weeks. Staging was according to the 4th edition of the UICC TNM classification.

Study design and treatment plan

The anticancer drug regimen consisted of combined administration of CPT-11 plus infusional cisplatin with rG-CSF support. CPT-11 (Daiichi Pharmaceutical Co., Japan), 160 mg/m^2 in 500 ml normal saline or 5% glucose, was infused intravenously (i.v.) over 90 min on day 1. Cisplatin (20 mg/m^3) was given daily for 5 days by continuous i.v. infusion. One-third of the daily dose was administered every 8 h dissolved in 800 ml physiological saline [18]. rG-CSF (Chugai Pharmaceutical Co., Japan) for injection was administered subcutaneously at a dose of 2 μg/kg for, in principle, 16 days (days 6 to 21), beginning on the day after completion of cisplatin administration, once every day, at the same time whenever possible. However, if the granulocyte count increased to more than 5000/mm^3 or the white blood cell count increased to more than 10 000/mm^3 after reaching the nadir, administration was discontinued. The course was repeated every 4 weeks. Antiemetic drugs used were 5-HT$_3$ antagonists (3 or 4 mg bolus infusion, days 1–7), metoclopramide (3 mg/kg per day, continuous infusion for 5 days), methylprednisolone (125 mg bolus infusion every 8 h, days 1–5), diphenhydramine (30 mg orally, days 1–7) and alprazolam (1.2 mg orally, days 1–7). No prophylactic measures such as antidiarrheal drugs were used. However, loperamide hydrochloride for grade 2 or higher diarrhea under the common toxicity criteria [22], and codeine phosphate and electrolyte parenteral fluid for grade 3 or 4 diarrhea were administered when the diarrhea occurred.

Patients were treated for at least two cycles of therapy unless disease progression or unacceptable toxicity was encountered or the patient's wishes intervened. The dose of CPT-11 was reduced to 120 mg/m^2 for the subsequent course if grade 3 or 4 diarrhea occurred. The dose of cisplatin was reduced to 15 mg/m^2 per day for the subsequent course if grade 2 renal toxicity occurred. Therapy was discontinued if the disease progressed or if the patient refused further treatment. In patients with a partial response (PR) or complete response (CR) treatment was continued. Patients with limited disease who responded received chest radiation therapy (RT) (50–60 Gy) after their chemotherapy. Patients who were resistant to chemotherapy or who worsened after two courses of this treatment received RT, second-line chemotherapy or observation, depending on the patient's clinical condition.

The criteria for response were as follows. CR was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. PR 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. WHO response criteria were used.

Toxicity was graded according to the common toxicity criteria [22]. The duration of each response was defined as the number of days from the documentation of the response until tumor progression. Survival curves from day 1 of treatment until death were generated by the method of Kaplan and Meier.

Results

From December 1994 to October 1996 41 patients were enrolled in this study and 100 courses of the regimen were administered. Table 1 shows the patient characteristics. There were 10 women and 31 men, with a median age of 60.7 years (range 37 to 74 years). Two patients had stage IIIA, 9 patients stage IIIB, and 30 stage IV disease. The mean number of cycles administered per patient was 2.4, ranging from 1 to 5.

The response rate was 58.5% (95% confidence interval, 42.2% to 74.8%); a CR was not observed in any patient and a PR was observed in 24 patients (Table 1). The response rate was 64% in stage III and 57% in stage IV disease; 61% in adenocarcinoma and 50% in squamous carcinoma; and 58% in the PS 0–1 group, and 60% in the PS 2 group. The response rate was not significantly different between these stages, histologies, and PS groups. The median duration of response was 32.1 weeks (range 6–120 weeks; stage III, 41.8 weeks; stage IV, 28.1 weeks). The median survival time was 44.8 weeks (14–176 weeks; stage III, 79.5 weeks; stage IV, 33.5 weeks) and the 1-year survival rate was 44% (stage III, 64%; stage IV, 37%). There were no significant differences between stage III and IV patients. Five patients were still alive at the time of writing.

Table 1 Patient characteristics and response to treatment

		No. of patients
Eligible patients		41
Age (years)		
Median	60.7	
Range	37–74	
Sex		
Male		31
Female		10
Performance status		
0		5
1		31
2		5
Stage		
IIIA		2
IIIB		9
IV		30
Histology		
Adenocarcinoma		28
Squamous		12
Adenosquamous		1
Response		
Complete response		0
Partial response		24 (58.5%)
Stable disease		16
Progressive disease		1

After chemotherapy, of the 41 patients, the number of responders and nonresponders who received RT, observation, or second-line chemotherapy was as follows: 11 responders, 5 nonresponders (RT); 12 responders, 11 nonresponders (observation); 1 responder, 1 nonresponder (second-line chemotherapy).

The types and grades of toxicities using the common toxicity criteria resulting from the treatment are shown in Table 2. The dose of CPT-11 was reduced in nine patients for the subsequent course due to diarrhea of grade 3 or 4. All 41 patients were evaluable for toxic reactions. The major toxicities were myelosuppression and diarrhea. Leukocyte count $<2000/mm^3$ (grade 3 or 4) was observed in six patients (15%), four of whom (10%) showed grade 4. Granulocyte count $<1000/mm^3$ (grade 3 or 4) was observed in 12 patients (29%), 8 of whom (20%) showed grade 4. Nine patients developed neutropenic pyrexia. Platelet count $<5 \times 10^4/mm^3$ (grade 3 or 4) was observed in nine patients (22%), two of whom (5%) showed grade 4, and a hemoglobin nadir (grade 3 or 4) in three patients (7%). There were no episodes of bleeding or fluid overload.

Diarrhea grade 3 or 4 was observed in nine patients (22%), four of whom (10%) showed grade 4. Only one patient experienced grossly bloody diarrhea. Vomiting grade 2 developed in 19 patients (46%). Grade 2 liver dysfunction was observed in one patient and grade 1 or 2 alopecia in 21 patients. None of the patients showed renal dysfunction of grade 2 or more. Finally, there were no treatment-related deaths.

Table 2 Numbers of patients showing each grade of toxicity ($n = 41$)

	Maximum toxicity grade (common toxicity criteria)				
	0	1	2	3	4
Leukopenia	26	4	5	2	4
Granulocytopenia	24	4	1	4	8
Thrombocytopenia	23	6	3	7	2
Anemia	12	19	7	3	0
Diarrhea	2	12	18	5	4
Vomiting	13	9	19	0	0
Alopecia	20	3	18		
Fever	32	6	3	0	0
Elevated SGOT/SGPT	31	9	1	0	0
Elevated serum creatinine	38	3	0	0	0

Discussion

Combination chemotherapy with CPT-11 plus infusional cisplatin has been evaluated in patients with previously untreated NSCLC [11, 12]. The addition of rG-CSF to the combination of CPT-11 and infusional cisplatin permitted an increase in the dose of CPT-11 from 80 mg/m^2 to 160 mg/m^2. The importance of dosage for obtaining a response has been reported for various malignancies [2]. Taguchi et al. [21] performed a phase I study of CPT-11 alone every 3–4 weeks. Anticancer effects were obtained with doses of 165 mg/m^2 or more.The current phase II study of CPT-11 plus infusional cisplatin with rG-CSF support was conducted to evaluate the response and safety of this regimen in the treatment of patients with advanced NSCLC who had received no prior therapy.

Our results are compared in Table 3 with the clinical results reported by Masuda et al. [9] and Oshita et al. [15]. The dose intensity of cisplatin in our study was 1.25 times that in the study by Masuda et al. The dose intensity of CPT-11 in our study was 0.67 times that in the other studies. The response rate was slightly higher in our study than in the other studies. The median survival time and 1-year survival were slightly better in our study than in the study by Oshita's et al.

The main side effects were myelosuppression and diarrhea. The incidence of myelosuppression and diarrhea did not markedly differ among the three studies. Diarrhea could be managed with loperamide hydrochloride and codeine phosphate in addition to i.v. fluid and electrolyte replacement. There were no treatment-related deaths in our study or in the study by Masuda et al., and in the study by Oshita et al. one patient (1.6%) died.

Table 3 A comparison of trials using CPT-11-based chemotherapy with rG-CSF support in NSCLC (*BI* bolus infusion, *CI* continuous infusion)

	Present study	Masuda et al. [15]	Oshita et al. [19]
Treatment schedule	CPT-11 160 mg/m^2 BI day 1 Cisplatin 20 mg/m^2 CI days 1–5 every 4 weeks	CPT-11 80 mg/m^2 BI days 1, 8, 15 Cisplatin 80 mg/m^2 BI day 1 every 4 weeks	CPT-11 60 mg/m^2 BI days 1–3 Etoposide 60 mg/m^2 BI days 1–3 every 3 weeks
Dose intensity (mg/m^2 per week)			
CPT-11	40	60	60
Cisplatin	25	20	
Response (%)	58.5	50	21.3
Median survival time (months)	10.2	–	10
1-year survival rate (%)	44	–	36.1
Toxicity (grade 3 or 4)			
Leukopenia	15%	7%	23%
Granulocytopenia	29%	–	39%
Thrombocytopenia	22%	4%	3%
Diarrhea	22%	7%	16%

In conclusion, combination chemotherapy of CPT-11 plus infusional cisplatin with rG-CSF support was an effective and tolerable regimen in patients with advanced NSCLC.

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