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Short Communication

A Phase I Study of Irinotecan and Infusional Cisplatin with Recombinant Human Granulocyte Colony-stimulating Factor Support in the Treatment of Advanced Non-small Cell Lung Cancer

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We conducted a phase I study to examine whether support with recombinant human granulocyte colony-stimulating factor (rG-CSF) would permit dose intensification of irinotecan (CPT-11) in combination with cisplatin (20 mg/m^2 × 5 days) in non-small cell lung cancer (NSCLC) patients. CPT-11 was administered by bolus infusion at a starting dose of 100 mg/m^2 on day 1, followed by serial increments at 20 mg/m^2, given every 4 weeks. The major toxic effects were granulocytopenia and diarrhoea. The response rate was 55% (11/20). The optimum dose for phase II studies appears to be 20 mg/m^2/day (5-day continuous infusion) for cisplatin and 160 mg/m^2 (day 1) for CPT-11 with rG-CSF support in NSCLC. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: non-small cell lung cancer, cisplatin, irinotecan, rG-CSF, phase I study

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INTRODUCTION

WE HAVE previously studied the effect of irinotecan and cisplatin in advanced non-small cell lung cancer (NSCLC) [1]. An encouraging response rate of 47% was obtained in previously untreated patients. However, in combination with cisplatin at 100 mg/m^2 (20 mg/m^2/day, continuous infusion, on 5 days), irinotecan hydrochloride (CPT-11) could only be safely administered at 20% of the dose intensity that could be achieved when it was administered as a single agent (80 mg/m^2 on day 1 every 4 weeks versus 100 mg/m^2/week weekly) [2], with dose-limiting toxicity being granulocytopenia. The importance of dosage for obtaining a response has been reported for various malignancies [3].

We conducted a phase I trial to examine whether support with recombinant human granulocyte colony-stimulating factor (rG-CSF) would permit further increase of the irinotecan dose in combination with a fixed cisplatin dose.

The purposes of this study were to determine the optimal doses of irinotecan and a fixed dose of cisplatin under rG-CSF support, and to assess the toxicity of irinotecan in combination chemotherapy. The therapeutic effect of the combination in patients with advanced NSCLC were also examined.

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PATIENTS AND METHODS

Patient population

All hospitalised patients with histologically or cytologically confirmed advanced NSCLC (IIIB, IV) were eligible for this phase I trial. None of the patients had received prior therapy. Other eligibility criteria included expected survival of ≥12 weeks, age <75 years, ECOG performance score of 0–2, measurable lesions, adequate haematological function, renal function and hepatic function. The protocols used were approved by the ethical committee of the Tochigi Cancer Center (Tochigi). Written informed consent was obtained.

Study design and treatment plan

We studied dose escalation of irinotecan (day 1) with a fixed dose of cisplatin plus rG-CSF support, given every 4 weeks. The initial dose of irinotecan in the present study, based on the results of our previous study [1], was determined to be 100 mg/m^2 (day 1) and the dosage was

Table 1. Dose escalation schedule

Dose level	Dose (mg/m^2) Irinotecan	Cisplatin**	No of patients	Total no. of courses
1*	100	20 × 5	3	9
2*	120	20 × 5	3	5
3*	140	20 × 5	3	4
4*	160	20 × 5	8	18
5*	180	20 × 5	3	4

*Support with rG-CSF (2 μg/kg, subcutaneously, days 6–21).
**20 mg/m^2/day × 5 days (continuous i.v. infusion).

increased in subsequent increments of 20 mg/m^2 (Table 1). Irinotecan (Daiichi Pharmaceutical Co., Ltd., Japan) was infused i.v. over 90 min on day 1. Cisplatin (20 mg/m^2) was given daily for 5 days by continuous intravenous infusion (CI). rG-CSF (Chugai Pharmaceutical Co., Ltd., Japan) was administered subcutaneously (s.c.) at a dose of 2 μg/kg (days 6–21). No prophylactic measures, such as antidiarrhoeal drugs, were used.

The maximal tolerated dose (MTD) was defined by the same method of Masuda's report [4]. Dose escalation was not permitted in the same patient. Toxicity was graded according to the common toxicity criteria.

RESULTS

20 patients were enrolled in this study. There were 6 women and 14 men, with a median age of 61 years (range 51–74 years). 6 patients had stage IIIB disease and 14 stage IV disease. A total of 40 courses of therapy were given, and all were assessable for toxicity. The mean number of cycles administered per patient was 2, and ranged from one to three (1 cycle in 6 patients, 2 in 8 patients, and 3 in 6 patients). Table 1 shows the number of patients and courses per dose level.

Toxicity

Side-effects are shown in Table 2. This table shows side-effects at each dose level in the first course. At dose level 4, grade 4 granulocytopenia and leucopenia developed in 1 patient each, and grade 3 thrombocytopenia in 2 of the 8 patients. Neutropenic fever occurred in 1 patient. In addition, grade 3 diarrhoea was observed in 1 patient, who also showed grade 2 granulocytopenia and grade 3 anaemia. At dose level 5, grade 4 leucopenia, granulocytopenia and thrombocytopenia were observed in 2 of the 3 patients. One of the 2 patients had neutropenic fever and pneumonia, and also developed grade 4 diarrhoea. The other patient showed grade 3 granulocytopenia and grade 3 diarrhoea. From these results, the MTD in this phase I study was 180 mg/m^2 of irinotecan on day 1 in combination with cisplatin (20 mg/m^2/day, CI, on 5 days).

Granulocytopenia ⩽ grade 2 were observed in 10 of all 40 courses. The median nadir occurred on day 14 (range, day 10–18). The median day of recovery (recovery from the nadir to a granulocyte count $\geqslant 2 \times 10^3/mm^3$) was day 17 (range, day 15–22).

Diarrhoea ⩽ grade 3 was observed in 6 of the 40 courses. Diarrhoea ⩽ grade 3 developed on median day 10 (range, day 7–13), and recovery was observed on median day 15 (range, day 11–20). Diarrhoea could be managed with loperamide hydrochloride and codeine phosphate in addition to i.v. fluid and electrolyte replacement. No patients experienced tarry stool or grossly bloody diarrhoea.

There were no treatment-related deaths.

Response to treatment

No patient showed a complete response. 11 of the 20 patients exhibited partial responses. At dose level 4 (irinotecan at 160 mg/m^2 on day 1), 5 of the 8 patients showed a partial response. There were 11 partial responses (IIIB; 5, IV; 6) lasting from 41 to 365 days, with a median duration of 210 days. 9 patients showed stable disease.

DISCUSSION

In the phase I trial of a combination of irinotecan and cisplatin with rG-CSF support reported by Masuda and associates [4], cisplatin was administered at 80 mg/m^2 every 4 weeks. Since it was administered at 20 mg/m^2/day on 5 consecutive days every 4 weeks in this study, the dosage of cisplatin in this regimen was 1.25 times higher than that in the study of Masuda and associates. However, Masuda and associates [4] administered irinotecan at a dose of 80 mg/m^2 on days 1, 8 and 15 (total dose, 240 mg/m^2). In the present study, irinotecan was administered at a dose of 160 mg/m^2 on day 1, and its dose intensity was 67% of that in Masuda's study.

The response rate in the present study was 55%, comparable with results of previously reported trials of other combination chemotherapy regimens in patients with NSCLC [5] as well as the rates reported in studies of the combination of cisplatin and irinotecan at other institutions [4, 6, 7]. In our previous study without rG-CSF [1], the response rate was 47%.

In conclusion, addition of rG-CSF to the combination of irinotecan and cisplatin permitted an increase in the dose of irinotecan from 80 mg/m^2 to 160 mg/m^2, resulting in a 2-fold dose intensification compared with the previous phase I

Table 2. Toxicity of irinotecan and infusional cisplatin with rG-CSF

Dose level	No. of patients with DLT/Total number	WBC (grade) 2	3	4	Granulocytes (grade) 2	3	4	Platelets (grade) 2	3	4	Haemoglobin (grade) 2	3	Diarrhoea (grade) 2	⩾3	Nausea/vomiting (grade) 2	3	Alopecia (grade) 1	2
1	0/3	0	0	0	0	0	0	0	0	0	0	0	2	0	1	0	2	0
2	0/3	0	1	0	0	1	0	0	1	0	2	0	2	0	1	0	1	0
3	0/3	0	0	0	0	0	0	1	0	0	2	0	2	0	2	0	2	0
4	2/8	1	0	1	1	0	1	0	2	0	3	1	2	1	5	0	6	1
5	3/3	1	0	2	0	1	2	0	0	2	0	2	1	2	0	0	1	0

*DLT, dose limiting toxicity.

trial without rG-CSF [1]. The major dose-limiting toxic effects of this regimen were diarrhoea and granulocytopenia. The recommended irinotecan dose in combination with infusional cisplatin at 20 mg/m^2/day on days 1–5 with rG-CSF support is 160 mg/m^2 on day 1. In the future phase II study of patients with previously untreated NSCLC, this combination therapy will be repeated every 4 weeks.

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