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Phase I/II study of cisplatin, ifosfamide and irinotecan with rhG-CSF support in patients with stage IIIB and IV non-small-cell lung cancer

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Abstract *Purpose*: We conducted a phase I/II study in previously untreated patients with stage IIIB or IV non-small-cell lung cancer (NSCLC) to: (1) determine the maximum tolerated dose (MTD) of cisplatin combined with a fixed schedule of ifosfamide and irinotecan with rhG-CSF support; and (2) to determine the overall response rate and median survival of patients entered on this study. *Methods*: Ifosfamide (1.5 g/m^2) and irinotecan (60 mg/m^2) were administered at fixed doses on days 1–4 and on days 1, 8 and 15, respectively. Cisplatin was given on day 1 at 60 mg/m^2 and was increased in 10-mg/m^2 increments. This regimen was repeated every 4 weeks. rhG-CSF (nartograstim) was administered subcutaneously at a dose of 1 μg/kg on days 5–18 except on the day of irinotecan treatment. *Results*: Between June 1995 and April 1998, 46 patients were registered onto this phase I/II study. The MTD of cisplatin was defined according to toxicity and the dose during three courses was increased. Since at the 80 mg/m^2 dose level more than one-third of the patients were treated with dose modification, the dose of 70 mg/m^2 was recommended for phase II study. The dose-limiting toxicity was leukopenia. The overall response rate was 62.2% (95% CI 48.0–76.4%), the median response duration was 144 days, and the median survival time was 393 days. *Conclusion*: For phase II study, we recommend doses of cisplatin 70 mg/m^2 on day 1 combined with ifosfamide and irinotecan with rhG-CSF support. Both the response rate and preliminary survival data in this study suggest a high degree of activity of this combination in previously untreated NSCLC.

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Introduction

Irinotecan is a semisynthetic water-soluble derivative of camptothecin. Its mechanism of action is inhibition of DNA topoisomerase I through the formation of topoisomerase I-DNA cleavable complexes [1, 2]. Leukopenia and diarrhea are its major toxicities. In a phase II study of irinotecan on a schedule of 100 mg/m^2 weekly in patients with advanced non-small-cell lung cancer (NSCLC) without prior chemotherapy, the response rate was 32% [3]. Masuda et al. conducted a phase I study of escalating doses of irinotecan on days 1, 8 and 15 combined with 80 mg/m^2 of cisplatin on day 1 and recommended a dose of 60 mg/m^2 for phase II study [4]. In a phase II study of irinotecan and cisplatin in patients with stage IIIB or IV disease, the response rate was 52% and the median survival time was 44 weeks [5]. Studies have been conducted of escalating doses of irinotecan combined with a fixed dose of cisplatin with rhG-CSF support [6], and of the combination of the three drugs, irinotecan, cisplatin and vindesine [7]. An increase in the dose of irinotecan, however, resulted in a high incidence of diarrhea, and with the three-drug regimen hematological toxicity, in particular leukopenia, was severe. Consequently, combining irinotecan and cisplatin with another drug is difficult without rhG-CSF support.

We conducted a phase I/II study of escalating doses of cisplatin on day 1 combined with a fixed schedule of ifosfamide and irinotecan with rhG-CSF support in previously untreated patients with stage IIIB or IV NSCLC. The primary objectives of the phase I portion of the study were to define the maximum tolerated dose (MTD) of cisplatin in this three-drug regimen with rhG-CSF and to describe the dose-limiting toxicities (DLT). The primary aim during the phase II portion was to determine the overall response rates of patients entered

on this study. In April 1999, 1 year had passed since the completion of patient registration and the survival time was evaluated in addition to the objective response.

Patients and methods

Patient eligibility

Patients were enrolled in the study if they met all of the following eligibility criteria and did not meet any of the exclusion criteria: (1) histologically or cytologically confirmed advanced NSCLC (stage IIIB or IV), (2) no prior chemotherapy, (3) a life expectancy of at least 3 months, (4) a performance status (PS) of 0–2 on the ECOG scale, but at the cisplatin dose level of more than 70 mg/m^2 restricted to a PS of 0 or 1, (5) between 15 and 75 years of age, (6) adequate bone marrow function (hemoglobin ≥9 g/dl, leukocyte count ≥4000/mm^3, platelet count ≥100,000/mm^3), renal function (serum creatinine <1.5 mg/dl) and liver function (S-GOT and S-GPT less than twice the upper limit of normal), and (7) the provision of informed consent for participation.

Exclusion criteria were as follows: (1) severe concurrent medical conditions, (2) pregnant or nursing mothers, (3) active concomitant malignancy, (4) active uncontrolled infection, (5) intestinal paralysis and obstruction, (6) interstitial pneumonia or pulmonary fibrosis, and (7) large amount of ascites and/or pleural effusion.

Pretreatment and follow-up evaluations

Mandatory preregistration evaluations included medical history, physical examination, chest X-radiography, chest computed tomography (CT), bronchoscopy, head magnetic resonance imaging or CT, abdominal CT or ultrasonography, bone scintigraphy, hematology, blood biochemistry, urinalysis, ECG, and pulmonary function test. After the initiation of treatment, physical examination, chest X-radiography, hematology, blood biochemistry, and urinalysis were performed at least once weekly. Tumor responses were evaluated after every course on measurable lesions determined before registration by repeating the appropriate radiographic studies. WHO evaluation criteria [8] were used for efficacy analysis. Toxicities were graded according to the Common Toxicity Criteria [9].

Dose-escalation criteria

Ifosfamide was given at 1.5 g/m^2 over 2 h as a drip infusion on days 1–4 and irinotecan was administered at 60 mg/m^2 over 90 min as a drip infusion on days 1, 8 and 15. Cisplatin was administered at a starting dose of 60 mg/m^2 over 120 min as a drip infusion on day 1. Subsequent doses of cisplatin were increased in increments of 10 mg/m^2. rhG-CSF (nartograstim) was given subcutaneously at a dose of 1 μg/kg on days 5–18 except on the day of irinotecan treatment. All patients received azasetron 10 mg and dexamethasone 8 mg intravenously on days 1–4 and azasetron only on days 8 and 15. Mesna was given intravenously at 20% of the dose of ifosfamide at 0, 4 and 8 h after the administration of ifosfamide. Antidiarrheal drugs were not used prophylactically. If grade 2 or worse diarrhea was observed, a daily dose of 7.5 g Hange-shasinto (a Kampo medicine) divided into three portions was given.

Irinotecan was administered on days 8 and 15 when all of the following three conditions were met on the day of treatment: leukocyte count ≥2000/mm^3, platelet count ≥50,000/mm^3, and no grade 3 or worse diarrhea. Cycles were repeated every 4 weeks if the leukocyte count was ≥4000/mm^3 or the platelet count was ≥100,000/mm^3.

The dose of cisplatin for the subsequent course was reduced by 10 mg/m^2 if the leukocyte count was <1000/mm^3, or if the platelet count was <25,000/mm^3, and if irinotecan was omitted on days 8 and 15 due to toxicity. If grade 4 diarrhea occurred, the doses of cisplatin and irinotecan for the subsequent course were reduced by 10 mg/m^2. Dose delays of less than 1 week were permitted and the treatment was continued at the same doses after recovery from toxicity. If recovery from toxicity took more than 1 week but less than 2 weeks, the dose of cisplatin was reduced by 10 mg/m^2. Patients were excluded from the study if recovery took longer than 2 weeks.

DLT was defined as (1) grade 4 neutropenia lasting more than 5 days, (2) grade 4 thrombocytopenia, and (3) grade 4 nonhematological toxicity except for vomiting. At least six patients were enrolled at each dose level. The MTD of cisplatin was defined as the dose at which one-third of the patients experienced DLT during three courses or dose adjustment due to toxicity was required in more than one-third of the patients. If at least four of the first six patients entered did not experience DLT at the first course, patient registration was continued at the same dose level until these six patients had received three courses of treatment. Dose escalation in individual patients was not permitted. Patients who responded to treatment could continue therapy according to the above dose modification procedure until disease progression or the development of unacceptable toxicity.

Results

Patient characteristics

Between June 1995 and April 1998, 46 patients were registered in this phase I/II study. Patient characteristics according to cisplatin dose level are listed in Table 1. There were 34 men and 12 women with a median age of 55 years (range 37–73 years). Of the 46 patients, 31 had stage IV and 15 had stage IIIB disease.

The dose of cisplatin was 60 mg/m^2 for 11 patients, 70 mg/m^2 for 20, and 80 mg/m^2 for 15. Since at the 70 mg/m^2 dose level all 10 patients entered at the beginning were aged 60 years or less, the number of patients at the 70 mg/m^2 dose level was increased to 20,

Table 1 Patient characteristics

	Cisplatin dose (mg/m^2)		
	60	70	80
Sex			
Male	6	15	13
Female	5	5	2
Age (years)			
Median	56.0	49.5	57.0
Range	47–73	37–72	43–68
Performance status (ECOG)			
0	1	5	3
1	8	15	12
2	2	0	0
Histology			
Adenocarcinoma	10	20	11
Squamous cell carcinoma	1	0	2
Large cell carcinoma	0	0	2
Stage			
IIIB	3	7	5
IV	8	13	10
Prior therapy			
Surgery	1	1	0
Total	11	20	15

including 4 more than 60 years of age. At the 60 mg/m^2 cisplatin dose level one patient had ileus due to intestinal metastases on day 2 of the first course and withdrew on that day. Therefore, 45 patients were assessable for toxicity and response.

Toxicity

The hematological toxicities occurring during the first course at each cisplatin dose level and observed during three courses are listed in Table 2. At each cisplatin dose level, cumulative myelotoxicity was observed. However, escalation of the cisplatin dose was not associated with severity of myelotoxicity. This may have partly been due to our dose modification procedure, in which irinotecan was omitted on days 8 and 15 if the leukocyte count was $<2000/mm^3$ or platelet count was $<50{,}000/mm^3$. In addition, during the first course at the 60 mg/m^2 dose level, one patient with a PS of 2 experienced grade 4 thrombocytopenia. At the cisplatin dose levels of 70 and 80 mg/m^2, patients with a PS of 0 or 1 were enrolled onto the trial. The leukocyte nadir occurred at around day 12 during the first course, with recovery in all patients by day 30. During the third course the leukocyte nadir was observed at around day 15, but recoveries were delayed. Thrombocytopenia was observed less frequently than leukopenia and four patients required platelet transfusion. Anemia was prominent: seven patients at the dose level of 60 mg/m^2, 12 at 70 mg/m^2 and five at 80 mg/m^2 required RBC transfusion during three courses.

Table 3 shows nonhematological toxicities occurring up to the third course. Grade 2 or worse nausea, vomiting and anorexia were observed in most patients, but these symptoms proved to be transient. No grade 3 or worse diarrhea was observed during three courses. Gastric ulcer developed in two patients. One of these patients experienced hematemesis during the first course at the 70 mg/m^2 dose level of cisplatin, and was treated with a proton pump inhibitor. Elevation of serum transaminase was observed in 21 patients, but was transient and not severe. During the first course acute nephritis developed in one patient which improved with corticosteroid treatment. This might have been caused

Table 2 Hematological toxicity (*CTC* Common Toxicity Criteria)

Toxicity	No. of courses	Cisplatin dose (mg/m^2) Toxicity grade (CTC)											
		60				70				80			
		1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	1	0	1	1	4	3	2	1	3	4	1	2	0
	3	0	2	2	5	6	5	1	4	6	2	2	3
Neutropenia	1	1	2	0	4	2	2	0	4	1	2	1	1
	3	1	1	2	5	3	3	2	4	1	2	4	2
Thrombocytopenia	1	2	0	0	1	2	3	0	0	3	0	0	0
	3	2	2	1	2	1	2	1	1	1	3	0	1
Anemia	1	1	7	1	0	5	8	1	0	6	3	0	0
	3	0	8	2	0	3	9	6	0	2	11	2	0

Table 3 Nonhematological toxicity (*CTC* Common Toxicity Criteria)

Toxicity	Cisplatin dose (mg/m^2) Toxicity grade (CTC)											
	60				70				80			
	1	2	3	4	1	2	3	4	1	2	3	4
Gastrointestinal												
Nausea	0	0	10	0	2	2	16	0	1	6	8	0
Vomiting	1	5	4	0	3	9	2	1	4	7	0	0
Anorexia	0	0	10	0	3	1	16	0	1	4	10	0
Diarrhea	1	2	0	0	4	3	0	0	2	2	0	0
Gastric ulcer	0	0	0	0	0	0	1	0	0	1	0	0
Hepatic												
GOT	5	3	0	0	7	1	0	0	5	0	0	0
GPT	3	3	1	0	7	2	0	0	4	1	0	0
Renal/genitourinary												
BUN	1	2	0	0	7	2	0	0	12	1	0	0
Creatinine	0	0	0	0	1	0	0	0	1	1	0	0
Hematuria	9	0	0	0	14	0	0	0	8	0	0	0
Cardiovascular												
Thrombosis/embolism	0	0	0	0	0	0	0	0	0	0	1	0
Allergy	0	1	0	0	0	1	0	0	0	2	0	0
Alopecia	0	10	0	0	0	20	0	0	0	15	0	0

by the combination of cisplatin and ifosfamide. There were no treatment-related deaths.

DLT during three courses developed in two patients at the cisplatin dose level of 60 mg/m^2, in one patient at 70 mg/m^2 and in two patients at 80 mg/m^2. Three patients experienced both grade 4 neutropenia lasting more than 5 days and grade 4 thrombocytopenia, one patient only grade 4 thrombocytopenia, and one patient acute nephritis.

Treatment Delivery

Of the 46 patients, 40 received three or more courses of chemotherapy. Chemotherapy was discontinued in four patients after two courses due to disease progression. One of these patients experienced grade 4 thrombocytopenia during the first course. One patient did not receive further treatment after the first course because of acute nephritis considered to be drug-related, and another patient experienced ileus due to intestinal metastases on day 2 of the first course.

At the 60 mg/m^2 and the 70 mg/m^2 dose levels, three patients and two patients, respectively, required cessation of irinotecan treatment on days 8 and/or 15. The corresponding number of patients at the 80 mg/m^2 dose level was five patients as irinotecan treatment on day 15 was omitted due to hematological toxicity, particularly leukopenia and renal toxicity. Since at the 80 mg/m^2 dose level more than one-third of patients were treated with dose modification, a dose of 80 mg/m^2 was defined as the MTD. The mean number of chemotherapy courses until recurrence was 4.1 in 46 patients.

Response and survival

Of the 46 patients, 45 were assessable for response. No marked difference emerged in response rates between the three dose levels of cisplatin. No patient showed a complete response, but 28 patients achieved a partial response, and 17 no change. The overall response rate was 62.2% (95% CI 48.0–76.4%). The response rates for stage IIIB and IV were 86.7% (13 of 15 patients) and 50.0% (15 of 30 patients), respectively. The median time to remission was 47 days and the median response duration was 144 days. All patients were assessed for survival, on the basis of intent to treat. The median survival time was 393 days with 1- and 2-year survival rates of 54.3% and 19.5%, respectively (Fig. 1). Median survival times according to stage were 417 days in stage IIIB and 382 days in stage IV.

Discussion

As a single agent, irinotecan results in a significant response rate in previously untreated NSCLC patients, and with the combination of irinotecan and cisplatin, an encouraging response rate of 52% has been found. We performed a phase I/II study with cisplatin and irinotecan combined with ifosfamide to develop a more effective regimen. Since the combination of cisplatin and ifosfamide induced mild hematological toxicity in a previous study of cisplatin combined with ifosfamide and 5-FU (CIF therapy) at respective doses of 20 mg/m^2, 1.5 mg/m^2 and 1.0 g/m^2 for 4 consecutive days [10], combining cisplatin and ifosfamide with irinotecan at the same dose levels as CIF therapy was considered possible. However, it was reported that 46% of patients experienced grade 3 leukopenia in the phase II study of combined cisplatin and irinotecan chemotherapy without rhG-CSF support.

With prophylactic administration of rhG-CSF, from May 1994 to June 95 we conducted a phase I study of irinotecan on days 1, 8 and 15 combined with a fixed schedule of cisplatin and ifosfamide [11]. At the

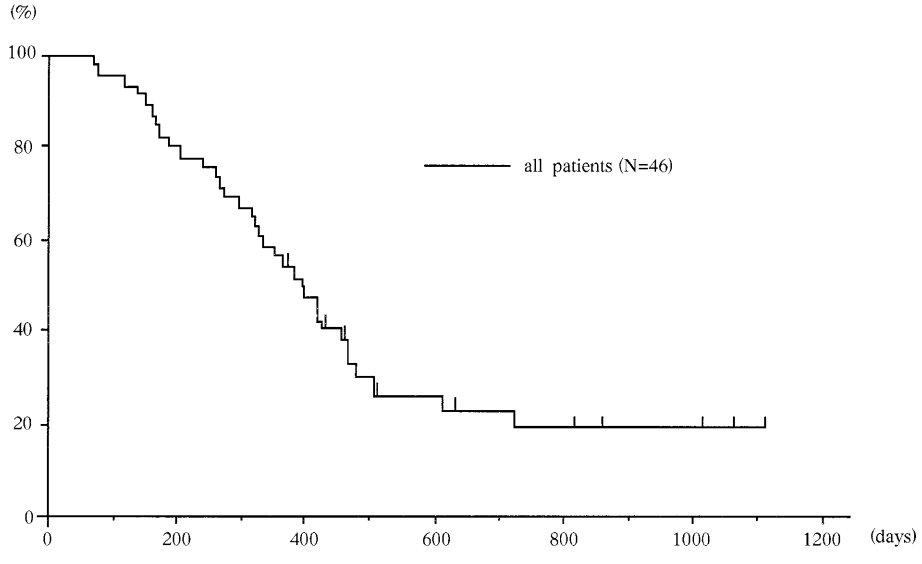

Fig. 1 Survival curve of all patients

70 mg/m^2 dose level, only 8 of 18 patients received irinotecan treatment on day 8 and 15 of the third course without dose modification, and cumulative hematological toxicity was detected and interpatient variability was also great. Thrombocytopenia was considered to be the DLT. The recommended irinotecan dose in this combination was 60 mg/m^2 which was the same as that recommended for the combination with cisplatin without rhG-CSF support in the study reported by Masuda et al. [4]. In chemotherapy-naive patients, a very encouraging response rate of 65.7% and median survival time of 513 days were obtained in this trial. However, cisplatin treatment at doses of 60–80 mg/m^2 on day 1 has been used widely for NSCLC.

A phase I/II study was conducted in previously untreated patients with stage IIIB or IV NSCLC to determine the MTD of cisplatin combined with a fixed schedule of ifosfamide and irinotecan with rhG-CSF support and the overall response rates and survival. Ifosfamide (1.5 g/m^2) and irinotecan (60 mg/m^2) were administered at fixed doses on days 1–4 and on days 1, 8 and 15, respectively. Since the combination of cisplatin on day 1 and ifosfamide induced severe renal toxicity in the previous study of cisplatin on day 1 combined with ifosfamide and vindesine [12], cisplatin was given on day 1 at 60 mg/m^2 and increased in 10 mg/m^2 increments. Escalation of the cisplatin dose was not associated with the severity of myelotoxicity. No grade 3 or worse diarrhea was observed. Patients with diarrhea received Hange-shasinto (a Kampo medicine) with no inhibitory effect on intestinal motility. At each dose level of cisplatin, DLTs occurred in fewer than one-third of the patients during the first three courses. However, in five patients irinotecan treatment on days 8 and/or 15 was omitted secondary to hematological toxicity, particularly leukopenia and renal toxicity at the 80 mg/m^2 dose level. Therefore as we considered the MTD to be 80 mg/m^2, the recommended dose for phase II study was 70 mg/m^2.

The response rate of 62.2% obtained in the current study was comparable to the found in a previous phase I study with four divided cisplatin treatments. Phase II and III trials are required to determine whether this combination of three drugs with rhG-CSF support will improve response rate and survival in previously untreated patients with NSCLC.

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