Anti-Cancer Drugs 2002, **13,** pp. 505–509

Clinical report

Phase I study of carboplatin, irinotecan and docetaxel on a divided schedule with recombinant human granulocyte colony stimulating factor support in patients with stage IIIB or IV non-small cell lung cancer

Akihisa Fujita,[1] Toshihiko Ohkubo,[1] Hideaki Hoshino,[1] Hirotsugu Takabatake,[1] Shigeru Tagaki[1] and Kyuhichiro Sekine[1]

[1]Division of Respiratory Disease, Minami-ichijo Hospital, Sapporo 060-0061, Japan.

A phase I study was conducted to determine dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of carboplatin combined with irinotecan and docetaxel on a divided schedule with recombinant human granulocyte colony stimulating factor (rhG-CSF) support in patients with stage IIIB or IV non-small cell lung cancer. Carboplatin was given at the dose of AUC5 on day 1. Irinotecan and docetaxel on days 1 and 8 were administered at a starting dose of 40 and 30 mg/m^2 as level 1. Subsequent levels were: irinotecan/docetaxel (in mg/m^2), 50/30 (level 2), 60/30 (level 3) and 60/35 (level 4). rhG-CSF was given at 50 mg/m^2 on days 5–15. Cycles were repeated every 3 weeks. Between May 1999 and April 2001, 31 patients were registered in this phase I study. Level 4 was judged as the MTD. The DLTs were considered diarrhea and febrile neutropenia. The overall response rate was 32.3% and median survival was 490 days with 1-year survival of 65.1%. We conclude that both irinotecan 60 mg/m^2 and docetaxel 30 mg/m^2 on days 1 and 8 in combination with an AUC5 of carboplatin on day 1 with rhG-CSF support is recommended for phase II study. The response rate and survival data in this phase I study are encouraging. We considered that the pathogenesis of diarrhea involved not only direct cytotoxic damage to the mucosa, but also bacterial overgrowth. [© 2002 Lippincott Williams & Wilkins.]

Key words: Diarrhea, docetaxel, irinotecan, non-small cell lung cancer, phase I study.

Introduction

Both docetaxel[1] and irinotecan[2] have demonstrated encouraging activity in non-small cell lung cancer (NSCLC). Trials using carboplatin as a less toxic analog of cisplatin in combination with docetaxel[3] or irinotecan[4] in NSCLC showed promising results. The combination of docetaxel with irinotecan has been shown to have a comparable activity and toxicity to docetaxel with cisplatin.[5] We developed this three-drug regimen reported in this study on the basis of the encouraging activity of two-drug combinations of these three drugs. We performed a pilot study on irinotecan on days 1 and 8 combined with docetaxel and carboplatin; however, irinotecan treatment on day 8 was omitted because of leukopenia despite recombinant human granulocyte colony stimulating factor (rhG-CSF) support. Consequently, we conducted a phase I study escalating the dose of irinotecan on day 1 only combined with a fixed schedule of docetaxel and carboplatin with rhG-CSF support.[6] The maximum tolerated dose (MTD) of irinotecan in combination with 60 mg/m^2 of docetaxel and carboplatin (AUC5) all given on day 1 was found to be 60 mg/m^2. Diarrhea was considered to be the dose-limiting toxicity (DLT). The relationship of diarrhea of this severity to irinotecan was not clear because of the low dose intensity of irinotecan. Recent clinical trials with docetaxel on a weekly schedule have shown mild myelosuppression.[7,8] Using docetaxel on a divided schedule on days 1 and 8, we conducted an additional phase I study of the same dose of carboplatin on day 1 combined with irinotecan on days 1 and 8 with rhG-CSF support.

Patients and methods

Patient eligibility

Patients were enrolled onto the study if they met the following eligibility criteria: histologically or cytologically proven advanced NSCLC (stage IIIB or IV); no

Correspondence to A Fujita, Division of Respiratory Disease, Minami-ichijo Hospital, South-1 West-13, Chuo-ku, Sapporo 060-0061, Japan.
Tel: (+81) 11 271 3711; Fax: (+81) 11 281 0275;
E-mail afujita@sa2.so-net.ne.jp

prior chemotherapy or no therapy for at least 4 weeks before study entry; a life expectancy of at least 3 months; a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale; between 15 and 75 years of age; adequate bone marrow function (hemoglobin 9 g/dl, neutrophil count 2000/mm^3, platelet count 100 000/mm^3); adequate renal function (serum creatinine <1.5 mg/dl); adequate liver function (asparatate aminotransferase and alanine aminotransferase $<2\times$ normal upper limit); written informed consent was obtained from all patients.

Exclusion criteria were as follows: severe concurrent medical conditions; pregnant or nursing mothers; active concomitant malignancy; active uncontrolled infection; intestinal paralysis and obstruction; interstitial pneumonia or pulmonary fibrosis; and/or large amount of ascites and/or pleural effusion.

Pretreatment and follow-up evaluations

Mandatory pretreatment evaluations included a baseline history, physical examination, chest X-ray, chest computed tomography (CT), bronchoscopy, brain magnetic resonance imaging or CT, abdominal CT or ultrasonography, bone scintigraphy, complete blood cell counts (CBC) with differential, routine chemistry profiles, urinalysis, ECG and pulmonary function tests. During the chemotherapy courses, all patients were reviewed daily for symptoms of toxicity and underwent clinical examination. CBC, including differential, was performed at least twice weekly. Chest X-ray, routine chemistry profiles 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[9] were used for efficacy analysis. Toxicity from treatment was graded according to the National Cancer Institute common toxicity criteria (CTC), version 1.0.

Treatment plan

Drug administration. Irinotecan was diluted in 250 ml of 0.9%. saline solution and administered as an i.v. infusion over 90 min followed by an i.v. infusion of docetaxel diluted in 250 ml of 0.9% saline solution over 1 h on days 1 and 8. Carboplatin was dissolved in 100 ml of 0.9% saline solution and infused over 30 min immediately on completion of the docetaxel infusion on day 1. All patients received azacetron 10 mg i.v. on day 1. Intravenous dexamethasone, 16 mg, was given on day 1 and 8 mg on days 2–4. Additionally all patients were given azacetron 10 mg and dexamethasone 16 mg on day 8. rhG-CSF (Filgrastim) was given s.c. at a dose of 50 $\mu g/m^2$ on days 5–15 except on day 8.

Dose escalation. The dose of carboplatin was calculated using the Calvert formula to achieve an estimated AUC of 5.0. Irinotecan and docetaxel were administered at a starting dose of 40 and 30 mg/m^2, respectively (level 1) to the first group of patients. Subsequent levels were defined in advance as follows: level 2, irinotecan 50 mg/m^2 and docetaxel 30 mg/m^2; level 3, irinotecan 60 mg/m^2 and docetaxel 30 mg/m^2; level 4, irinotecan 60 mg/m^2 and docetaxel 35 mg/m^2. Irinotecan and docetaxel were administered on day 8 when all of the following three conditions were met on the day of treatment: neutrophil count was 1000/mm^3, platelet count was 75 000/mm^3 and no grade 3 or worse diarrhea. At all levels, cycles were repeated every 3 weeks if the neutrophil count was 2000/mm^3 or the platelet count was 100 000/mm^3.

DLT was defined as follows: grade 4 neutropenia lasting more than 5 days, febrile neutropenia (fever $>38^\circ C$ with grade 4 neutropenia), grade 4 thrombocytopenia, grade 4 non-hematological toxicity and cessation of chemotherapy on day 8 due to toxicity. At least six patients were enrolled at each dose level. If two of six patients at a given dose level experienced DLT, an additional three patients were entered at that dose. If one more instance of DLT was observed, this dose was considered as the MTD. The MTD of the combination was defined as the dose at which one-third of patients developed DLT during two courses. Dose escalation in individual patients was not permitted. Patients with response could continue to receive treatment until disease progression or the development of unacceptable toxicity.

Results

Patient characteristics

Between May 1999 and April 2001, 31 patients were registered in this phase I study. All patients were assessable for toxicity and response. Patient characteristics are listed in Table 1. One patient did not receive prior chemotherapy. Twenty-nine patients

Table 1. Patient characteristics

Characteristics	No. of patients
Sex	
male	16
female	15
Age	
median	57
range	38–72
Performance status (ECOG)	
0	6
1	20
2	5
Histology	
adenocarcinoma	25
squamous cell carcinoma	4
large cell carcinoma	2
Stage	
IIIB	11
IV	20
Prior therapy	
no	1
chemotherapy only	26
chemotherapy and radiotherapy	4

had been treated with the combination chemotherapy regimen of cisplatin, ifosfamide and irinotecan with rhG-CSF support.[10,11] Six patients had received prior radiotherapy; the site of irradiation was the chest in four patients and the bone in two patients.

MTD and DLT

The number of patients treated by each dose level and the DLT encountered during two courses is shown in Table 2. There was no case of DLT in patients entered at level 1 and 3. One patient at level 2 developed grade 4 diarrhea. At level 4, four of 10 patients experienced DLT. These toxicities were febrile neutropenia in one patient, febrile neutropenia and grade 4 neutropenia lasting more than 5 days in one patient, grade 4 thrombocytopenia in one patient and grade 4 diarrhea in one patient. Thus, dose level 4 was considered as the MTD.

Treatment delivery

A total of 132 cycles of treatment was given to the 31 patients. The median number of cycles was 3. No patient required cessation of irinotecan and docetaxel treatment on day 8. The start of second cycle was delayed by greater than 1 week due to hematologic toxicity in six patients. There were no treatment-related deaths at either level.

Toxicity

Toxicities occurring during two courses at each level are listed in Table 3. Neutropenia was the predominant type of toxicity even with rhG-CSF support. Six patients experienced grade 4 neutropenia. However, the duration of grade 4 neutropenia was relatively short. During the first course the time to nadir of neutropenia was 16 days. Thrombocytepenia was observed less frequently and grade 4 was observed in only one patient. Anemia was prominent: four patients at level 1, three at level 2, three at level 3 and four at level 4 required red blood cell transfusion during two courses.

The most frequent non-hematologic toxicity was diarrhea. Grade 2 or worse diarrhea occurred in 21 of 31 patients during two courses. Diarrhea developed on median day 9 with recovery by median day 16. Most patients experienced severe abdominal pain due to suspected bacterial enterocolitis. There were 11 patients whose stools were positive for pathogenic bacteria. Five patients were infected with *Clostridium perfringens*, five with *Escherichia coli* and one with *Vibrio fluvialis*. Most patients were treated with antibiotics, mainly levofloxacin, and showed improvement. After improvement of diarrhea, stools were negative for pathogenic

Table 2. Dose level

Level	Irinotecan (mg/m^2)	Docetaxel (mg/m^2)	No. of patients	No. of patients with DLT	
1	40	30	6	0	
2	50	30	7	1	grade 4 diarrhea
3	60	30	8	0	
4	60	35	10	4	febrile neutropenia febrile neutropenia and grade 4 neutropenia lasting more than 5 days grade 4 diarrhea

Table 3. Toxicity (number of patients)

	Level/grade (CTC)															
	1				2				3				4			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hematological																
leukopenia	2	2	1	0	1	3	1	1	2	4	2	0	4	0	3	2
neutropenia	2	1	2	0	1	0	4	1	2	3	0	2	2	0	2	3
thrombocytopenia	1	2	0	0	1	1	3	0	3	2	1	0	2	0	1	1
anemia	0	5	1		0	5	2		1	7	0		1	5	4	
Renal/genitourinary																
Cr	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
hematuria	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Hepatic																
AST	2	0	0	0	3	0	0	0	3	0	0	0	2	0	0	0
ALT	1	0	0	0	3	0	0	0	3	0	0	0	2	0	0	0
Gastrointestinal																
nausea	0	0	1		1	1	0		2	2	1		3	4	0	
vomiting	0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
anorexia	0	0	1	0	1	1	0	0	1	1	1	0	2	3	3	0
diarrhea	0	2	2	0	0	1	3	1	0	2	3	0	2	4	2	1
Neurogenic	0	0	0	0	2	1	0	0	1	0	0	0	0	0	0	0
Fatigue	1	3	1	0	0	1	0	0	0	2	1	0	1	3	1	0
Allergy	4	0	0	0	3	0	0	0	3	0	0	0	5	0	0	0

bacteria. In the next cycle, levofloxacin was administered prophylactically to patients with a diagnosis of bacterial enterocolitis. Elevation of serum transaminase was observed in 10 patients, but was transient and mild. Neurotoxicity was observed in four patients, but well tolerable. Fourteen patients experienced transient fatigue.

Response and survival

Thirty-one patients were assessable for response. There were no complete responses. Ten patients (32%) achieved a partial response (PR), 19 (61%) had no change and two (6%) had progressive disease. The overall response rate was 32.3%. The median time to response was 63 days and the median response duration was 139 days. The median time to progression was 146 days. In the one patient who had not received prior chemotherapy, PR was observed. All patients were assessed for survival, using an intention-to-treat analysis. The median survival time was 490 days in all patients with a 1-year survival rate of 65.1%.

Discussion

In the previous phase I study, the MTD of irinotecan in combination with 60 mg/m^2 of docetaxel and AUC of 5 mg/ml · min of carboplatin all given on day 1 was found to be 60 mg/m^2. We also considered when the second administration of irinotecan could be given. However, when the leukocyte nadir occurred around day 8 with recovery by median day 11, the second administration of irinotecan was abandoned. Irinotecan 50 mg/m^2 in combination with 60 mg/m^2 of docetaxel and carboplatin on day 1 with rhG-CSF support is recommended for the phase II study. However, this corresponds to a dose intensity of 16.7 mg/m^2/week for irinotecan, which appears to be low compared to the 45 mg/m^2/week that was used in the phase II study of irinotecan and cisplatin.[12]

Recent clinical trials with docetaxel on a weekly schedule have shown a higher dose intensity and mild myelotoxicity. We performed an additional phase I study of the same dose of carboplatin combined with irinotecan on days 1 and 8, and docetaxel on a divided schedule on days 1 and 8. Both irinotecan 60 mg/m^2 and docetaxel 30 mg/m^2 on days 1 and 8 in combination with an AUC of 5 mg/ml · min of carboplatin on day 1 with rhG-CSF support is recommended for the phase II study. Diarrhea, neutropenia and febrile neutropenia were considered to be the DLTs. Docetaxel could be administered on a divided schedule with markedly reduced myelosuppression while maintaining the same dose intensity and the second administration of irinotecan could be given.

In the previous phase I study on the same three drugs, we reported that diarrhea was a prominent non-hematologic toxicity. Diarrhea is a major toxicity of irinotecan; however, the dose intensity of irinotecan was low. With single-agent docetaxel, significant diarrhea rarely develops. In a phase I study on docetaxel and cisplatin, Millward *et al*. reported that diarrhea was a prominent non-hematologic toxicity and that its pathogenesis involved both bacterial overgrowth and direct cytotoxic damage to the mucosa.[13] In this our trial, 19 patients developed grade 2 or worse diarrhea during the two courses. Most patients experienced severe abdominal pain due to suspected bacterial enterocolitis. Eleven patients whose stools were positive for pathogenic bacteria were mainly treated with antibiotics, levofloxacin, and showed improvement of diarrhea. After improvement of diarrhea, stools were negative for pathogenic bacteria. We considered that the pathogenesis involved not only direct cytotoxic damage to the mucosa, but also bacterial overgrowth.

Except for the one chemotherapy-naive patient who achieved PR, in patients having received prior chemotherapy, the response rate was 30.0%, median survival time 490 days and 1-year survival rate 63.9%. Although determining antitumor activity and survival was not the primary objectives of this study, an encouraging response rate and survival were found in patients with prior chemotherapy.

Conclusion

Both irinotecan 60 mg/m^2 and docetaxel 30 mg/m^2 on days 1 and 8 in combination with AUC of 5 mg/ml · min of carboplatin on day 1 with rhG-CSF support is recommended for the phase II study. In the combination chemotherapy regimen reported here, an encouraging response rate and survival were found, in spite of the fact that most patients had had prior chemotherapy.

References

1. Kunitoh H, Watanabe K, Onoshi T, Furuse K, Niitani H, Taguchi T. Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: a Japanese Cooperative Study. *J Clin Oncol* 1996; **14**: 1649–55.
2. Fukuoka M, Niitani H, Suzuki A, *et al*. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* 1992; **10**: 16–20.
3. Belani CP. Use of docetaxel and carboplatin for patients with non-small-cell lung cancer. *Oncology* 1997; **7**: 31–3.
4. Okamoto H, Nagatomo A, Kunitoh H, Kunikane H, Watanabe K. A phase I clinical and pharmacologic study of a carboplatin and irinotecan regimen combined with recombinant human granulocyte-colony stimulating factor in the treatment of patients with advanced nonsmall cell lung carcinoma. *Cancer* 1998; **82**: 2166–72.
5. Takeda K, Yamamoto N, Negoro S, *et al*. Randomized phase II study of docetaxel (DOC) plus cisplatin (CDDP) versus DOC plus irinotecan in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000; **19**: 497a (abstr 1994).
6. Fujita A, Takabatake H, Tagaki S, Sekine K. Phase I study of carboplatin, docetaxel and irinotecan with recombinant human granulocyte colony stimulating factor support in patients with advanced non-small cell lung cancer. *Anti-Cancer Drugs* 2000; **11**: 821–4.
7. Hainsworth JD, Burris III HA, Thomas M, Greco FA. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. *J Clin Oncol* 1998; **16**: 2164–8.
8. Greco FA. Docetaxel (Taxotere) administered in weekly schedules. *Semin Oncol* 1999; **26**(suppl 11): 28–31.
9. WHO. *Handbook for reporting results of cancer treatment*. Geneva: WHO 1979.
10. Fujita A, Takabatake H, Tagaki S, Sekine K. Phase I study of cisplatin, ifosfamide and irinotecan with rhG-CSF support in advanced non-small cell lung cancer. *Oncology* 1999; **56**: 301–7.
11. Fujita A, Takabatake H, Tagaki S, Sekine S. 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. *Cancer Chemother Pharmacol* 2000; **45**: 279–83.
12. Masuda N, Fukuoka M, Fujita A, *et al*. A phase II trial of combination of CPT-11 and cisplatin for advanced non-small cell lung cancer. *Br J Cancer* 1998; **78**: 251–6.
13. Millward MJ, Zalcberg J, Bishop JF, *et al*. Phase I trial of docetaxel and cisplatin in previously untreated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 1997; **15**: 750–8.

(Received 4 February 2002; accepted 12 March 2002)