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Clinical report

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

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A phase I study was conducted in patients with stage IIIB or IV non-small cell lung cancer to determine the maximum tolerated dose (MTD) of irinotecan combined with a fixed schedule of docetaxel and carboplatin with recombinant human granulocyte colony stimulating factor (rhG-CSF) (nartograstim) support. Docetaxel was given at 60 mg/m^2 on day 1 with carboplatin. The dose of carboplatin was calculated using the Calvert formula to achieve an estimated AUC of 5.0 mg/ml·min. Irinotecan was administered at a starting dose of 40 mg/m^2 on day 1 and increased in increments of 10 mg/m^2. rhG-CSF was given at 1 μg/kg on days 5–15. Cycles were repeated every 3 weeks. Between February 1998 and March 1999, 22 patients were enrolled in this phase I study. Five patients were chemotherapy naive. The MTD of irinotecan was 60 mg/m^2. Diarrhea was considered to be the dose-limiting toxicity. The irinotecan dose intensity of 16.7 mg/m^2/week was low compared with other irinotecan-containing regimens. The overall response rate was 38.1% and median survival was 278 days. Irinotecan 50 mg/m^2 in combination with 60 mg/m^2 docetaxel and 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. [© 2000 Lippincott Williams & Wilkins.]

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

Introduction

Both docetaxel[1] and irinotecan[2] have shown encouraging activity in non-small cell lung cancer (NSCLC). Phase I studies investigated the feasibility using carboplatin in combination with docetaxel[3] or irinotecan[4] in NSCLC showed promising results. On the basis of a phase I study of docetaxel and irinotecan for previously untreated NSCLC, a dose of docetaxel 50 mg/m^2 on day 1 combined with 50 mg/m^2 of irinotecan on days 1, 8 and 15 was recommended for phase II study.[5] We developed the 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 of 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, nartograstim) support. Consequently, we conducted a phase I study escalating the dose of irinotecan on day 1 combined with a fixed schedule of docetaxel and carboplatin with rhG-CSF support. The primary objectives of the phase I study were to define the maximum tolerated dose (MTD) of irinotecan in this three-drug regimen with rhG-CSF and to describe the dose-limiting toxicity (DLT). We also examined the question of when the second dose of irinotecan could be administered bearing in mind toxicity, particularly leukopenia.

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Patients and methods

Patient eligibility

Patients were enrolled in the study if they met the following eligibility criteria: histologically or cytologically confirmed advanced NSCLC (stage IIIB or IV), no 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 $\geqslant$9 g/dl, leukocyte count

$\geqslant 4000/mm^3$, platelet count $\geqslant 100\,000/mm^3$), adequate renal function (serum creatinine <1.5 mg/dl) and adequate liver function (asparatate aminotransferase and alanine aminotransferase <2 times the upper limit of normal). All patients provided written informed consent.

Exclusion criteria were as follows: sever 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 preregistration evaluations included medical history, physical examination, chest X-ray, chest computed tomography (CT), bronchoscopy, head magnetic resonance magnetic imaging or CT, abdominal CT or ultrasonography, bone scintigraphy, hematology, blood biochemistry, urinalysis, ECG and pulmonary function tests. After the initiation of treatment, physical examination, chest X-ray, 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[6] were used for efficacy analysis. Toxicities were graded according to the Common Toxicity Criteria.[7]

Administration of regimen

Docetaxel, carboplatin and irinotecan were administered on day 1 of each cycle. The dose of docetaxel was 60 mg/m^2 and the carboplatin dose was calculated using the Calvert formula to achieve an estimated AUC of 5.0. These were the single-agent phase II doses for docetaxel in the Japanese study[1] and the most usual carboplatin dose in combination chemotherapy regimens in Japan. Irinotecan was administered at a starting dose of 40 mg/m^2 on day 1 to the first group of patients. This dose was the lowest dose at which an objective response occurred in a phase I study by Masuda *et al.* In combination with cisplatin and irinotecan.[8] The dosage was subsequently increased in increments of 10 mg/m^2 to new groups of patients. rhG-CSF was given s.c. at a dose of 1 μg/kg on days 5–15. Nartograstim 1 μg/kg is equivalent to filgrastim 50 μg/m^2. Cycles were repeated every 3 weeks if leukocyte count was $\geqslant 4000/mm^3$ or platelet count was $\geqslant 100\,000/mm^3$. DLT was defined as follows: grade 4 neutropenia lasting more than 5 days, grade 4 thrombocytopenia and grade 4 non-hematological toxicity. At least six patients were enrolled at each of the first two dose levels. The MTD of the combinations was defined as the dose at which one-third of patients experienced DLT during two courses. Dose escalation in individual patients was not permitted. Patients with response or no change could continue to receive treatment until disease progression or the development of unacceptable toxicity.

Results

Patients characteristics

Between February 1998 and March 1999, 22 patients were registered in this phase I study. Patient characteristics are listed in Table 1. Five patients did not receive prior chemotherapy. Seventeen patients had been treated with the combination chemotherapy regimen of cisplatin, ifosfamide and irinotecan with rhG-CSF support.[9] No patients had experience grade 3 or more diarrhea in the prior chemotherapy.

Treatment delivery

The doses of irinotecan administered are shown in Table 2. Chemotherapy was discontinued in one patient at the 50 mg/m^2 dose level of irinotecan after the first course due to disease progression. One previously untreated patient at the 60 mg/m^2 dose

Table 1. Patient characteristics

Characteristics	No. of patients
Sex	
male	18
female	4
Age	
median	59
range	42–74
Performance status (ECOG)	
0	5
1	13
2	4
Histology	
adenocarcinoma	18
squamous cell carcinoma	3
large cell carcinoma	1
Stage	
IIIB	4
IV	18
Prior therapy	
no	5
chemotherapy only	11
chemotherapy and radiotherapy	6

level of irinotecan developed massive hemoptysis on day 14 of cycle 1 and did not receive further treatment. The median number of chemotherapy courses was 2.5.

Toxicity

Toxicities occurring during two courses at each irinotecan dose level are listed in Table 3. Escalation of the irinotecan dose was not associated with severity of myelotoxicity. One patient at the 40 mg/m^2 dose level of irinotecan experienced both grade 4 neutropenia lasting more than 5 days and grade 4 thrombocytopenia. The leukocyte nadir occurred at around day 8 with recovery by median day 11. Diarrhea occurred in 17 of 22 patients. Diarrhea developed on median day 7 recovery by median day 11. Two patients at the 50 mg/m^2 and two at the 60 mg/m^2 dose level of irinotecan developed grade 4 diarrheas. There were no treatment-related deaths

Response and survival

Twenty-one patients were assessable for response. The previously described patient who developed hemoptysis was excluded. There were no complete responses. Eight patients (38%) achieved a partial response (PR), 11 (52%) had no change and two (10%) had progressive disease. The overall response rate was 38.1%. The median time to response was 53 days and the median response duration was 98 days. The median time to progression was 170 days. In the four patients who had not received prior chemotherapy, PRs were observed in three patients and no change in one. There were three PRs in 12 patients who had responded to prior chemotherapy and two PRs in five patients with no change on prior therapy. All patients were assessed for survival, using an intention-to-treat analysis. The median survival was 278 days.

Table 2. Dose level

Level	Irinotecan (mg/m^2)	No. of patients	No. of patients with DLT
1	40	7	1
2	50	11	2
3	60	4	2

Discussion

The MTD of irinotecan in combination with 60 mg/m^2 docetaxel and carboplatin (AUC 5) all given on day 1 was found to be 60 mg/m^2. Diarrhea was considered to be the DLT.

Diarrhea is a major toxicity of irinotecan; however, the dose intensity of irinotecan was low in this trial. No patients had experienced diarrhea of grade 3 or higher in the prior chemotherapy containing irinotecan. 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-hematological toxicity, and that its pathogenesis involved both bacterial overgrowth and

Table 3. Toxicity (no. of patients)

Grade (CTC)	Irinotecan dose (mg/m^2)											
	40				50				60			
	1	2	3	4	1	2	3	4	1	2	3	4
Hematological												
leukopenia	0	1	3	3	1	2	8	0	0	2	1	0
neutropenia	1	0	0	6	1	2	3	4	0	1	0	2
thrombocytopenia	3	0	1	1	1	1	2	0	2	0	0	0
anemia	0	4	1	0	1	5	3	0	1	2	1	0
Renal/genitourinary												
Cr	1	0	0	0	2	0	0	0	0	0	0	0
hematuria	2	0	0	0	3	0	0	0	3	0	0	0
Hepatic												
AST	1	1	0	0	3	0	0	0	1	0	0	0
ALT	2	0	0	0	3	0	0	0	1	0	0	0
Gastrointestinal												
nausea	3	2	0	0	2	3	1	0	1	2	0	0
vomiting	2	0	0	0	2	2	0	0	1	1	0	0
anorexia	1	2	1	0	2	2	2	0	1	2	0	0
diarrhea	1	2	2	0	0	7	0	2	1	0	0	2
Allergy	4	1	0	0	6	1	0	0	0	0	0	0

direct cytotoxicity damage to the mucosa.[10] In this trial, some patients experienced severe abdominal pain due to suspected bacterial enterocolitis. Five of six patients who experienced grade 3 or more diarrhea developed grade 4 neutropenia.

Since two patients of the four patients at the 60 mg/m^2 dose level for irinotecan experienced grade 4 diarrhea, the dose of 50 mg/m^2 was recommended for phase II study. 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.[11]

We also considered when the second administration of irinotecan could be given. The leukocyte nadir occurred around day 8 with recovery by median day 11. Leukopenia was not completely eliminated by rhG-CSF support. Diarrhea developed on median day 7 with recovery by median day 11. We conjectured that almost all patients were unable to receive irinotecan treatment on day 15, but it was not certain whether the next course criteria had been satisfied by day 22. Myelosuppression of this severity precludes the second administration of irinotecan. Recent clinical trials with docetaxel on a weekly schedule have shown mild myelosuppression. An additional phase I study of carboplatin and irinotecan combined with docetaxel using a weekly schedule is required.

In the four chemotherapy-naive patients who could be assessed, PRs were observed in three patients. The response rate was high (29.4%) in patients having received prior chemotherapy. This compares favorably with the 19.4% response rate achieved with docetaxel.[12] Although determining antitumor activity was not the primary objective of this study, an encouraging response rate was found in patients with and without prior chemotherapy.

Conclusion

Irinotecan 50 mg/m^2 in combination with 60 mg/m^2 docetaxel and carboplatin on day 1 with rhG-CSF support is recommended for phase II study. In the combination chemotherapy regimen reported here, an encouraging response rate and survival were found, in spite of the low dose intensity of irinotecan.

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