Phase I Study of Irinotecan and Gemcitabine in Previously Untreated Patients with Advanced Non-small Cell Lung Cancer

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Background: Irinotecan and gemcitabine are effective against non-small cell lung cancer. We conducted a phase I study of the combined use of irinotecan and gemcitabine in previously untreated patients with advanced non-small cell lung cancer to determine dose-limiting toxicities and maximum tolerated dose.

Methods: Patients were treated with irinotecan followed by gemcitabine on days 1 and 8 every 3 weeks. Gemcitabine dose was fixed at 1000 mg/m2, and irinotecan dose was increased from 60 mg/m2.

Results: A total of 16 patients was enrolled. Maximum tolerated dose of irinotecan was determined up to level 3 (irinotecan 100 mg/m2). In Japan, the maximum approved weekly dose of irinotecan is 100 mg/m2, so this was the dose that was used. Only very mild hematological and non-hematological toxicities were noted.

Conclusion: Use of 100 mg/m2 irinotecan followed by 1000 mg/m2 gemcitabine on days 1 and 8 every 3 weeks warrants a phase II study.

Key words: non-small cell lung cancer – chemotherapy – irinotecan – gemcitabine

INTRODUCTION

Non-small cell lung cancer (NSCLC) is a leading cause of cancer death in many countries around the world. Cisplatin has been considered a key drug in the treatment of advanced NSCLC (1). Recently, several new agents with anti-tumor activity for NSCLC have been developed, including gemcitabine, paclitaxel, docetaxel, vinorelbine and irinotecan (2). Combination chemotherapy with cisplatin and these new drugs has led to improved survival compared with older combinations in several randomized phase III trials (3,4). However, physicians have no choice but to avoid cisplatin-containing regimens in some patients, such as those with renal or cardiac diseases, because of nephrotoxicity, the need for pretreatment with massive hydration, peripheral neuropathy and emesis (5). Carboplatin is considered as an alternative to cisplatin, with lower rates of emesis, neurotoxicity and nephrotoxicity. However, a recent meta-analysis suggests that combination chemotherapy of cisplatin with one of the new agents provides significantly longer survival than carboplatin with the same agents (6). Several phase III trials have suggested that non-platinum doublets may be equivalent to platinum doublets in terms of efficacy with comparable toxicities (4). Non-platinum doublets may thus offer an alternative treatment in patients with advanced NSCLC. The main non-platinum doublets that have previously been examined in phase III studies are gemcitabine and vinorelbine, or gemcitabine and a taxane. No phase III studies of non-platinum doublets including irinotecan have been reported.

Irinotecan is a semi-synthetic water-soluble camptothecin analog (7). The active metabolite SN-38 inhibits topoisomerase I activity by stabilizing the topoisomerase I-DNA cleavable complex (8). In chemotherapy-naïve patients with advanced NSCLC, irinotecan as a single agent has a response rate of approximately 30% (9). Conversely,
gemcitabine is an analog of the pyrimidine antimetabolite cytarabine, which exerts anti-tumor effects by targeting the S-phase of the cell cycle (10). Gemcitabine as a single agent has a response rate of 20–30% in previously untreated patients with advanced NSCLC (11).

A preclinical study found a dose-dependent synergistic interaction between gemcitabine and irinotecan in cancer cell lines (12). Irinotecan and gemcitabine have different mechanisms of action and their toxicity profiles do not overlap. Several investigators have reported that the combination of irinotecan and gemcitabine displays modest activity as a second-line treatment for patients with advanced NSCLC (13,14). However, the efficacy of this combination in chemotherapy-naïve patients needs evaluation. We therefore conducted a phase I study of combination chemotherapy with irinotecan and gemcitabine in previously untreated patients with advanced NSCLC. The aims of this study were to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of the combination and the recommended dose for a subsequent phase II study.

METHODS

ELIGIBILITY

Written informed consent was obtained from all patients prior to treatment. The protocol and informed consent procedures were reviewed and approved by the Institutional Review Board of each participating institute. Eligibility criteria were as follows: histologically or cytologically confirmed NSCLC; stage IIIB or IV disease; no prior chemotherapy; no prior thoracic radiotherapy within the previous 6 months; no prior non-cancer surgery; no prior immunological therapy; no major obstruction. Women who were pregnant or breast-feeding were also excluded.

TREATMENT AND DOSE ESCALATION

Treatment was started within 1 week of enrollment. Both irinotecan and gemcitabine were administered on days 1 and 8 by 90- and 30-min intravenous infusion, respectively. If a patient displayed a leukocyte count <3000/μl or platelet count <100 000/μl, or experienced watery diarrhea on day 8, the treatment scheduled for day 8 was postponed until day 15. This treatment protocol was repeated every 3 weeks until the patient refused treatment or showed progressive disease. Subsequent treatments were given only when leukocyte and platelet counts had reached >3000/μl and >100 000/μl respectively.

Irinotecan diluted in 250 ml of 5% dextrose was infused first, followed by the administration of gemcitabine dissolved in 100 ml of physiological saline. Starting doses of irinotecan and gemcitabine were 60 mg/m2 and 1000 mg/m2 respectively. Dose level of gemcitabine was fixed and dose of irinotecan was increased as shown in Table 1.

Toxicities were assessed according to the US National Cancer Institute Common Toxicity Criteria version 2.0 (15). In the present study, dose-limiting toxicity (DLT) was defined as follows: grade 4 hematological toxicity lasting ≥4 days; grade 4 febrile neutropenia; grade 3 or worse non-hematological toxicities, except for nausea, vomiting, anorexia, constipation, fever, and alopecia; irinotecan and gemcitabine scheduled to be given on day 8 not given until day 15; and failure to start the second cycle until day 29. To assess the irinotecan dose increase, at least three patients were enrolled at each dose level and dose was increased to the next level if none of the patients displayed any DLT. If two of three patients showed DLT, then this dose level was defined as the maximum tolerated dose (MTD). If one of three patients had DLT, an additional three patients were treated at the same level; if none of these additional patients showed DLT, the dose was increased to the next level. When ≥1 of the three additional patients had DLT, this dose level was defined as the MTD. The recommended dose for phase II study was the drug dose that was given just prior to the MTD. If MTD had not been reached by level 3, level 3 became the recommended dose for this study.

When grade 3 or worse leukocytopenia or neutropenia occurred, recombinant human granulocyte colony stimulating factor could be given. Prior to treatment, all patients received prophylactic anti-emetic therapy with a type-3 serotonin receptor antagonist and dexamethasone.

ASSESSMENT OF TREATMENT

Tumor staging was based on the medical history and physical examination, chest radiography, bone scintigraphy, computed tomography of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bronchoscopy. Prior to the first course of therapy, complete blood cell counts, electrolytes, urinalysis and biochemistry tests for the assessment of renal and hepatic function were performed. During the study, complete blood cell counts and biochemistry tests were repeated at least once weekly, whereas other investigations were repeated as needed to evaluate marker lesions. After completion of chemotherapy, all tests performed during the initial work-up were repeated to restage each patient.
Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (16). In brief, complete response (CR) was defined as the disappearance of all known disease. Partial response (PR) was defined as a 30% reduction from baseline in the sum of the longest diameters of the target lesions and a lack of disease progression in non-target lesions. Progressive disease (PD) was defined as the development of any new lesions or an increase of 20% in the sum of the longest diameters of the target lesions. Patients with stable disease (SD) did not meet the criteria for PR or PD.

Survival curves were estimated using the Kaplan–Meier method and results were expressed with 95% confidence interval (CI). Analysis was conducted using StatView version 5.0 software (SAS Institute, Cary, NC).

RESULTS

DETERMINATION OF MTD

A total of 16 patients were enrolled in this trial from January 2003 to November 2003, and all of them received chemotherapy. Patient characteristics included: median age, 66 years; male/female ratio, 12/4; six patients, stage IIIB disease; 10 patients, stage IV disease (Table 2). The study used three dose levels and a total of 37 cycles of treatment. One cycle was administered to five patients (31.3%), two cycles to five patients (31.3%), three cycles to two patients (12.5%), and four cycles to four patients (25.0%) (Table 2).

No patient displayed hematological DLT. One of three patients at level 1 had DLT (grade 3 AST and ALT elevation). The three additional patients at level 1 had no DLT. None of the three patients at level 2 had any DLT. At level 3, none of the three patients had DLT. Dose escalation was discontinued at level 3, as the maximum approved weekly dose of irinotecan is 100 mg/m² in Japan. To evaluate toxicities and safety at the recommended dose level more accurately, the protocol was modified to enroll more patients at the level 3 dose until DLT was recorded. While none of the additional three patients at level 3 enrolled displayed DLT, the next patient enrolled experienced grade 3 fatigue and refused to start the second cycle of chemotherapy on day 29. We thus determined level 3 as the recommended dose for this regimen.

TOXICITIES

All 16 patients were fully assessable for toxicity. Hematological toxicity during the first cycle is shown in Table 3. Neutropenia was the principal hematological toxicity, but none of the hematological toxicities were severe. Grade 3 neutropenia occurred in seven of 16 patients (43.8%), and leukocytopenia occurred in one of 16 patients (6.3%). No patients experienced grade 4 neutropenia or leukocytopenia. Thrombocytopenia and anemia were rarely observed, and no patients required blood transfusion. Furthermore, in a total of 37 cycles, no grade 4 hematological toxicities were recorded.

Non-hematological toxicities during the first cycle are listed in Table 3. One patient at the level 1 dose experienced...
grade 3 AST and ALT elevations, but AST and ALT levels normalized within 7 days without medication. One patient at the level 1 dose experienced grade 3 neutropenia, but conventional anti-emetic treatment led to recovery within 24 h. Other non-hematological toxicities, including diarrhea, were mild.

Compliance with treatment was good and no cumulative toxicity occurred with subsequent courses (Table 1). A total 37 courses of treatment was given in this study, and relative dose intensities of each drug were 95.8–100%. Delay of day 8 dosing was observed in eight of 37 courses, owing to grade 2–3 leukocytopenia in six courses and grade 1–2 diarrhea in two courses.

**Clinical Response and Survival**

Responses for all 16 patients were able to be assessed (Table 1). Three patients had PR, with a response rate of 18.8% (95% CI, 4.1–45.7%), while nine patients had SD and four had PD. Disease control rate including SD was 75.0% (95% CI, 47.6–92.7%). No clear dose–response relationship was identified.

Of the 16 patients, 13 received second-line systemic chemotherapy after recurrence, comprising platinum-containing regimens in eight patients, non-platinum regimens in four patients, and gefitinib in one patient. Response for platinum regimens was SD in five patients and PD in three patients. Response for non-platinum regimens and gefitinib was PR in two patients and PD in three patients.

Survival data were updated in December 2006. While 15 of the 16 patients died, one remains alive as of the time of writing. Median progression-free survival was 80 days (95% CI, 31–129 days), and 1-year progression-free survival rate was 12.5% (95% CI, 0.0–28.7%). Median overall survival was 15.6 months (95% CI, 13.2–18.5 months) and 1-year overall survival rate was 68.8% (95% CI, 46.1–91.5%). No significant difference in survival was identified among patients receiving subsequent platinum regimens, non-platinum regimens or no systemic therapy (data not shown).

**DISCUSSION**

The current study demonstrated that the recommended dose of irinotecan and gemcitabine on days 1 and 8 in a 3-week cycle is 100 and 1000 mg/m², respectively. At these doses, hematological and non-hematological toxicities were very mild. Although the current study was a phase I study, the median overall survival of 15.6 months and 1-year survival rate of 68.8% is noteworthy.

The combination of irinotecan and gemcitabine has been investigated as a second-line treatment in patients with advanced NSCLC (13, 15, 17). Various drug administration schedules have been used, including both drugs given on days 1 and 15 (14, 15), and gemcitabine given on days 1 and 8 and irinotecan given on day 8 (13). With all these regimens, all toxicities, including diarrhea, have been mild and well tolerated. These studies have recommended the following doses for these two drugs: irinotecan 150–180 mg/m² with gemcitabine 1000–1800 mg/m² on days 1 and 15 (14, 17); irinotecan 300 mg/m² on day 8 and gemcitabine 1000 mg/m² on days 1 and 8 (13). Treatment with irinotecan or gemcitabine in combination with cisplatin is conducted in Japan as follows: 60 mg/m² irinotecan on days 1, 8 and 15 every 4 weeks, or 1000 mg/m² gemcitabine on days 1 and 8 every 3 weeks in combination with 80 mg/m² cisplatin on day 1 (18). Considering dose intensity, we adopted a 3-week regimen in this trial and irinotecan on day 15 was omitted.

Gemcitabine is an S-phase-specific antimetabolite, and anti-tumor activity may vary with the cell-cycle status of cancer cells. A recent phase I study showed that irinotecan treatment followed 24 h later by gemcitabine treatment increased the percentage of tumor cells in the S-phase (19). In addition, grade IV neutropenia was observed in 10 of 18 patients treated with this regimen (19), although toxicity was mild when gemcitabine was administered immediately after irinotecan. Duration of administration of irinotecan and gemcitabine given in combination may increase the toxicities seen with this combination.

In conclusion, given our results, combined use of 100 mg/m² irinotecan followed by 1000 mg/m² gemcitabine on days 1 and 8 in a 3-week cycle warrants additional phase II study. A phase II trial of this combination regimen in previously untreated patients with advanced NSCLC is thus ongoing.

**REFERENCES**


