Short Communication

A Phase I Study of Gemcitabine Plus Irinotecan for Advanced NSCLC: Japan Clinical Oncology Group Trial (JCOG9904)

Takayasu Kurata1,*, Nobuyuki Yamamoto1, Takefumi Komiya1, Junji Tsurutani1, Masaki Miyazaki1, Kenji Tamura1, Koji Takeda2, Kazuhiko Nakagawa1 and Masahiro Fukuoka1

1Department of Medical Oncology, Kinki University School of Medicine, Osaka and 2Department of Clinical Oncology, Osaka City General Hospital, Osaka, Osaka-Sayama, Japan

*For reprints and all correspondence: Takayasu Kurata, Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka, 589-8511, Japan. E-mail: t-kurata@med.kindai.ac.jp

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A combination Phase I study of gemcitabine and irinotecan in patients with previously untreated advanced non-small-cell lung cancer was conducted. Patients received gemcitabine and irinotecan on Days 1 and 8 every 3 weeks. A total of 11 patients were enrolled. Three of six patients who received the starting dose (gemcitabine, 800 mg/m²; irinotecan, 80 mg/m²) experienced dose-limiting toxicities (Grade 4 neutropenia, Grade 3 elevation of transaminase and Grade 5 interstitial pneumonia). At the reduced dose level (gemcitabine, 800 mg/m²; irinotecan, 60 mg/m²), all two assessable patients could not meet the administration criteria of Day 8 (one, Grade 2 elevation of transaminase; the other, Grade 1 diarrhea). No objective response was observed in eight evaluable patients. We could not determine the recommended dose of this combination because of intolerable toxicities and no efficacy. Therefore, it is difficult to forward this combination chemotherapy toward further studies.

Key words: combination Phase I study – maximum tolerated dose – gemcitabine – irinotecan – NSCLC

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for about 80–85% of primary lung cancer and chemotherapy plays an important role for treatment of advanced NSCLC. The first-line standard chemotherapy is the platinum-doublet combination therapy including one of the third generation agents including paclitaxel, docetaxel, gemcitabine (GEM), vinorelbine and irinotecan hydrochloride (CPT-11). Nevertheless, the cisplatin-based chemotherapy is realized as an unfavorable therapeutic procedure in the clinical practice, because a large amount of intravenous infusion is needed due to renal toxicities and most patients hate digestive tract toxicities such as nausea, vomiting. Therefore, an attention was paid to a non-platinum regimen composed of two agents of the third generation agents. From these backgrounds, we were interested in the combination chemotherapy with GEM and CPT-11 and planned to conduct Phase I study of this combination regimen. The purpose of this study was to establish the toxicity and the maximum tolerable dose (MTD) of this combination, to determine the recommended dose (RD) for further studies, and to assess the antitumor activity.

PATIENTS AND METHODS

Patients with histologic or cytologic confirmation of NSCLC who had received no previous chemotherapy were eligible. Prior radiation other than evaluable lesions was allowed if such treatment had been completed at least 2 weeks before study enrollment. The other eligibility criteria were as follows: (i) Stage IV or Stage IIIIB; (ii) measurable lesions; (iii) aged, ≤20, ≤75; (iv) Eastern Cooperative Oncology Group performance status (PS) 0–2; (v) adequate organ function [4000/μl ≤ white blood cell count (WBC) ≤ 12 000/μl,
platelet count ≥ 100,000/μl, hemoglobin count ≥ 9.5 g/dl, serum transaminase ≤ 2.5 × normal upper limit, serum creatinine ≤ normal upper limit, partial arterial pressure oxygen ≥ 60 torr, normal electrocardiogram.

The main exclusion criteria were as follows: (i) active concurrent malignancies; (ii) severe comorbidities such as uncontrolled angina pectoris, myocardial infarction developed within 6 months, ileus, uncontrollable diabetes, pulmonary fibrosis or heart failure; (iii) massive pleural effusion, pericardial effusion or ascites; (iv) Grade 1 or more diarrhea. This study was approved by the Institutional Review Board at each institute. Written informed consent was obtained from all patients.

GEM and CPT-11 were given intravenously on Days 1 and 8 every 3 weeks. The dose on Day 8 was given if WBC was ≥2000/μl, platelet count ≥ 50,000/μl and no fever elevation with infection, no diarrhea and less than Grade 2 of liver dysfunction were noted. Administration of both agents was withdrawn if drug-induced interstitial pneumonia was shown apparently by chest X-ray. The subsequent courses were delayed if any of the laboratory data shown in the eligibility criteria was not met, and if treatment-related diarrhea did not recover.

If dose-limiting toxicities (DLTs) occurred, the patient was withdrawn from the study in principle, but when an anti-tumor effect could be expected, treatment was possible to was withdrawn from the study in principle, but when an anti-tumor effect could be expected, treatment was possible to continue by reducing doses of GEM by 200 mg/m² and tumor effect could be expected, treatment was possible to continue by reducing doses of GEM by 200 mg/m² and CPT-11 by 10 mg/m². Furthermore, if Grade 2 of diarrhea occurred, only dose of CPT-11 was reduced by 20 mg/m². If Grade 2 of other non-hematological toxicities except nausea, vomiting and alopecia occurred, doses of GEM and CPT-11 were reduced by 200 and 10 mg/m², respectively.

GEM and CPT-11 were started with the dose of 800 and 80 mg/m², respectively (Level 1), and subsequent dose levels were as follows (GEM/CPT-11): Level 2, 1000/80 mg/m²; Level 3, 1000/90 mg/m²; Level 4, 1000/100 mg/m². Since, after this study had initiated, DLTs occurred at Level 1, the new reduced dose level (Level 0–1, 800/60 mg/m²) was made. At least three patients were treated at each dose level and three additional patients were entered if DLT was observed. The MTD was defined as the dose level at which all of the first three patients, or three of any six patients, experienced DLTs. The definitions of DLT were as follows: (i) Grade 4 leukopenia or neutropenia for 4 days or more; (ii) Grade 3 or more febrile neutropenia; (iii) platelet count <20,000/μl; (iv) Grade 3 or more non-hematological toxicities (except nausea and vomiting); (v) omission of administration of Day 8.

RESULTS

Between December 1999 and October 2002, 11 patients (Level 1, 7 and Level 0–1, 4) were enrolled from two institutions. Nine patients were male. The median age was 65 years (range 46–74). The majority of cases (10 cases) had PS of 1. Histologically, seven patients had adenocarcinoma and two had squamous cell carcinoma. One of seven patients at Level 1 was excluded from the assessment of dose escalation because of a high WBC at registration (38,800/μl), but was assessable for safety analysis. Two patients at Level 0–1 were not assessable for safety analysis because one could initiate treatment due to rapid disease progression, and the other had developed accidental cerebral infarction before the administration of Day 8. Among evaluable nine patients, the total and median numbers of courses were 16 and 2, respectively. As the reason for discontinued treatment, six patients had progressive disease and two had toxicities that were impossible to control.

Nine and 8 of 11 patients were assessable for safety and dose escalation analysis, respectively. The major toxicities following all courses are listed in Table 1. Grade 3/4 leukopenia, neutropenia, thrombocytopenia and anemia occurred in 19/0, 25/12.5, 6.3/0 and 12.5/0% of the patients, respectively. One treatment-related death was observed as the result of interstitial pneumonia developed after the second course. A 57-year-old man developed febrile neutropenia on Day 12 after the administration of the second course. Furthermore, chest X-ray revealed the interstitial shadow in the lower lobe of the right lung 3 days later. We performed chest computer tomography and bronchoalveolar lavage and suggested drug-induced pneumonia. He died of interstitial pneumonia and complicated infection on Day 29 after the administration of the second course in spite of oxygen inhalation and antibiotic treatment. No other cases had developed interstitial pneumonia.

As three of six assessable patients at Level 1 suffered from DLTs, which consisted of Grade 4 neutropenia, Grade 3 elevation of transaminase and Grade 5 interstitial pneumonia developed after the second course, Level 1 was considered to be intolerable. At the reduced dose Level 0–1,

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<th>Grade</th>
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<th>4</th>
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both of two assessable patients had experienced DLTs. Both cases could not meet the administration criteria of Day 8 (one, Grade 2 elevation of transaminase; the other, Grade 1 diarrhea). According to the protocol criteria, each of two dose levels was intolerable, therefore, we were not able to determine MTD and RD for further Phase II study.

No objective response was observed in eight evaluable patients for response.

**DISCUSSION**

At the starting dose level (GEM: 800 mg/m², CPT-11: 80 mg/m²), three cases with DLTs including one case of death due to pulmonary toxicity were encountered. Furthermore, DLT was noted in both of two cases at the reduced dose level (GEM: 800 mg/m², CPT-11: 60 mg/m²) and RD could not be estimated within the dose range tested in the present study.

A Phase I study of increasing doses of CPT-11 with a fixed dose of 1000 mg/m² of GEM on Days 1 and 8 was reported. MTD was not reached, as toxicities were generally mild and further dose escalation was halted because of the maximum weekly available dose of CPT-11 in Japan. Thus, RDs were 1000 mg/m² for GEM and 100 mg/m² for CPT-11 (1). Moreover, two Phase I studies were conducted using biweekly schedule (2,3). Both studies also reported that this combination was well tolerated and RDs were 1000 mg/m² for GEM, 150 mg/m² for CPT-11 (2), 1500 mg/m² for GEM and 180 mg/m² for CPT-11 (3).

Consequently, it is not clear why this combination could not be tolerated and RD could not be determined in our study unlike others. The difference in the results between other studies and ours might be related to the difference in patient’s background, treatment schedule or definition of DLT. The definition that omission of administration of Day 8 was considered to be DLT might be one of the possibilities.

In conclusion, we could not determine MTD and RD of this combination chemotherapy in the present study, because of intolerable toxicities and no efficacy. This combination chemotherapy is not feasible for advanced NSCLC.

**Conflict of interest statement**

None declared.

**References**

