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ORIGINAL ARTICLE

A triplet chemotherapy with cisplatin, docetaxel and gemcitabine in patients with advanced non-small-cell lung cancer: a phase I/II study

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Abstract
Purpose We conducted a phase I/II study of triplet chemotherapy consisting of cisplatin (CDDP), docetaxel (DCT) and gemcitabine (GEM) in patients with advanced non-small-cell lung cancer (NSCLC).
Methods Fifty-three untreated patients with stage IIIB or IV NSCLC were enrolled. All drugs were given on days 1 and 8. The doses of CDDP and DCT were fixed at 40 mg/m^2 and 30 mg/m^2, respectively. In the phase I portion, a dose escalation study of GEM with starting dose of 400 mg/m^2 was conducted and primary objective in the phase II portion was response rate.
Results The maximally tolerated dose (MTD) and recommended dose (RD) of GEM were determined as 800 mg/m^2 because grade 3 non-hematological toxicity (liver damage, diarrhea, and fatigue) developed in three of nine patients evaluated at that dose level. In pharmacokinetic analysis, C_{max} and AUC of dFdC and dFdU were increased along with the dose escalation of GEM. However, no relationship between pharmacokinetic parameters and toxicity or response was observed. Objective response rate was 34% and median survival time was 11.7 months. Though major toxicity was myelosuppression, there were no life-threatening toxicities.

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Conclusion These results indicate that this triplet chemotherapy is feasible and effective in patients with advanced NSCLC.

Keywords Phase I/II study · Cisplatin · Docetaxel · Gemcitabine · Non-small-cell lung cancer

Introduction

A recent meta-analysis of randomized clinical studies demonstrated that cisplatin (CDDP)-based chemotherapy plus best supportive care (BSC) had statistically significant survival advantage compared with BSC alone in patients with advanced non-small-cell lung cancer (NSCLC) [14]. Since then, CDDP has been a key drug in the treatment of advanced NSCLC. Afterwards, in an attempt to improve the treatment outcome of advanced NSCLC, the usefulness of various new antineoplastic agents such as paclitaxel, docetaxel (DCT), vinorelbine (VNR), gemcitabine (GEM) and irinotecan were investigated [3]. A few randomized trials that compared the effectiveness of these new agents with existing drugs such as vindesine or etoposide in a CDDP-based doublet chemotherapy showed the superiority of new agents to the existing drugs [2, 13]. These results were recently confirmed by a meta-analysis [20]. Accordingly, a doublet consisting of platinum and one of the new agents is currently considered to be a standard regimen for advanced NSCLC. However, since survival benefit by this treatment is very limited and unsatisfactory, further improvement of chemotherapy is urgently desired. One strategy to improve the treatment outcome is to add a third active drug with a different mechanism of action to the platinum-based doublet.

GEM, a fluorine-substituted cytarabine analog, inhibits cellular DNA synthesis by reducing cellular deoxycytidine triphosphate levels. GEM has been shown to have high activity for NSCLC, and its combination with CDDP is currently considered to be one of the standard regimens in the treatment of advanced NSCLC [3, 4, 6, 16, 17].

DCT exerts its cytotoxicity through binding to beta-tublin, promoting the polymerization and inhibiting the dissembly of microtubles, which causes cell arrest in mitosis, leading to cell death. The effectiveness of DCT in patients with advanced NSCLC, both as a single agent and in combination with CDDP, has already been confirmed [3, 7, 11, 17].

On the basis of these results, we planned a phase I/II study of combination chemotherapy consisting of CDDP, DCT and GEM to investigate the safety and effectiveness of this triplet chemotherapy in patients with advanced NSCLC.

Materials and methods

Patient selection

Eligibility requirements for entry into the study were as follows: (1) histologically or cytologically proven NSCLC, (2) no prior chemotherapy, radiotherapy or surgery, (3) age of 75 years or less, (4) clinical stage of IIIB with malignant pleural effusion or IV, (5) performance status (PS) of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale [15], (6) presence of measurable disease, (7) adequate functional reserves of the kidney (creatinine clearance $\geq$60 ml/min), liver (ALT, AST <twice the upper limit of normal), and bone marrow (a leukocyte count $\geq$4,000/cmm and a platelet count $\geq$100,000/cmm), (8) no concomitant malignancies, and (9) receipt of a written form of informed consent.

Nine institutions participated in this study, and each of their Institutional Review Boards approved this study. The central registration office (Department of Internal Medicine II, Okayama University Medical School) enrolled the patients into this study after verification of eligibility.

Evaluation

Staging procedures included complete history and physical examination, a complete blood cell count (CBC), standard blood chemistry profile, 24-h creatinine clearance (Ccr), electrocardiogram, a chest radiograph, fiberoptic bronchoscopy, computed tomographic (CT) scans of the chest and abdomen, magnetic resonance imaging of the brain, and radionuclide bone scan.

For evaluation of response and toxicity, the CBC was repeated two or three times a week. Blood chemistry, Ccr, and chest radiography were repeated at least once a week during treatment. CT scans of the chest were repeated once per treatment cycle. After completion of the chemotherapy, each patient was restaged on the basis of all the tests used during the initial work-up and followed up at the outpatient clinic with a monthly chest radiograph. CT scans of the chest were repeated every 3 months.

Response was assessed according to the ECOG criteria [15]. The response to treatment including eligibility and assessability was determined for each patient by extramural reviewers. Complete response (CR) was defined as the disappearance of all measurable lesions lasting for at least 4 weeks. Partial response (PR) was defined as a $\geq$50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions lasting for at least 4 weeks without the

development of new lesions. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of the perpendicular diameters of all measurable disease or the appearance of new lesions. Between <50% decrease and <25% increase in the sum of the products of the perpendicular diameters of all measurable lesions were defined as no change (NC). Toxicity was evaluated by the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0). Dose-limiting toxicity (DLT) was defined as grade 4 hematological toxicity lasting for 3 days or more, grade 3 hematological toxicity accompanied with fever (>38°C), or grade 3 non-hematological toxicity except for nausea, vomiting and alopecia.

Phase I study

The primary objective of a phase I study was to determine the DLT, maximally tolerated dose (MTD) and recommended dose (RD) of GEM for a phase II study in combination with fixed doses of DCT and CDDP.

All the drugs were given on days 1 and 8. GEM was given first by 30-min intravenous infusion with 100 ml of physiologic saline, followed by administration of DCT and CDDP. The starting dose of GEM was 400 mg/m^2 and the dose was increased by 200 mg/m^2 for dose escalation. Both DCT and CDDP were given by 1-h intravenous infusion with 500 ml of physiologic saline. The doses of DCT and CDDP were fixed at 30 mg/m^2 and 40 mg/m^2, respectively. Ondansetron (4 mg) or granisetron (3 mg) was administered intravenously just before CDDP administration. The treatment was repeated every 4 weeks up to four cycles if possible. If grade 4 hematological toxicity or grade 3 non-hematological toxicity was observed in one course, the dose of GEM was reduced by 200 mg/m^2 in the next cycle. The dose of CDDP was reduced by 30 mg/m^2 if grade 3 renal toxicity developed. Before the next course was started, leukocyte and platelet counts had to be at least 3,500/cmm or more and 100,000/cmm or more, respectively.

Initially, three patients were enrolled at each dose level. If all patients developed the DLT, the dose level was determined to be the MTD. If 1 or 2 of the patients developed DLT, at least six patients in total were subjected to the same dose level. When DLT developed in half or more of the patients, the dose was also determined to be the MTD. No intrapatient dose-escalation was performed.

Pharmacokinetics

Blood samples (4 ml) were obtained from the cubital vein opposite to the injection site at eight time points as follows: before and 15 min after the start of GEM infusion, at the end of infusion, and 15, 30, 60, 90, and 120 min postinfusion. The blood was placed into heparinized tubes containing 5 micromole of cytidine deaminase inhibitor, tetrahydrouridine. The samples were centrifuged immediately, and the plasma was stored at −20°C until analysis. Plasma levels of 2′,2′-difluorodeoxycytidine (dFdC: GEM) and 2′,2′-difluorodeoxyuridine (dFdU) were determined by high-performance liquid chromatography (HPLC). Pharmacokinetic parameters on each day were compared using the unpaired two-tailed Student's *t* test.

Phase II study

The primary objective of the phase II study was to determine the response rate and the secondary objectives were survival and toxicity.

Response rate and survival were determined on an intent-to-treat basis. The time to progression and overall survival time were calculated from the date of initiation of chemotherapy until the first documentation of disease progression and death, respectively, using the Kaplan–Meier method. Statistical analyses were performed using SPSS Base System™ and Advanced Statistics™ Program (SPSS Inc., Chicago, IL, USA). The sample size for the phase II study was calculated as 42 patients based on the assumption that response rate was 40% with a 95% confidence interval of 15%.

Results

Patient characteristics

Between October 1999 and July 2001, 53 patients were allocated to this study. The median age was 67 years ranging from 41 to 74. There were 41 men and 12 women. PS was 0 in 24 patients and 1 in 29. Forty patients had adenocarcinoma and 11 squamous cell carcinoma, 1 adenosquamous cell carcinoma and 1 large cell carcinoma. Nine patients had stage IIIB disease and 44 stage IV disease.

Phase I study

Determination of MTD

Up to the dose level 2 (600 mg/m^2 of GEM), no patient developed DLT. One patient allocated to dose level 3 (800 mg/m^2 of GEM) developed grade 3 liver damage. Then three additional patients were treated at dose level 3, and two of these developed DLT (grade 3 diarrhea

and fatigue). Accordingly, this dose level was considered to be the MTD because three of six patients developed DLT. Finally, to determine the RD for a phase II study, an additional three patients received the treatment at the same dose level, but no patients developed DLT. Then the RD was determined to be dose level 3.

Toxicity

All patients were assessable for toxicity. Hematological toxicity was generally mild. No grade 4 hematological toxicity was experienced in the phase I study. Grade 3 leukopenia and neutropenia were observed in two of three patients (67%) and all three patients (100%) at dose level 1, and in one each of the three patients (33%) at dose level 2, respectively. At dose level 3, of the nine patients enrolled, three each (33%) developed grade 3 leukopenia and neutropenia, respectively, and two patients (22%) developed grade 3 thrombocytopenia. Non-hematological toxicity was also mild and reversible. The most frequent grade 3 toxicity was nausea which was observed in 3 of 15 patients (20%) but controlled with conventional antiemetics. The dose-limiting toxicities were grade 3 diarrhea, liver damage, and fatigue, which were manageable and reversible.

Pharmacokinetics

A total of eight patients were evaluated for plasma pharmacokinetics of dFdC and dFdU. The pharmacokinetic parameters of dFdC and dFdU are summarized in Table 1. Time courses of dFdC and dFdU concentrations in plasma according to the dose of GEM are shown in Fig. 1. The plasma concentration of dFdC reached peak concentration at the end of infusion. The mean beta-half lives of dFdC and dFdU were 11.5 and 132.3 min, respectively. The C_{max} and AUC of dFdC and dFdU increased with dose escalation of GEM administration. However, no clear correlation between toxicity or response and C_{max} or AUC was observed.

Phase II study

A total of 47 patients including nine patients treated at the RD level in the phase I portion were analyzed together.

Completion of therapy

Median number of chemotherapy was two cycles ranging from 1 to 4. Eleven (23%) patients completed four cycles of the planned chemotherapy, 12 (26%) received

Table 1 Pharmacokinetic data

Dose level	No. of patients	C_{max} (ng/ml)	T1/2 (min)	AUC (mg/l/h)	CLp (l/h)
dFdC					
400	3	6,498 ± 603	9.5 ± 2.2	3.3901 ± 0.2077	181.91 ± 20.12
600	2	7,761 ± 2,893	12.9 ± 1.4	3.7475 ± 1.2572	263.22 ± 97.74
800	3	9,272 ± 3,598	12.6 ± 11.0	4.2743 ± 0.8769	315.70 ± 79.10
dFdU					
400	3	12,297 ± 892	144.1 ± 35.5	46.693 ± 5.219	13.207 ± 0.773
600	2	17,400 ± 1,937	117.5 ± 15.6	53.921 ± 15.222	17.963 ± 5.727
800	3	24,700 ± 3,740	130.4 ± 53.6	78.979 ± 21.541	17.727 ± 6.711

Average ± SD

dFdC 2′,2′-difluorodeoxycytidine, *dFdU* 2′,2′-difluorodeoxyuridine, C_{max} maximum plasma concentration, *AUC* area under curve, *CLp* plasma clearance

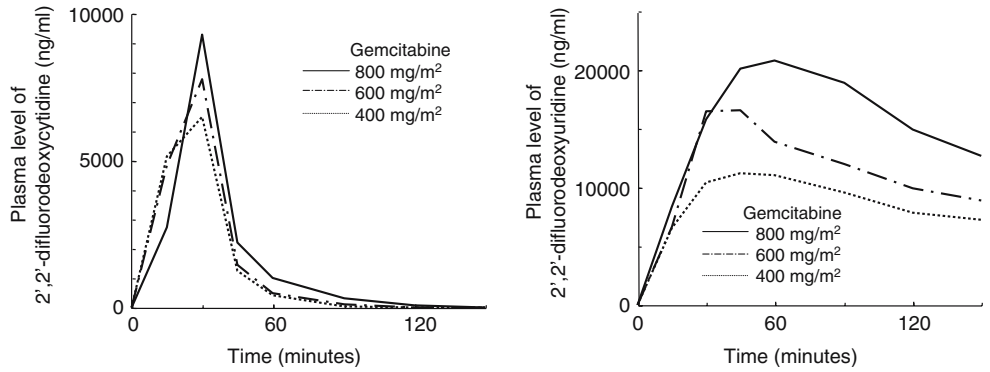

Fig. 1 Pharmacokinetic study

three cycles, 14 (30%) two cycles and 10 (21%) only one cycle. As the cause of discontinuance of the treatment before four cycles, doctor's discretion (39%) was most frequent and followed by disease progression (28%), toxicity (22%), and patient refusal (11%). Ratios of actual to projected doses of CDDP, DCT and GEM at the first cycle were 93, 99 and 93%, respectively. Dose intensities of these drugs were gradually decreased, however, they were sufficiently maintained even at the fourth cycle.

Response and survival

Responses were PR in 16 patients (34%), NC in 22 (47%), and PD in 9 (19%), for an overall response rate of 34% (95% CI, 21–49%). At a median follow-up time of 46.0 months (range, 19.3–55.0 months), 42 (89%) patients had died and 5 (11%) were still alive. Median time to progression was 4.8 months, and progression-free survival rates at 1-year and 2-year were 12 and 3%, respectively. Median survival time was 11.7 months and survival rates at 1-year, 2-year and 3-year were 49, 23 and 12%, respectively.

Toxicity

Toxicities observed in 47 patients are listed in Table 2. The major toxicity was myelosuppression. Grade ≥3 leukopenia and neutropenia occurred in 19 (40%) and 29 (62%) patients, respectively. Recombinant human granulocyte colony stimulating factor (rhG-CSF) was administered in 13 of 47 complete cycles at the first cycle with a median duration of 6 days (range, 2–15 days). Similarly, rhG-CSF was administered in 8 of 37 complete cycles at the second cycle, 9 of 23 complete cycles at the third cycle and 1 of 11 complete cycles at the fourth cycle. Grade ≥3 thrombocytopenia and anemia occurred in 22 (47%) and 12 (26%) patients, respectively. Three (6%) patients received RBC transfusion and 5 (11%) platelet transfusion. Non-hematological toxicities were generally mild. As grade ≥3 toxicities, nausea, infection, hepatic dysfunction, diarrhea and febrile neutropenia were observed in 11 (23%), 9 (19%), 3 (6%), 2 (4%) and 1 (2%) patients, respectively. However, all the toxicities were reversible and there were no treatment related deaths.

Table 2 Toxicities

No. of patients ($n = 47$)	NCI-CTC grade				Percentage of grade 3 + 4
	1	2	3	4	
Leukopenia	5	16	16	3	40
Neutropenia	5	5	19	10	62
Anemia	12	18	9	3	26
Thrombocytopenia	9	11	21	1	47
Nausea	16	17	11	0	23
Vomiting	12	9	0	0	0
Diarrhea	5	7	2	0	4
Hepatic dysfunction	8	3	3	0	6
Infection	3	0	9	0	19
Febrile neutropenia	0	0	1	0	2

NCI-CTC National cancer institute-Common toxicity criteria

Initial relapse site

Most frequent site of initial relapse was primary lesion or mediastinal lymph node (40%), followed by intrapulmonary metastasis (23%), pleural effusion (17%), brain metastasis (13%), bone metastasis (11%), liver metastasis (9%) and adrenal metastasis (4%).

Discussion

This phase I/II study demonstrated that a triplet chemotherapy consisting of CDDP, DCT and GEM could be given at sufficient doses with acceptable toxicity in patients with advanced NSCLC. In the phase I portion, escalated doses of GEM were added to the fixed doses of CDDP and DCT. Hematological toxicities were generally mild and no grade 4 toxicity was experienced. Although non-hematological toxicities such as liver damage, diarrhea and fatigue occurred as dose-limiting toxicities, they were reversible and manageable by conventional treatment, and no life-threatening toxicity was experienced. Pharmacokinetic analysis revealed that both C_{max} and AUC of dFdC and dFdU increased as the dose of GEM increased. However, no definite correlation between pharmacokinetic parameters and response, survival or toxicity was observed. The RD of GEM was determined to be 800 mg/m^2 in combination with CDDP 40 mg/m^2 and DCT 30 mg/m^2, and a phase II study was performed.

Several randomized trials investigating the effectiveness of triplet chemotherapy for advanced NSCLC have been already reported. Comella et al. [5] showed a substantial survival advantage of a triplet chemotherapy consisting of CDDP, GEM and VNR compared with a doublet chemotherapy of CDDP plus VNR in a randomized study. On the other hand, Souquet [19] et al reported that a triplet chemotherapy consisting of CDDP, VNR and ifosfamide had no survival benefit over a doublet chemotherapy of CDDP plus VNR. Similarly, Alverola et al. [1] reported that a triplet chemotherapy consisting of CDDP, GEM and VNR

showed no significant survival improvement compared with a doublet chemotherapy of CDDP plus GEM, although both hematological and non-hematological toxicities were significantly severer in a triplet chemotherapy. Furthermore, Laack et al. [12] showed that the CDDP-based triplet chemotherapy (CDDP + VNR + GEM) had no survival benefit in advanced NSCLC when compared with the CDDP-free doublet (GEM + VNR). Thus, a definite advantage of a triplet chemotherapy in comparison with a doublet chemotherapy has not been confirmed to date. In the phase II portion of the present study, although the objective response rate, 34%, was slightly lower than the expected response rate, the MST 11.7 months, was better than the previous reports of the platinum-based doublet chemotherapy [7, 11, 17]. This suggested that this triplet chemotherapy might be effective for advanced NSCLC.

As a possible explanation of the favorable results in the present study, the following was considered. First, planned dose-intensity in this study was considered to be sufficient. Planned dose-intensities of CDDP, DCT and GEM in this phase II study were 20 mg/m^2/week, 15 mg/m^2/week and 400 mg/m^2/week, respectively. In the previous CDDP-based doublets, dose intensities of CDDP, DCT and GEM were 20–33 mg/m^2/week, 15–25 mg/m^2/week, and 750–833 mg/m^2/week, respectively. In this triplet, planned dose intensities of two drugs, CDDP (20 mg/m^2/week) and DCT (15 mg/m^2/week), were equivalent to those of the previously reported doublets of CDDP plus DCT, and additionally GEM at a dose of 400 mg/m^2 which was almost half of standard dose was given. Therefore, we considered that sufficient dose-intensity was planned and actually administered in this regimen.

Second, a majority of patients received at least two cycles of chemotherapy and marked dose attenuation was not necessary due to low toxicity of this regimen. In this regimen, almost 80% of patients achieved a clinical response of PR or NC, although hematological toxicities were extremely mild. Grade 4 neutropenia was frequently observed in the previous doublet chemotherapy of CDDP plus DCT. On the other hand, grade 4 thrombocytopenia was often experienced in addition to moderately frequent grade 4 neutropenia in the doublet chemotherapy of CDDP plus GEM. Therefore, it is of note that a considerable reduction of GEM was necessary in the previous studies of CDDP-based doublets, and GEM doses were less than 80% in the studies by Crino [6] and Sandler [16]. Because incidences of both neutropenia and thrombocytopenia were considerably low in this triplet chemotherapy compared with the results of the previous doublet chemotherapy, relatively high delivered dose intensity could be maintained. These results probably resulted in the good survival rates seen in this study.

Third, it was reported that salvage therapy such as docetaxel [8, 18] and gefitinib [9, 10] might improve survival. In this study, second-line or salvage treatment after completion of this regimen was not defined. Eighteen patients were treated with salvage chemotherapy, however, no objective response was obtained. On the other hand, 4 (31%) of 13 patients receiving gefitinib as salvage therapy achieved partial response. In those 13 patients, MST and 2-year survival rate were 27.8 months and 54%, respectively, which might have partly affected the results of this study.

In conclusion, these results indicate that a triplet chemotherapy consisting of CDDP, DCT and GEM is feasible and may be effective in patients with advanced NSCLC.

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