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ORIGINAL ARTICLE

Phase I study of the combination of nedaplatin and gemcitabine in previously untreated advanced squamous cell lung cancer

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Abstract
Purpose The objectives of this phase I trial were to evaluate the toxicity of the nedaplatin/gemcitabine regimen, determine the maximum tolerated doses (MTDs) of these agents, and observe the anti-tumor effects of this regimen on advanced squamous cell lung cancer.
Methods Patients with previously untreated advanced squamous cell lung cancer were eligible if they had a performance status of 0 or 1 with adequate organ function. The doses of gemcitabine (days 1 and 8) and nedaplatin (day 8) studied were 800/70, 1,000/80, 1,000/90, and 1,000/100 (mg/m^2), repeated every 3 weeks.
Results Toxicity and response could be assessed in all 13 patients enrolled. The patients included 12 men and one woman with a median age of 69 years (range 57–81 years). Three patients had stage IIIB disease and 10 patients had stage IV disease. The MTDs were reached at 1,000 mg/m^2 gemcitabine and 80 mg/m^2 nedaplatin. The most frequent toxic effects were thrombocytopenia and neutropenia; grade 3 or 4 thrombocytopenia was observed in 23% of patients, and grade 3 or 4 neutropenia was seen in 46% of patients. Non-hematologic toxicities were mild. Grade 3 fatigue, nausea/vomiting, and appetite loss occurred in two patients. The overall response rate was 62%.
Conclusions We recommend doses of 800 mg/m^2 gemcitabine and 70 mg/m^2 nedaplatin for phase II study. This combination chemotherapeutic regimen is active and well tolerated.

Keywords Squamous cell lung cancer · Nedaplatin · Gemcitabine · Phase I

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Introduction

Lung cancer is a major cause of cancer-related mortality worldwide and is expected to remain a major health problem for the near future. Chemotherapy is the cornerstone for the management of this disease. However, its therapeutic impact on patient survival has been modest. Understanding of the signal-transduction pathways that facilitate neoplastic transformation and progression has led to the development of molecular-targeted anticancer agents. Recent discoveries have provided greater understanding of the molecular basis of lung cancer, yielding the successful treatment of non-small-cell lung cancer (NSCLC) with platinum-based chemotherapy combined with a monoclonal antibody (bavacizumab) to vascular endothelial growth factor (VEGF) [1]. The inhibition of kinase activation with small molecule drugs has proved to be an effective approach in the treatment of malignant tumors [2, 3]; epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors are approved for the therapy of NSCLC.

Squamous cell carcinoma arises from the epithelial tissues of many different organs. Although localized disease can be treated using surgical resection or curative

radiotherapy, advanced squamous cell carcinoma continues to have a poor prognosis, and a standard treatment has not yet been established. Approximately 25% of non-small cancers have squamous cell pathology; however, there has not yet been a breakthrough in this therapeutic field compared with advanced adenocarcinoma of the lung.

(Glycolate-O,O′)-diamine platinum (II) (nedaplatin) is a second-generation platinum derivative synthesized by Shionogi & Co., Ltd. (Osaka, Japan) that has shown equivalent antitumor activity and lower toxicity—less nausea and lower nephrotoxicity and neurotoxicity—than cisplatin [4, 5]. A phase I study demonstrated that nedaplatin had therapeutic effects in nasopharyngeal carcinoma, adenocarcinoma of the cervix, and lung and gastric cancers [6]. A phase I study of nedaplatin monotherapy demonstrated that the maximum tolerated dose (MTD) and recommended dose (RD) for phase II studies of nedaplatin were 120 and 100 mg/m^2, respectively, and the dose-limiting toxicity (DLT) was thrombocytopenia [5]. Two phase II studies of nedaplatin for NSCLC have been conducted in Japan [7, 8]. Objective response rates in these studies were 14.7 and 20.5%.

Gemcitabine, a nucleoside analog related to cytarabine, is one of the most effective cytotoxic agents for NSCLC. It is a novel pyrimidine metabolite that is anabolized sequentially to the nucleoside monophosphate, diphosphate, and triphosphate forms intracellularly. The triphosphate, difluorodeoxycytidine triphosphate, is incorporated into DNA and results in chain termination. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that catalyzes the formation of the deoxynucleosides required for DNA synthesis [9]. As a single agent, gemcitabine had a response rate of 18–19% and a median survival of 6.6–8.6 months in advanced NSCLC [10]. The main toxicity of gemcitabine is mild-to-moderate myelosuppression [11–13]. Response rates in the combination trials with monthly cisplatin range from 28 to 54%, with a median survival of 7.6–15.4 months [14]. Moreover, in a study that used an area under the concentration–time curve (AUC) of 5 mg carboplatin/ml/min and 1,000 mg/m^2 gemcitabine, responses were seen in 50% of patients, and the median survival was 16 months [15].

Sasaki et al. [16] reported that nedaplatin shows equivalent antitumor activity to cisplatin against lung cancer cell lines in vitro. In mice bearing NSCLCs of either H460 or Ma44 cell lines, combination therapy of gemcitabine and nedaplatin inhibited tumor growth to a significantly greater degree than did monotherapy with either gemcitabine or nedaplatin alone [17]. In another recent preclinical model, the combination of nedaplatin and gemcitabine suggested a synergy between the two drugs [18, 19]. Furthermore, this combination was superior to gemcitabine plus either cisplatin or carboplatin in the H460 tumor model [17]. Osawa et al. [20] also reported that treatments involving both nedaplatin and 5-fluorouracil might yield a higher complete response rate and better survival for each stage of esophageal squamous cell carcinoma. Therefore, the combination regimen involving nedaplatin and gemcitabine may be effective, especially against squamous cell lung cancer.

To our knowledge, no phase I trials of the combination therapy of nedaplatin and gemcitabine in patients with advanced squamous cell lung cancer have been published. Therefore, we conducted a phase I study of this treatment combination in patients with advanced squamous cell lung cancer during which nedaplatin was administered on day 8 to diminish hematologic toxicity [21, 22]. The objectives of this phase I trial were (1) to evaluate the toxicity of the regimen and to determine the maximum tolerated doses (MTDs) of nedaplatin and gemcitabine, and (2) to observe the antitumor effects of this regimen on squamous cell lung cancer.

Patients and methods

Patient selection

Patients with histologically or cytologically proven stage IIIB or IV squamous cell lung cancer who had not previously received chemotherapy or radiotherapy were eligible for this study. Other eligibility criteria were as follows: (1) age greater than 20 years; (2) a lesion of measurable size; (3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (4) adequate bone marrow function (neutrophil count of $\geq$2,000/ml, platelet count of $\geq$100,000/ml, and hemoglobin level of $\geq$9.5 g/dl), adequate renal function (serum creatinine levels $<$1.5 mg/dl and creatinine clearance rate of $\geq$60 ml/min), adequate hepatic function (total serum bilirubin level $<$ the upper limit of the normal range, and AST and ALT levels $\leq$2.5 times the upper limits of the normal ranges), and arterial oxygen pressure of 70 mmHg or greater; and (5) life expectancy of 3 months or greater. Patients were excluded if they had active infections, severe heart disease, interstitial pneumonia or lung fibrosis, peripheral neuropathy pleural effusion or pericardial effusion that required drainage, symptomatic brain metastasis, or an active second malignancy. Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine.

Treatment schedule

The levels and respective doses (mg/m^2) of gemcitabine and nedaplatin are shown in Table 1. Gemcitabine was diluted

Table 1 Dose-escalation scheme and DLT in the first cycle of chemotherapy

Level	Gemcitabine (mg/m^2)	Nedaplatin (mg/m^2)	Patients (*n*)	Courses (*n*)	Patients with DLT (*n*)
0	800	70	8	28	0
1	1,000	80	5	11	3

DLT dose-limiting toxicity

with 100 ml normal saline and administered as an intravenous drip infusion over 30 min on days 1 and 8. Nedaplatin was diluted with more than 500 ml normal saline immediately before injection and was given as an intravenous drip infusion over 60 min on day 8. Full doses of gemcitabine and nedaplatin were given if the neutrophil count was greater than 1,000/ml, the platelet count was more than 75,000/ml, there was no fever of 38°C for 4 days after treatment, and non-hematologic toxicity was grade 2 or less on day 8 of treatment. If the neutrophil count was less than 1,500/ml, the platelet count was less than 100,000/ml, serum creatinine was more than 1.2 mg/dl, there was a fever of 38°C during the 4 days following treatment, or non-hematologic toxicity was grade 3 or more on day 22, the second round of chemotherapy was withheld until the count(s) and physical condition of the patient improved. Doses of gemcitabine were reduced by 200 mg/m^2 for a week treatment delay after administration of nedaplatin on day 8. Doses of nedaplatin were reduced by 10 mg/m^2 for grade 4 bone marrow suppression and grade 3 or higher non-hematologic toxicity, except for alopecia. Prophylactic antiemetics (i.e., ondansetron and dexamethasone) were routinely administered to all patients prior to nedaplatin treatment. If the white blood cell or neutrophil count decreased to more than grade 3 after chemotherapy, granulocyte stimulating factor (G-CSF) was administered until the count recovered. This chemotherapy regimen was repeated every 3 weeks and was given for more than two cycles. If either the treatment outcome was progressive disease or intolerable toxicity developed at any time, chemotherapy was discontinued. If the outcome was no change after two cycles of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient's treatment. We treated two additional patients at the recommend dose to obtain further information about that dose level.

DLT and MTD

The DLT was defined as grade 4 neutropenia lasting for 5 days, grade 4 thrombocytopenia and grade 3 or greater non-hematological toxicity other than nausea and vomiting, and grade 2 or greater pneumonia. Doses were escalated according to the frequency of DLT evaluated during the first cycle of chemotherapy. Three patients were initially enrolled at each dose level. If none of the patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level, bringing the total to six patients for that dose level. If no more than one patient experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. If two or all of the initial three patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Toxicity and response evaluation and statistical consideration

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed at least once per week throughout the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria, version 3.0, issued in 2004. The Standard Response Evaluation Criteria in Solid Tumors was used for response evaluation. The overall survival time was estimated using the Kaplan–Meier method. Survival time was measured from the date of study registration until the date of death from any cause.

Results

Patient characteristics

Ten patients were enrolled between May 2006 and November 2009. All patients were Japanese. The median age was 69 years (range 57–81). Twelve (92.3%) patients were males and one (7.7%) patient was female. One (7.7%) patient was a non-smoker and 12 (92.3%) patients were former or current smokers. All pathologic diagnoses of the 13 patients were squamous cell carcinoma; the stages of disease are listed in Table 2.

Determination of MTD

The number of patients in whom DLT occurred at each level is shown in Table 2. DLT occurred in three of five

Table 2 Patient characteristics

Total no. of patients	13
Gender (male/female)	12/1
Median age (years)	69 (57–81)
Performance status (0/1)	4/9
Stage (IIIB/IV)	3/10
Smoking status (never/former or current)	1/12

patients at 1,000 mg/m^2 gemcitabine and 80 mg/m^2 nedaplatin. These DLTs were grade 4 thrombocytopenia in one patient, grade 3 thrombocytopenia continuing for more than 2 weeks in one patient, and grade 3 general fatigue continuing for more than 2 weeks in one patient. No DLTs occurred at 800 mg/m^2 gemcitabine or 70 mg/m^2 nedaplatin; therefore, a gemcitabine dose of 800 mg/m^2 and a nedaplatin dose of 70 mg/m^2 were recommended for the phase II study.

Toxicity

Thirty-nine courses were given. The median number of courses given per patient was three (range 1–4). The most frequent hematologic toxicities developing during all courses were thrombocytopenia and neutropenia (Table 3). Grade 3–4 thrombocytopenia and grade 3 neutropenia occurred in 23 and 46% of patients, respectively. Platelet transfusion and G-CSF were not required in any course.

Appetite loss was the most frequent non-hematologic toxicity and developed in 69% of patients. However, most of these non-hematologic toxicities were only mild to moderate in severity with no grade 4 episodes. All non-hematologic toxicities were resolved rapidly after treatment (Table 3).

Dose intensity

Of the 13 patients treated, one patient underwent a toxicity-based dose reduction of gemcitabine, and one patient underwent a dose reduction of nedaplatin after two cycles of chemotherapy at a gemcitabine dose of 1,000 mg/m^2 and a nedaplatin dose of 80 mg/m^2. The reason for the dose reduction of gemcitabine was grade 3 neutropenia, and the reason for the dose reduction of nedaplatin was grade 3 general fatigue. The delay of the next cycle occurred during two courses. The main reason for the delay was thrombocytopenia.

Responses to treatment and survival

All 13 patients were assessed for treatment response. Of the 13 patients, eight partial responses (PRs) and two stable diseases (SDs) were noted, and the overall response rate was 62% (Table 4). At present, seven patients are alive, and no patients have been lost to follow-up. The median survival time was 314 days (Fig. 1).

Discussion

In this phase I study, we showed that the combination of nedaplatin and gemcitabine was feasible with acceptable toxicity, the RD of gemcitabine was 800 mg/m^2 over 30 min on days 1 and 8, and the RD of nedaplatin was 70 mg/m^2 over 60 min on day 8. These doses are less than those previously determined by earlier phase I trials of nedaplatin in combination with gemcitabine [23, 24]. However, Shirai et al. [25] reported in a phase II study of nedaplatin and gemcitabine that at a gemcitabine dose of

Table 3 Toxicity in all courses

	Level 0 ($n = 8$)				Level 1 ($n = 5$)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	1	3	1	0	2	0	1	0
Neutropenia	0	2	2	1	1	0	3	0
Anemia	1	2	0	0	1	1	1	0
Thrombocytopenia	3	2	1	0	0	1	1	1
AST	1	1	0	0	0	0	0	0
ALT	0	1	0	0	1	0	0	0
Elevation of creatinine	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0
Nausea/vomiting	2	2	1	0	4	0	0	0
Appetite loss	3	1	1	0	4	0	0	0
Diarrhea	0	0	0	0	0	0	0	0
Fatigue	1	0	1	0	2	0	1	0

Table 4 Response at each dose level

Level	Evaluable patients (*n*)	CR (%)	PR (%)	SD (%)
0	8	0	6 (80)	2 (20)
1	5	0	2 (40)	0

CR complete response, *PR* partial response, *SD* stable disease

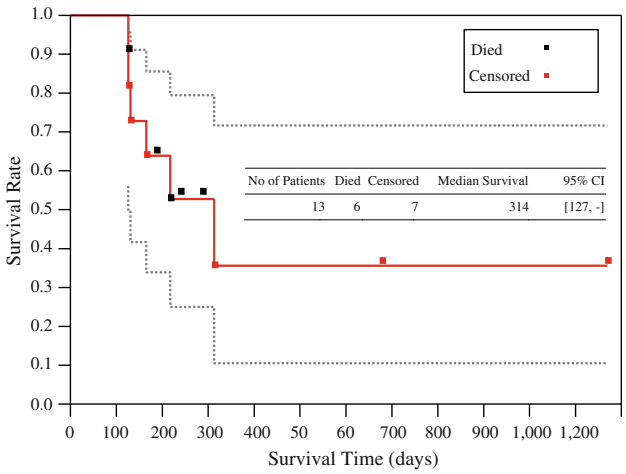

Fig. 1 Kaplan–Meier analysis of all patients ($n = 10$). Median survival time: 314 days

1,000 mg/m^2 and a nedaplatin dose of 100 mg/m^2, 63.7% patients (21 of 33 patients) had grade 3–4 neutropenia, 57.6% (19 of 33 patients) had grade 3–4 thrombocytopenia, and 45.5% (15 of 33 patients) had grade 3–4 anemia. In terms of hematologic toxicity, these results appear to be slightly unfavorable from the standpoint of dose intensity and for elderly patients with a good performance status (PS). Our recommended doses seem to be proper, especially for a poor PS population that constitutes a large population with advanced squamous cell lung cancer. Moreover, side effects were minimal and primarily limited to mild myelosuppression, which is a common side effect of most chemotherapeutic agents, resulting in dose reduction but not requiring the withdrawal of the chemotherapeutic agent used.

To our knowledge, two phase I studies [23, 24] and one phase II study [25] of gemcitabine and nedaplatin were previously described. Subjects of those studies were NSCLC patients; there are no other reports on the efficacies and safety profiles of gemcitabine and nedaplatin for squamous cell lung cancer. Research on cisplatin analogs is scant and has not progressed beyond phase II clinical trials, which means that there is currently little information to suggest safe dosages and evidence of side effects. In terms of hematologic toxicity, Shirai et al. reported 64% of grade 3–4 neutropenia and 56% of grade 3–4 thrombocytopenia in their phase II study, which appears to be a relatively high frequency of hematologic side effects. Although to our knowledge there are no reports concerning the pharmacokinetics of these two drugs, some pharmacokinetic studies of nedaplatin indicated a degree of bone marrow suppression was well correlated with both total and free-platinum AUCs [26, 27]. In terms of the schedule of platinum administration, several reports indicated that a modification of the administration schedule reduced the incidence of grade 3–4 neutropenia and thrombocytopenia [21, 22]. Ricci et al. [22] indicated that the schedule of cisplatin administration when combined with weekly gemcitabine therapy had significant effects on the incidence of grade 3–4 thrombocytopenia and anemia; the best schedule was cisplatin administered on day 15. Masters et al. [21] showed that the best schedule was carboplatin administered on day 8. Our regimen involved nedaplatin administered on day 8. The doses of gemcitabine (days 1 and 8) and nedaplatin (day 8) used were 800/70, 1,000/80, 1,000/90, and 1,000/100 (mg/m^2), repeated every 3 weeks; however, we could not conduct dose escalation because of the DLT at level 1, although we expected that the modification of the administration schedule of nedaplatin would lead to an increase in the tolerance for these two drugs. This result was consistent with a previous report [24]. A phase II study of our recommended dose may be necessary to validate the effectiveness of diminishing the grade 3–4 hematologic toxicity.

New drugs, such as EGFR tyrosine kinase inhibitors (e.g., erlotinib and gefitinib), the monoclonal antibody to VEGF (bavacizumab), and a potent inhibitor of thymidylate synthase (pemetrexed), cannot be used for advanced *squamous* cell lung cancer because of the lethal side effects of hemorrhage due to bavacizumab (relatively rare) or the marginal clinical responses of EGFR tyrosine kinase inhibitors or pemetrexed compared with *non-squamous* cell lung cancer. In an era of individualized therapy for advanced lung cancer, it may be necessary to investigate the treatment process specifically for advanced squamous cell lung cancer.

In conclusion, the combination of nedaplatin and gemcitabine is well tolerated and effective for advanced NSCLC. The MTDs and RDs are 800 mg/m^2 gemcitabine and 70 mg/m^2 nedaplatin, respectively. This regimen yielded encouraging response rates with minimal toxicity. We believe our results warrant a phase II study of this combination, so we are now conducting a phase II study with this RD.

Conflict of interest statement The authors indicate no potential conflicts of interest.

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