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Phase II study of nedaplatin and paclitaxel for patients with previously untreated advanced squamous cell lung cancer

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MICROABSTRACT

New treatment agents have not shown sufficient efficacy against advanced squamous cell lung cancer. In the present phase II study, the primary endpoint was the objective response rate, and the combination of nedaplatin and paclitaxel appeared safe and effective for untreated advanced squamous cell lung cancer. The objective response rate was 72.2%, and the disease control rate was 100%.

Introduction

Non-small cell lung cancer (NSCLC) is a major cause of cancer-related death [1,2]. Platinum-based chemotherapy regimens have been the most extensively studied as standard first-line therapy of advanced NSCLC. Meta-analyses of clinical studies and randomized clinical studies have shown the benefits of platinum-based chemotherapy for survival of patients with advanced NSCLC, but their prognosis remains poor [3–5].

Squamous cell lung cancer accounts for 20–30% of lung cancer cases [6,7]. Recently, chemotherapy regimens for advanced non-small cell lung cancer have been selected by histology. A randomized, phase III study showed the significant survival benefit of a cisplatin and gemcitabine regimen compared with that of a cisplatin and pemetrexed regimen in patients with advanced squamous cell lung cancer [8]. However, new treatment agents including bevacizumab, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), and anaplastic lymphoma kinase (ALK) inhibitors have not shown sufficient survival benefits in patients with advanced squamous cell lung cancer [9–12].

Nedaplatin is a second-generation platinum compound that is active against NSCLC, especially squamous cell lung cancer. A phase I study of nedaplatin demonstrated that the overall response rate was 92.3% in squamous cell lung cancer [13]. In addition, a phase II study of the combination of nedaplatin and weekly paclitaxel demonstrated that the overall response rate was 52.3%, and the median survival time was 13 months in advanced non-small cell lung cancer. However, only 4 of 47 patients had squamous cell carcinoma in this phase II study. Therefore, insufficient data on the combination of nedaplatin and weekly paclitaxel for advancer squamous cell lung cancer patients are available [14].

Thus, a phase II study of nedaplatin and paclitaxel for patients with previously untreated advanced squamous cell lung cancer was conducted. The main objectives of the study were to investigate the efficacy and safety of this regimen for previously untreated advanced squamous cell lung cancer. The primary endpoint of this study was the response rate, and the secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicities.

Patients and methods

Patient eligibility

Patients with histologically or cytologically documented squamous cell lung cancer were candidates for this study. Other eligibility criteria included: stage IIIB (without indications for radiation therapy) or IV; age ≥ 20 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1; no prior chemo- or radiotherapy within 4 weeks of study entry; adequate hematopoietic function (leukocyte count ≥ 3000/μL, neutrophil count ≥ 1500/μL, hemoglobin count ≥ 9.0 g/dL, platelet count ≥ 1×10^5/μL), hepatic function (total serum bilirubin level ≤ 1.5 mg/dl, and AST and ALT levels ≤ the upper limit of normal

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value × 2.5), and renal function (serum creatinine levels ≤ 1.2 mg/dl); and no co-existing severe medical problems. Specific exclusion criteria included a massive pleural or pericardial effusion, interstitial pneumonia, uncontrolled brain metastasis, and unresolved bowel obstruction.

Study design and treatment

This single-arm, phase II clinical trial was registered with the UMIN Clinical Trials Registry (number UMIN 000008872). Eligible patients were treated with nedaplatin (80 mg/m^2, day 1) and paclitaxel (90 mg/m^2, days 1 and 8), repeated every 3 weeks. The criteria to start the next cycle included the following: leukocyte count > 3000/μL, neutrophil count > 1500/μL, platelet count > 100,000/μL, AST and ALT levels ≤ the upper limit of the normal value × 2.5, total bilirubin < 1.5 mg/dl, serum creatinine < 1.2 mg/dl, and non-hematologic toxicities ≤ grade 1. Eligible patients received a minimum of two cycles, and the maximal number of chemotherapy cycles was 6.

Paclitaxel administration on day 8 was suspended for leukocyte count < 2000/μL, neutrophil count < 1000/μL, platelet count < 75,000/μL, AST and ALT levels > the upper limit of the normal value × 2.5, total bilirubin > 1.5 mg/dl, serum creatinine > 1.2 mg/dl, and non-hematologic toxicities ≥ grade 3.

This study protocol was approved by the ethics committee of Tochigi Cancer Center and Ibaraki Prefectural Central Hospital and Regional Cancer Center. This study was conducted in accordance with the Declaration of Helsinki. All patients provided their written, informed consent according to the protocol.

Assessments

Before commencement of therapy, a complete medical history, physical examination, and resting 12-lead electrocardiogram were performed. Tumor staging was determined by physical examination, routine chest radiography, computed tomography (CT) of the chest and abdomen, bone scintiscanning or positron emission tomography (PET), and magnetic resonance imaging of the head. Staging was performed according to the tumor, node, metastasis (TNM) system. A complete blood count including differential leukocyte count, urinalysis, and biochemical analyses were performed two or three times per month. The following evaluations were performed weekly: history, physical examination, and adverse event (AE) assessment according to the Common Terminology Criteria for Adverse Events (CTCAE), v4.0. Tumors were evaluated radiologically after each course of therapy.

Efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RESIST) v.1.1. A complete response (CR) was defined as resolution of all measurable and assessable disease for at least 4 weeks. A partial response (PR) required at least 30% reduction in the sum of the products of the maximum perpendicular diameters of measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as an at least 20% increase in measurable disease or the appearance of new tumor lesions. Stable disease (SD) was defined as disease status failing to meet the above-described criteria. All tumor responses and durations of responses were confirmed by two extramural reviewers.

Statistical analysis

The primary endpoint was the confirmed objective response rate (ORR). The secondary endpoints were PFS, OS, and AEs. Sample size was based on the two-stage accrual design described by Simon. Assuming an overall response rate of 25% for standard therapy, a target response rate of 55% was established, with one-sided alpha = 0.05 and beta = 0.2, and the estimated required number of patients was 15. Therefore, 18 assessable patients were required, including withdrawn or drop-out cases. OS was estimated by the Kaplan-Meier method.

Table 1
Patients' characteristics.

Characteristic	No. of patients
Age (years)	
Median (range)	68 (49–77)
Sex	
Male	17
Female	1
Performance status (ECOG)	
0	3
1	15
Stage	
IIIB	7
IV	11
Pathology	
Squamous cell carcinoma	18

ECOG, Eastern Cooperative Oncology Group.

Results

Patient characteristics

A total of 18 patients were entered into this study between May 2010 and May 2013. Patients were recruited at two investigational sites in Japan. Patient characteristics are listed in Table 1. All 18 patients were eligible and assessable for toxicity and response to chemotherapy. All patients had received no prior chemotherapy. The median age of all patients was 68 years (range, 49–77 years). Seventeen (94%) patients were male, fifteen (83%) patients were PS 1, and eleven (61%) patients were stage IV.

Treatment administration

The total number of treatment cycles was 93. The median number of treatment cycles was six per patient: two and three cycles in one patient each (6%), four cycles in four patients (22%), and six cycles in 12 patients (67%). During a total of 93 cycles, 9 (9.7%) doses of paclitaxel were skipped on day 8.

Antitumor activity

All 18 patients were assessable for response to chemotherapy (Table 2). One patient achieved CR (5.6%), and 12 (66.7%) showed PR. Five (27.8%) patients achieved SD, and none of the patients showed PD. Finally, the overall response rate to chemotherapy was 72.2% [95% confidence interval (CI), 46.5–90.3%], and the disease control rate was 100.0% (95% CI, 81–100%).

Fig. 1 shows the best overall response per patient. Tumor reduction was seen in all 18 patients. Fourteen patients had tumor measurement reductions from baseline > 30%. Although one patient had tumor measurement reductions from baseline > 50%, the 4-week response duration of that patient could not be confirmed. The PFS of all 18 patients is shown in Fig. 2, and the OS of all 18 patients is shown in Fig. 3. The median PFS was 7.5 months (95%CI: 6.1–10.4 months), and the median OS was 14.4 months (95%CI: 9.9–33.1 months). The 1-year PFS

Table 2
Tumor response.

Response	No. of patients
Complete response	1
Partial response	12
Stable disease	5
Progressive disease	0
Response rate (%)	72.2
(95% CI)	(46.5–90.3)