Phase II study of nedaplatin and docetaxel in patients with advanced squamous cell carcinoma of the lung

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Background: The treatment of squamous cell carcinoma of the lung has not advanced sufficiently. Nedaplatin is a second-generation platinum compound that is active against squamous cell carcinoma of the lung, with a response rate of ~40%.

Patients and methods: Eligible patients with advanced squamous cell carcinoma of the lung were treated with docetaxel (60 mg/m²) and nedaplatin (100 mg/m²) administered i.v. on day 1; these doses were determined in an earlier phase I study. The treatment cycles were repeated every 3 weeks. The primary end point was the response rate, and the secondary end points were overall survival, progression-free survival, and toxicity.

Results: Twenty-one patients were enrolled. Eighteen of the patients were male, and the median age was 67 years. The objective response rate was 62%. The median progression-free survival time was 7.4 months. The median survival time was 16.1 months, and the 1-year survival rate was 66.7% (95% confidence interval 46.5% to 86.8%). The most common adverse event was neutropenia (grade 3/4, 86%). Non-hematological toxic effects were relatively mild. One patient died of sepsis.

Conclusions: Combination chemotherapy with nedaplatin and docetaxel is highly active and has an acceptable toxicity. Further investigation of nedaplatin and docetaxel is warranted.

Key words: chemotherapy, docetaxel, nedaplatin, non-small-cell lung cancer, squamous cell carcinoma

introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. More than half of patients with non-small-cell lung cancer (NSCLC) have advanced disease at the time of their diagnoses, and these patients are candidates for treatment with platinum-based combination chemotherapy [2–4]. A recent meta-analysis showed a significant but modest survival benefit of chemotherapy over supportive care alone, with a 9% increase in overall survival at 1 year [5]. Therefore, advances in treatment of NSCLC are urgently needed.

Historically, histological subtypes have not been used to select appropriate treatments for advanced NSCLC. NSCLC consists mainly of adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, and these classifications are grouped together as a single entity for therapy. However, recent advances in molecular-targeted agents have changed this paradigm [6–8]. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, such as erlotinib and gefitinib, produce dramatic and sustainable responses when used against adenocarcinoma, especially in the presence of an EGFR mutation [9–11]. Bevacizumab, an mAb for vascular endothelial growth factor, produces an additional survival benefit when combined with carboplatin and paclitaxel [12]. However, fatal hemoptysis has been reported in patients with hilar squamous cell carcinoma; therefore, the use of bevacizumab is now restricted to non-squamous NSCLC [13]. Moreover, the novel multitargeted antifolate pemetrexed shows a greater antitumor activity against adenocarcinoma than against squamous cell carcinoma [14]. As a result of these developments, the survival of patients with adenocarcinoma has been improving; however, that of patients with squamous cell carcinoma has remained the same [15].

Nedaplatin is a second-generation platinum compound that is active against NSCLC, especially squamous cell carcinoma, with a response rate of 40% [16, 17]. An earlier phase I study demonstrated that nedaplatin (100 mg/m²) could be safely administered in combination with docetaxel (60 mg/m²) [18]. Based on the results of this previous study, we conducted a phase II study to evaluate the efficacy and tolerability of nedaplatin and docetaxel.

patients and methods

patients and evaluations

The eligibility criteria were as follows: histologically or cytologically proven squamous cell carcinoma of the lung; stage III (unresectable and unfit for
definitive radiotherapy), stage IV, or recurrent disease after surgery; aged 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero or one; chemotherapy naïve; measurable lesion according to the RECIST version 1.0; and preserved organ function (white blood cell count ≥ 4.0 × 10⁹/l, absolute neutrophil count ≥ 2.0 × 10⁹/l, platelet count ≥ 100 × 10⁹/l, hemoglobin ≥ 9.5 g/dl, total bilirubin ≤ 1.5 mg/dl (0.3–1.2), aspartate aminotransferase ≤ 100 IU/l (13–33), alanine aminotransferase ≤ 100 IU/l (8–42 for male and 6–27 for female), serum creatinine ≤ 1.5 mg/dl (0.6–1.1 for male and 0.4–0.7 for female), and PaO₂ ≥ 60 Torr or oxygen saturation ≥ 94% at ambient air). Patients were excluded if pulmonary fibrosis was visible on a chest radiograph (pulmonary emphysema was allowed), uncontrolled pericardial or pleural effusion that needed immediate drainage was present, symptomatic brain metastasis had occurred, or a concomitant serious illness contraindicating systemic chemotherapy was present. Patients who were pregnant or breast-feeding were also excluded. All the patients provided their written informed consent before enrollment, and the study was approved by the institutional ethics boards of the National Cancer Center.

Clinical status, hematology, biochemistry and chest radiographs were assessed at least every 2 weeks. Disease status was assessed every 2 months. Toxicity was graded using the Common Terminology Criteria for Adverse Events version 3.0.

**protocol treatment**

Nedaplatin and docetaxel were administered on day 1 every 3 weeks for up to four cycles. Docetaxel diluted in 250 ml of 5% glucose was administered as a 1-h infusion. Nedaplatin was diluted in >300 ml of normal saline or 5% xylitol and was administered as a 90-min i.v. infusion. Dexamethasone (8 mg), granisetron, and fluids (1000 ml) were also administered i.v.

Dose reduction was required if patients experienced the following toxic effects: grade 3 or more non-hematological toxicity (except for nausea, vomiting, anorexia, hyperglycemia, hyponatremia, mucositis, constipation, rash), grade 4 leukopenia or neutropenia lasting for >4 days, grade 4 thrombocytopenia, febrile neutropenia, >14 days delay of the next chemotherapy cycle.

**design and statistics**

The primary objective was the response rate. The secondary objectives were progression-free survival, overall survival, and toxicity. The tumor responses were evaluated by radiologists. The planned sample size was 21, based on an alpha of 0.05, 90% power, H0 = 20% and H1 = 50% [19]. After the accrual of 12 patients, an interim analysis was planned. If only two or fewer responses had occurred, then the study would be stopped early. If seven or fewer responses were observed by the end of the trial, then no further investigation of this combination was deemed as being warranted. This study was registered with University Hospital Medical Information Network-Clinical Trials Registry, available at http://www.umin.ac.jp/ctr/index-j.htm (ID: UMIN000001227).

**results**

From August 2006 to January 2009, 21 patients were enrolled. The patient demographics and disease characteristics are summarized in Table 1. All the patients had confirmed squamous cell carcinoma; the median age was 67 years, 18 patients were male, and 16 patients had an ECOG PS of one. Nedaplatin and docetaxel were administered to all the patients. The median number of treatment cycles was 4 (range 1–4). Relative dose intensity for planned cycles of chemotherapy was 77.9% for both docetaxel and nedaplatin.

**efficacy**

At the interim analysis, 7 of 13 patients had achieved a partial response. Therefore, the accrual continued up to 21 patients. At the end of the study, the objective response rate was 62% (Figure 1 and Table 2). Figure 2 shows the progression-free survival. The median progression-free survival time was 7.4 months [95% confidence interval (CI) 3.5–11.4 months], and the progression-free survival rate at 1 year was 24.8% (95% CI 4.6% to 44.9%). Figure 3 shows the overall survival. The median overall survival time was 16.1 months (the median follow-up time was 20.9 months for the censored cases), and the overall survival rate at 1 year was 66.7% (95% CI 46.5% to 86.8%). Post-study treatment included radiotherapy (nine for local tumors, two for lymph node metastases, one for bone metastasis, and one for brain metastasis) and systemic chemotherapy (seven with gemcitabine and vinorelbine, two

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**Figure 1.** Waterfall plots for the degree of tumor shrinkage. Most patients achieved tumor shrinkage. Partial response was observed in 13 patients and the response rate was 62%.
with gemcitabine monotherapy, two with nedaplatin and docetaxel rechallenge, and four others).

**safety**
The incidence of treatment-related adverse events is listed in Table 3. Non-hematologic toxicity was generally grade 1 or 2 and consisted primarily of gastrointestinal disorders, with one patient (5%) experiencing grade 3 anorexia and two (10%) experiencing grade 3 nausea. None of the patients experienced grade 3 or higher diarrhea. Grade 3 or higher neutropenia occurred in 86% of the patients, and febrile neutropenia was observed in 24% of the patients. Dose modification was required in seven patients (33%). One patient died of sepsis on treatment day 9 of the first cycle. An autopsy revealed that the patient had previously undiagnosed liver cirrhosis.

**discussion**
Nedaplatin is a second-generation platinum compound and is comparable in efficacy with cisplatin against NSCLC, with a reduced renal toxicity. A randomized trial comparing nedaplatin and vindesine with cisplatin and vindesine showed similar survival outcomes, with a median survival time of 8.9 months for nedaplatin–vindesine and 9.1 months for cisplatin–vindesine [20]. However, only 36 of the 136 patients in this series had squamous cell carcinoma of the lung. Nedaplatin has been combined with gemcitabine, irinotecan, or paclitaxel in patients with NSCLC and with docetaxel mainly in patients with esophageal cancer [21–33].

Nedaplatin is more active against squamous cell carcinoma of the lung than adenocarcinoma as a single agent, based on the results of phase II trials [16, 17]; however, the reason for this difference in the antitumor activity among histological subtypes has not been fully investigated. A preclinical study demonstrated that in squamous carcinoma cells (PC-10), the intracellular concentration of nedaplatin promptly rose and reached a higher concentration than that in adenocarcinoma cells (PC-3), suggesting a higher antitumor activity of nedaplatin against squamous cell carcinoma [34].
The response rate of 62% in the current study met the criteria for further investigation. Furthermore, the median progression-free survival time of 7.4 months and the median overall survival time of 16.1 months were promising. A selection bias may have caused these survival outcomes. However, the median survival time of 16.1 months is comparable with that of stage III disease treated with definitive chemoradiotherapy and suggested a potential benefit of nedaplatin and docetaxel against squamous cell carcinoma of the lung.

In patients with unresectable squamous cell carcinoma, nedaplatin was also combined with paclitaxel in a phase I trial [35]. The response rate was 53%; however, paclitaxel was reported to be correlated with a shorter progression-free survival time compared with gemcitabine, docetaxel, and vinorelbine based on a meta-analysis [36]. Docetaxel is one of the most promising agents against NSCLC, including squamous cell carcinoma. In the TAX 301 JP trial, the combination of cisplatin and docetaxel showed a statistically significant survival benefit over cisplatin and vindesine [37]. A subgroup analysis showed similar survival benefits for patients with adenocarcinoma and those with squamous cell carcinoma. Therefore, nedaplatin and docetaxel is the most promising combination against squamous cell carcinoma of the lung.

Grade 3 or more neutropenia was observed in 86% of patients in the current study. High incidence of grade 3 or more neutropenia with 84% (74 of 88 patients) treated with docetaxel and cisplatin was also observed in the randomized phase III trial WJOG3405, which compared gefitinib with cisplatin and docetaxel in patients with EGFR-mutant NSCLC in Japan [38]. Moreover, single-agent docetaxel at a dose of 60 mg/m² resulted in 84.6% (632 of 747) of patients with grade 3 or more neutropenia [39]. In contrast, in the international phase III trial TAX 326 comparing docetaxel plus platinum with vinorelbine plus cisplatin, grade 3 or more neutropenia was observed in 74.5% of patients treated with cisplatin and docetaxel [40]. The reason for this difference is not known. Ethnic difference between the Japanese and the Caucasian is one of the explanations. However, in TAX 301 JP conducted in Japan, grade 3 or more neutropenia in patients treated with cisplatin and docetaxel was 74.1% (112 of 151), which is similar with TAX 326. Neutropenia should be carefully managed and the risk factor of serious neutropenia should be further examined.

In the current study, one patient died of sepsis. The autopsy revealed that the patient was affected by liver cirrhosis, which was been unaware of before treatment. Full dose of docetaxel is not appropriate for patients with impaired liver function and the administration of docetaxel in patients with liver cirrhosis should be avoided [41]. Other toxic effects were relatively mild.

In conclusion, the combination of nedaplatin and docetaxel showed a promising response rate and overall survival time, with acceptable toxic effects. A multicenter phase III trial comparing nedaplatin and docetaxel with cisplatin and docetaxel is currently under way (WJOG 5208L).

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**Disclosure**

The authors declare no conflict of interest.

**References**

39. Taxotere(R) the Japanese Package Insert.