Cancer Chemother Pharmacol (2008) 61:829–835
DOI 10.1007/s00280-007-0540-6

ORIGINAL ARTICLE

# Phase I study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer

**Kentaro Okuda · Takashi Hirose · Hiroo Ishida · Sojiro Kusumoto · Tomohide Sugiyama · Kohichi Ando · Takao Shirai · Tsukasa Ohnishi · Naoya Horichi · Tohru Ohmori · Mitsuru Adachi**

Received: 15 February 2007 / Accepted: 29 May 2007 / Published online: 23 June 2007


**Abstract**
*Purpose* This trial was conducted to determine the maximum tolerated dose (MTD), principal toxicity, and recommended dose for phase II study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer (NSCLC).
*Methods* Patients with previously untreated NSCLC, either stage IIIB with pleural effusion or stage IV, were eligible if they had a performance status of 0–2, were 75 years or younger, and had adequate organ function. The respective doses of nedaplatin (day 1) and weekly paclitaxel (days 1, 8, and 15) studied were 80/60, 80/70, 80/80, 80/90, and 100/90 (mg $m^{-2}$), repeated every 4 weeks.
*Results* From May 2004 through June 2005, 21 patients (18 men and 3 women; median age, 63 years; age range, 53–75 years) were enrolled. The MTD was determined to be 100 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel. Dose-limiting toxicities at the MTD were neutropenic fever and hepatic dysfunction. We recommend doses of 80 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel for phase II study. Grade 3–4 hematologic toxicities included neutropenia in 29% of patients, thrombocytopenia in 0%, and anemia in 5%. Although the most frequent non-hematologic toxicity was hepatic dysfunction, all cases were only mildly to moderately severe. Although two patients had grade 3 or 4 pulmonary toxicity due to *Pneumocystis carinii* pneumonia, these patients recovered after receiving trimetoprim-sulfamethoxazole, steroid therapy, and supplemental oxygen. There were no treatment-related deaths. The overall response rate was 19.0% (95% confidence interval, 5.4–41.9%), and all responses were in patients receiving the recommended doses. The median dose-intensities for nedaplatin and paclitaxel were 91.6 and 87.1%, respectively, of the planned doses.
*Conclusion* This combination chemotherapy is active and well tolerated and warrants phase II study.

**Keywords** Nedaplatin · Weekly paclitaxel · Non-small cell lung cancer · Phase I study

K. Okuda · T. Hirose (✉) · H. Ishida · S. Kusumoto · T. Sugiyama · K. Ando · T. Shirai · T. Ohnishi · N. Horichi · M. Adachi
The First Department of Internal Medicine,
Showa University School of Medicine, 1-5-8 Hatanodai,
Shinagawa, Tokyo 142-8666, Japan
e-mail: thirose-shw@umin.ac.jp

T. Ohmori
Institute of Molecular Oncology,
Showa University School of Medicine,
1-5-8 Hatanodai, Shinagawa, Tokyo 142-8666, Japan

## Introduction

Since the 1990s, many prospective, randomized, controlled trials have evaluated combination therapy regimens that include newly developed anticancer agents (paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan) and platinum-based agents in patients with advanced non-small cell lung cancer (NSCLC). However, results of these trials have been unsatisfactory, and no two-drug, platinum-based combination has been shown to be more effective than other regimens [7, 24]. Recently, Sandler et al. [18] reported that the addition of bevacizumab to paclitaxel plus carboplatin improved overall survival in patients with advanced non-squamous-cell, NSCLC and a good performance status. Therefore, the combination of doublet chemotherapy with bevacizumab is one of standard chemotherapy in patients with advanced non-squamous-cell and NSCLC. However,

bevacizumab cannot be used in patients with non-squamous-cell and NSCLC in Japan. Therefore, doublet platinum-based chemotherapy has been standard chemotherapy in patients with advanced NSCLC in Japan. Although standard doublet platinum-based chemotherapy has reached a therapeutic plateau, less toxic cytotoxic agents may improve quality of life.

In phase III studies of paclitaxel administered every 3 weeks in patients with advanced NSCLC, Paclitaxel significantly improved survival and time to disease progression compared with best supportive care [15]. In vitro experiments have suggested that prolonged exposure to paclitaxel through either continuous infusion schedules or weekly administration, can lead to enhanced cytotoxicity [6, 13]. In addition, paclitaxel has anti-angiogenic and apoptotic activity when delivered on low-dose weekly schedules [3, 17], making this approach of interest in advanced NSCLC. Akerley et al. [1] have reported that paclitaxel administered weekly had a maximum tolerated dose (MTD) of 175 mg $m^{-2}$ and achieved a response rate of 35%. Clinical studies with weekly paclitaxel in patients with advanced NSCLC yielded beneficial activity and low toxicity profile [10]. Belani et al. [2] have compared three regimens of weekly paclitaxel plus carboplatin in a randomized phase II trial and concluded that the regimen of 100 mg $m^{-2}$ of paclitaxel administered on days 1, 8, and 15 with carboplatin (the area under the plasma concentration versus time curve [AUC] of 6 mg $min^{-1}$ $ml^{-1}$) administered on day 1 was the most favorable.

Nedaplatin is a second-generation platinum derivative that has shown greater antitumor activity and lower toxicity in mice than does cisplatin [25]. Sasaki et al. [19] have reported that nedaplatin shows equivalent antitumor activity to cisplatin against lung cancer cell lines in vitro. In a phase III study in previously untreated patients with NSCLC the combination of nedaplatin and vindesine produced response rates and an overall survival rate similar to those of cisplatin and vindesine [5]. Leukopenia and renal and gastrointestinal toxicities were more frequent in the cisplatin arm than in the nedaplatin arm, although thrombocytopenia was more frequent in the nedaplatin arm [5]. The combination nedaplatin with new agents such as gemcitabine or irinotecan in patients with advanced NSCLC showed response rates of 30 and 31% [14, 20], indicating similar efficacy to gemcitabine or irinotecan with cisplatin or carboplatin.

In mice, combination therapy with paclitaxel and nedaplatin inhibited tumor growth to a significantly greater degree than did paclitaxel or nedaplatin monotherapy [28]. Sequential administration of paclitaxel and nedaplatin resulted in greater antitumor efficacy and lower toxicity than did the reverse schedule. Furthermore, the antitumor activity of the combination of paclitaxel and nedaplatin was superior to paclitaxel plus cisplatin or carboplatin [28].

To date, no trials of nedaplatin and weekly paclitaxel in patients with advanced NSCLC have been published. Therefore, we conducted a phase I study of nedaplatin and weekly paclitaxel in patients with advanced NSCLC. The primary end point of this study was to determine the MTD and the recommended dose for phase II study. The secondary end point of this study was to investigate toxicity and activity.

## Patients and methods

### Eligibility criteria

The criteria for study entry were: (1) histologically or cytologically confirmed NSCLC; (2) stage IIIB disease with pleural effusion or IV disease; (3) age between 20 and 75 years; (4) Eastern Cooperative Oncology Group (ECOG) performance status of two or less; (5) a measurable lesion; (6) life expectancy of 3 months or more; (7) adequate bone marrow function (white blood cell [WBC] count from 4,000 to 12,000 $\mu l^{-1}$, neutrophil count of 2,000 $\mu l^{-1}$ or more, platelet count of 100,000 $\mu l^{-1}$ or more, and hemoglobin level of 9.0 g $dl^{-1}$ or more), renal function (serum creatinine levels less than 1.5 mg $dl^{-1}$ and creatinine clearance rate of 50 ml $min^{-1}$ or more), and hepatic function (total serum bilirubin level less than the upper limit of the normal range, levels of aspartate aminotransferease and alanine aminotransferase less than or equal to twice the upper limits of the normal ranges), and arterial oxygen pressure of 70 mmHg or more; and (8) written informed consent. Patients who had previously received chemotherapy were not eligible for this study, but previous radiotherapy was permitted if it was not given to the target lesion used to assess response. Patients were excluded if they had active infections, severe heart disease, interstitial pneumonia, lung fibrosis, peripheral neuropathy, symptomatic brain metastasis, or an active second malignancy. This study was approved by the institutional review board of the Showa University School of Medicine.

### Treatment protocol

Paclitaxel was diluted with 250 ml of normal saline and administered as an intravenous drip infusion in 60 min on days 1, 8, and 15. Nedaplatin was diluted with 500 ml of normal saline immediately before injection and was given as an intravenous drip infusion over 60 min after administration of paclitaxel on day 1. This chemotherapy regimen was repeated every 4 weeks and given for more than two courses. If the treatment outcome was progressive disease or if intolerable toxicity developed at any time, chemotherapy was discontinued. If the outcome was no change after

two courses of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient's treatment. Palliative radiotherapy was permitted to control persistent pain associated with bone metastasis.

Full doses of paclitaxel were given if the WBC count was greater than 2,000 $\mu l^{-1}$ and the platelet count was more than 75,000 $\mu l^{-1}$ on day 8 or 15 of treatment. If the WBC count was less than 3,000 $\mu l^{-1}$ or the platelet count was less than 100,000 $\mu l^{-1}$ on day 29, the next course was withheld until the count recovered. Nedaplatin was permanently discontinued if the serum creatinine level became greater than 2.0 mg $dl^{-1}$. If the serum creatinine level was 1.5–2.0 mg $dl^{-1}$, nedaplatin was withheld for 2 weeks. Doses of both drugs were reduced one level for grade 4 leukopenia or neutropenia lasting 3 days or longer, thrombocytopenia less than 20,000 $\mu l^{-1}$, neutropenic fever during grade 3 or 4 neutropenia, or omission of paclitaxel on day 8 or 15 of treatment. Doses of paclitaxel were reduced 1 level for grade 2 neuropathy, arthlargia, or myalgia. No dose escalation was permitted in individual patients. Chemotherapy was discontinued for grade 3 or higher nonhematologic toxicity, except for alopecia, nausea/vomiting, anorexia, constipation, fever, and fatigue. Patients received paclitaxel after receiving intravenous dexamethasone (10 mg) and ranitidine (50 mg) and oral diphenhydramine (50 mg) to prevent hypersensitivity reactions, as described by Bookman et al. [4]. The dexamethasone dose was then progressively decreased to 8, 4, 2, and 1 mg to minimize corticosteroid side effects without severe hypersensitivity reactions. Ondansetron was routinely administered to all patients before nedaplatin as antiemetic prophylaxis. If the WBC or neutrophil count decreased to more than grade 4 after chemotherapy, granulocyte colony stimulating factor (G-CSF) was administered until the count recovered.

### MTD and dose-limiting toxicity

Five dose levels of nedaplatin and weekly paclitaxel were chosen for investigation and level 1 was chosen as starting dose (Table 1), level 0: 80/60 mg $m^{-2}$; level 1: 80/70 mg $m^{-2}$; level 2: 80/80 mg $m^{-2}$; level 3: 80/90 mg $m^{-2}$; and level 4: 100/90 mg $m^{-2}$. The MTD was determined on the basis of dose-limiting toxicity (DLT) events that occurred during the first course of chemotherapy. DLT was defined as follows: (1) grade 4 leukopenia or neutropenia lasting 3 days or longer; (2) a platelet count less than 20,000 $\mu l^{-1}$; (3) grade 3 febrile neutropenia; (4) any grade 3 nonhematologic toxicity except for alopecia, nausea/vomiting, anorexia, constipation, fever, and fatigue; (5) a serum creatinine level greater than 2.0 mg $dl^{-1}$; and (6) the next chemotherapy administration being withheld for more than 2 weeks. At least three patients were enrolled at each dose level. If DLT was observed in one patient, three additional patients were accrued. If DLT was observed in two or more of the first three patients or three or more of the six patients, patient accrual was discontinued, and the dose level was considered to be the MTD. Once the MTD was determined, the previous dose level was then chosen as the recommended dose. If MTD was determined at level 1, patients were accrued at level 0. We treated six additional assessable patients at the recommended dose to obtain more information about the safety and efficacy at that dose level.

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

| Level | Nedaplatin (mg $m^{-2}$) | Paclitaxel (mg $m^{-2}$) | Number of patients | Total number of courses | Patients with DLT |
|---|---|---|---|---|---|
| 0 | 80 | 60 | 0 | 0 | 0 |
| 1 | 80 | 70 | 6 | 12 | 1 |
| 2 | 80 | 80 | 3 | 6 | 0 |
| 3 | 80 | 90 | 9 | 21 | 1 |
| 4 | 100 | 90 | 3 | 5 | 2 |

*DLT* dose-limiting toxicity

### Toxicity and evaluation of response

Pretreatment evaluation included a baseline history and physical examination, complete blood cell count with differential, and routine chemistry profiles, urinalysis, electrocardiograms, chest radiography, chest and abdominal computed tomography (CT), brain magnetic resonance imaging, and a radionucleotide bone scan. Complete blood cell counts with differential and routine chemistry profiles were obtained at least twice a week during chemotherapy.

Toxicities were assessed and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Tumor response was classified according to Response Evaluation Criteria in Solid Tumors criteria. All patients who received at least two cycles of chemotherapy were assessable for response, and all patients who received at least one cycle were assessable for toxicity and survival.

Time to disease progression was defined as the time from the date of treatment to the date progressive disease was diagnosed. Survival time was measured from the start of treatment until death or latest follow-up. The Kaplan–Meier method was used to calculate survival curves.

## Results

### Patients characteristics

Twenty-one patients were enrolled from May 2004 through June 2005 (Table 2). All patients could be assessed for toxicity, and 19 patients could be assessed for response. Two

**Table 2** Patient characteristics

| | |
|---|---|
| Total number of patients | 21 |
| Sex (M/F) | 18/3 |
| Age in years (range) | 63 (57–75) |
| Performance status (0/1/2) | 5/15/1 |
| Stage (IIIB/IV) | 5/16 |
| Histologic type | |
| Adenocarcinoma | 18 |
| Squamous | 2 |
| Others | 1 |

patients could not be assessed for response because they had not received two courses of chemotherapy owing to intolerable toxicity during the first course of chemotherapy. One of these patients had grade 3 hepatic dysfunction and the other patient had grade 4 pulmonary toxicity due to *Pneumocystis carinii* pneumonia. These patients were considered nonresponders.

## Determination of MTD

The number of patients in whom DLT occurred at each level is shown in Table 1. DLTs occurred in 1 of 6 patients at level 1 and in 1 of 9 patients at level 3. These DLTs were grade 3 or 4 pulmonary toxicity owing to *P. carinii* pneumonia. Additionally, DLTs occurred in 2 of 3 patients at level 4. These DLTs were neutropenic fever during grade 4 neutropenia in 1 patient and grade 3 hepatic dysfunction in 1 patient. Therefore, the MTD was determined to be 100 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel. Recommended doses for phase II study were 80 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel.

## Toxicity

A total of 44 courses of chemotherapy were given. The median number of courses given per patient was 2 (range 1–4). The most frequent grade 3 or 4 toxicity was neutropenia, which developed in 29% of patients (6 of 21 patients; Table 3). However, the effects of nedaplatin and weekly paclitaxel on myelosuppression were likewise mild: G-CSF was administered during only 2 (4.5%) of the 44 assessable courses for 2 or 4 days. No patients had grade 3 or 4 thrombocytopenia or received a platelet transfusion. Only 1 (5%) patient had grade 3 or 4 anemia, and no patients received an erythrocyte transfusions.

Table 4 shows the maximum nonhematologic toxicity that developed during treatment. Hepatic dysfunction with transient increases in serum aminotransferase levels was the most frequent nonhematologic toxicity and developed in 48% (10 of 21) of patients. However, hepatic dysfunction in all cases was only mildly to moderately severe, and there was no evidence of persistent hepatic impairment. No patients had grade 3 or 4 nausea and vomiting, neurotoxicity, or arthlargia. No patients had hypersensitivity reactions. One patient had herpes zoster during the second course but rapidly recovered after receiving acyclovir. Two patients had grade 3 or 4 pulmonary toxicity due to microbiologically proven *P. carinii* pneumonia during the first course. These patients recovered after receiving trimetoprim–sulfamethoxazole, steroid therapy, and supplemental oxygen. There were no treatment-related deaths.

## Response to treatment and survival

The final outcomes were as follows: complete responses in no patients, partial responses in four patients, stable disease in five patients, and progressive disease in 10 patients. The overall response rate was 19.0% (95% confidence interval, 5.4–41.9%, Table 5). All responses were seen at the recommended dose. The response rate was 44.4% at the recommended dose. Survival analysis was performed when the median follow-up time of all assessable patients was 13 months. At present, five patients (23.8%) are still alive, and no patients have been lost to follow-up. The median survival time was 14 months (range 2–32 months). The 1 year survival rate was 52%. The median time to disease progression was 3 months (range 1–24 months).

## Dose intensity

Doses of both nedaplatin and paclitaxel were reduced in one patient because of neutropenic fever and omission of paclitaxel on day 15. During a total of 44 courses, a total of 6 (14%) doses of paclitaxel were skipped on day 8 (1 dose)

**Table 3** Hematologic toxicity by dose level in the first course

| Dose level | No. of patients | Neutropenia | | | | | Thrombocytopenia | | | | | Anemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 3–4 (%) | 1 | 2 | 3 | 4 | 3–4 (%) | 1 | 2 | 3 | 4 | 3–4 (%) |
| 1 | 6 | 1 | 1 | 2 | 0 | 33 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| 2 | 3 | 0 | 1 | 1 | 0 | 33 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 3 | 9 | 1 | 2 | 0 | 1 | 11 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 1 | 0 | 5 |
| 4 | 3 | 0 | 1 | 1 | 1 | 67 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |

**Table 4** Maximum nonhematologic toxicity by dose levels during treatment

| Dose level | No. of patients | Nausea/vomiting | | | | Neuro-toxicity | | | | Arthralgia | | | | Elevation of transaminase | | | | Infection | | | | Pulmonary toxicity | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| 1 | 6 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 2 | 3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 9 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

**Table 5** Response at each dose level

| Level | No. of patients | CR | PR | SD | PD | NE | RR (%) |
|---|---|---|---|---|---|---|---|
| 1 | 6 | 0 | 0 | 4 | 2 | 0 | 0 |
| 2 | 3 | 0 | 0 | 1 | 2 | 0 | 0 |
| 3 | 9 | 0 | 4 | 1 | 3 | 1 | 44.4 |
| 4 | 3 | 0 | 0 | 0 | 2 | 1 | 0 |
| Total | 21 | 0 | 4 | 5 | 10 | 2 | 19.0 |

*CR* complete response *PR* partial response *SD* stable disease *PD* progressive disease *NE* not evaluable *RR* response rate

or 15 (5 doses). The reasons for skipped doses were neutropenia, infection, or hepatic dysfunction. The next cycle was delayed in three courses. The main reason for delay was neutropenia. At the recommended dose, all nine patients could start the next course on day 29. The actual delivered dose intensities were 91.6 and 87.1%, respectively, of the planned doses of nedaplatin and paclitaxel.

## Discussion

Although cisplatin-based chemotherapy lengthens survival, it can cause vomiting, neurotoxicity, ototoxicity, and nephrotoxicity and necessitates additional hydration. Carboplatin, on the other hand, is less toxic than cisplatin [8]. Nedaplatin is a second-generation platinum derivative that appears to have a mechanism of action and a toxicity profile similar to those of carboplatin, although the two agents have not been directly compared. In mice the antitumor activity of the combination of paclitaxel and nedaplatin is superior to that of the combination of paclitaxel and cisplatin or carboplatin [28]. In addition, a study in sheep has shown that the distribution in the lung is greater after nedaplatin infusion than after cisplatin infusion [9]. These findings suggest that nedaplatin will have greater efficacy than other platinum compounds in patients with NSCLC.

Several phase I studies have evaluated monthly paclitaxel in combination with nedaplatin. Sekine et al. [23] have recommended a paclitaxel dose of 180 mg $m^{-2}$ with a nedaplatin dose of 100 mg $m^{-2}$ on day 1 every 3 or 4 weeks for phase II studies in patients with squamous cell carcinoma, including lung cancer, thymus cancer, and head and neck cancer. Yoshiike et al. [29] have recommended a paclitaxel dose of 180 mg $m^{-2}$ with a nedaplatin dose of 80 mg $m^{-2}$ on day 1 every 4 weeks for phase II studies in patients with NSCLC. However, no trials of nedaplatin and weekly paclitaxel in patients with advanced NSCLC have been published. In this phase I study, the MTD was determined to be 100 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel. The DLTs at the MTD were neutropenic fever and grade 3 hepatic dysfunction. We recommend 80 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel for phase II study.

In our study, most hematologic toxicities were only mildly to moderately severe: grade 3 to 4 hematologic toxicities included neutropenia in 29% of patients, thrombocytopenia in 0%, and anemia in 5%. These rates of toxicity compare favorably with those in most recently published trials in patients with advanced NSCLC. In recent phase II or III trials of paclitaxel with carboplatin for advanced NSCLC, rates of grade 3 to 4 neutropenia, thrombocytopenia, and anemia have ranged from 17 to 63%, 1 to 10%, and 4 to 13%, respectively [7, 21, 24, 26]. In addition, in phase I trials of monthly paclitaxel and nedaplatin, rates of grade 3–4 neutropenia at the recommended doses were 83 and 92%, although rates of both grade 3–4 thrombocytopenia and anemia were 0 and 0%, and 0 and 0%, respectively [23, 29].

In recent phase II or III trials of paclitaxel with carboplatin for advanced NSCLC, rates of grade 3–4 nausea and vomiting and neurotoxicity have ranged from 1 to 9% and from 3 to 29%, respectively [6, 19, 22, 24]. In our study, no patients had grade 3–4 nausea and vomiting or neurotoxicity. A previous study has reported that if the weekly paclitaxel dose is 100 mg $m^{-2}$ or less, neurotoxicity is absent or mild in most patients [22]. Although the rate of hepatic dysfunction was higher in our trial than in other recent trials, all cases of hepatic dysfunction in our trial were only mildly to moderately severe, and there was no evidence of persistent hepatic impairment. The rates of hepatic dysfunction in the combination of nedaplatin with other agents have ranged from 20 to 55% [5, 20]. On the other hand, in

recent phase II or III trials of paclitaxel with carboplatin for advanced NSCLC, hepatic dysfunction has not been reported [7, 21, 24, 26]. Therefore, nedaplatin might be responsible for hepatic dysfunction.

Although two patients had grade 3 or 4 pulmonary toxicity due to *P. carinii* pneumonia, they recovered after receiving trimethoprim-sulfamethoxazole, steroid therapy, and supplemental oxygen. In two previous studies of weekly or twice-weekly paclitaxel with thoracic radiation therapy *P. carinii* pneumonia developed in 1 (6.7%) of 15 patients or 2 (7.7%) of 26 patients [12, 16]. Reckzeh et al. [12] reported that all of the patients developed a moderate to severe lymphocytopenia during treatment of weekly paclitaxel with thoracic radiation therapy. Although whether the lymphocytopenia was the additive effect of the combination of paclitaxel with radiotherapy or whether it was induced by the relatively low doses of paclitaxel alone remained to be determined. In future, this combination chemotherapy should be carefully monitored for *P. carinii* pneumonia in a phase II trial. In addition, corticosteroids are thought to be a strong predisposing factor for *P. carinii* pneumonia in patients with cancer [27]. Frequent use of high-dose dexamethasone as a premedication for paclitaxel might have predisposed patients to opportunistic infections, although we decreased the dexamethasone dose from 10 to 8, 4, 2, and 1 mg to minimize side effects of corticosteroids. In the protocol of Lau et al. [11] dexamethasone was discontinued if a patient showed no hypersensitivity reaction after the first two doses of paclitaxel. Even when dexamethasone was not administered with subsequent doses of paclitaxel, no hypersensitivity reactions occurred. Additionally, no *P. carinii* pneumonia was observed [11]. We might need to change the premedication strategy for weekly paclitaxel to prevent opportunistic infections by dexamethasone.

Although evaluation of antitumor activity and survival was not a primary end point of our study, the response rate of 19.0%, the MST of 14 months, the overall 1-year survival rate of 52%, and the response rate of 44.4% at the recommended dose is interesting for further evaluation of response rate in a phase II study. Recent randomized phase II or III trials in patients with NSCLC have found that the regimen of weekly paclitaxel and weekly or 3-weekly carboplatin is as effective as the regimen of 3-weekly paclitaxel and carboplatin [21, 26]. However, the regimens had different toxicity profiles. Grade 3–4 sensory neuropathy or severe myalgias and arthralgias occurred more frequently with the regimen of 3-weekly paclitaxel and carboplatin, whereas, grade 3–4 diarrhea, thrombocytopenia, and anemia occurred more frequently with the regimen of weekly paclitaxel [21, 26]. In our study, no patients had grade 3–4 thrombocytopenia or diarrhea. Therefore, our weekly regimen is an acceptable option for patients with advanced NSCLC.

The tolerability of nedaplatin and weekly paclitaxel is further supported by the similarity of the planned and the actual dose intensities of the two drugs. The dose intensity of paclitaxel at the recommended dose in the present study was 1.5 times higher than that with monthly paclitaxel with nedaplatin [23, 29]. Nevertheless delivered dose intensities as percentages of planned dose intensities were 91.6% for nedaplatin and 87.1% for paclitaxel, respectively.

In conclusion, to our knowledge the present phase I study is the first to examine the combination therapy of nedaplatin and weekly paclitaxel for advanced NSCLC. The MTD was 100 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel. For phase II study, we recommend doses of 80 mg $m^{-2}$ of nedaplatin and 90 mg $m^{-2}$ of weekly paclitaxel. We believe the combination of nedaplatin and weekly paclitaxel could be an acceptable option for patients with advanced NSCLC. We are now performing a phase II study of nedaplatin and weekly paclitaxel in patients with advanced NSCLC.

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