# Phase I Study of Docetaxel Plus Nedaplatin in Patients With Metastatic or Recurrent Esophageal Squamous Cell Carcinoma After Cisplatin Plus 5-fluorouracil Treatment

転移性および再発食道扁平上皮癌患者における
シスプラチンと５フルオロウラシル治療後の
ドセタキセルとネダプラチン併用療法の第I相試験

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## Abstract

*Objectives.* To date, no second-line chemotherapy regimen for esophageal squamous cell carcinoma (SCC) has been established. This clinical trial aimed to assess the optimum dose of docetaxel plus nedaplatin (cis-diammine-glycolate platinum) as second-line chemotherapy.

*Methods.* Patients with metastatic or recurrent esophageal SCC after treatment with cisplatin plus 5-fluorouracil received docetaxel (50 or 60 mg/m$^2$) plus nedaplatin (70 mg/m$^2$) on day 1 every 4 weeks. The recommended dose was based on dose-limiting toxicities (DLTs) defined during the first cycle.

*Results.* From February 2009 to November 2011, nine patients were enrolled in the study. Their median age was 62 years (range 58–72 years). Six patients had undergone radiotherapy and four had undergone surgical resection of primary lesions. DLTs were observed in two patients at dose level 1 (60 mg/m$^2$ docetaxel, 70 mg/m$^2$ nedaplatin) but not at dose level 0 (50 mg/m$^2$ docetaxel, 70 mg/m$^2$ nedaplatin). Thus, the maximum tolerated dose was established at dose level 1. No severe nonhematological toxicity was observed. No patient achieved complete response, but two (22%; 95% confidence interval, 0%–49%) achieved partial response and three had stable disease. Median progression-free and overall survival times were 2.1 months and 9.5 months, respectively.

*Conclusions.* Docetaxel plus nedaplatin chemotherapy appears to be a safe and feasible second-line regimen for the treatment of esophageal SCC. We recommend the administration of 50 mg/m$^2$ docetaxel (day 1) plus 70 mg/m$^2$ nedaplatin (day 1) every 4 weeks in a phase II study.

**Key words**: esophageal cancer, second-line chemotherapy, docetaxel, nedaplatin

## 1. Introduction

Esophageal squamous cell carcinoma (SCC) is one of the most aggressive cancers. It is well known for its aggressive nature, which is manifested as invasiveness and metastasis to regional lymph nodes and distant organs. Chemotherapy can induce a response in approximately 30%–40% of patients that are inoperable or those that show postoperative relapse; however, the survival of patients with advanced esophageal SCC is poor (median survival time 7–8 months).[1,2] SCC is the most common histological type of esophageal cancer in Japan. A combination of cisplatin and continuous-infusion 5-fluorouracil is regarded as the standard regimen for esophageal SCC. A Japanese study reported an overall response rate of 33% and median survival time of 7.5 months.[2] Chemoradiotherapy with 5-fluorouracil plus cisplatin resulted in a complete response in 33% of patients with locally advanced disease[3] and 70% of patients with resectable disease.[4] However, no second-line chemotherapy regimen for esophageal SCC has been established to date. The few trials of second-line treatments that have been performed have reported poor results,[5] and there is an urgent need for the development of a suitable second-line regimen.

Nedaplatin (cis-diammine-glycolate platinum; Shionogi Pharma, Osaka, Japan) is a second-generation platinum derivative developed in Japan. It has been shown to have a high response rate in various cancers, particularly in esophageal SCC.[6] A cisplatin-resistant human leukemia cell line, which had 10-fold resistance to cisplatin, was as sensitive to nedaplatin (1.0-fold) as the parent cells.[7] The results indicate that nedaplatin may be used to overcome the drug resistance developed in the patients after treatment with cisplatin. Docetaxel (Sanofi-Aventis, Paris, France) has also been shown to have single-agent activity in patients with metastatic or recurrent esophageal SCC.[8] Docetaxel stabilizes the microtubules and inhibits mitosis, whereas nedaplatin primarily acts as an alkylating agent. The mechanisms of action of these two drugs are thus different. Therefore, a regimen of docetaxel plus nedaplatin would be expected to result in additive antitumor effects with nonoverlapping toxicity profiles. To assess the recommended dose of docetaxel plus nedaplatin to be used in a phase II study and to determine the toxicity and efficacy of the regimen, we conducted a phase I study of

docetaxel plus nedaplatin in patients with metastatic or recurrent esophageal SCC after cisplatin plus 5-fluorouracil treatment.

## 2. Materials and Methods

### *2.1. Eligibility criteria*

Patients with metastatic or recurrent esophageal SCC who had previously been treated with cisplatin plus 5-fluorouracil were enrolled in the study. The eligibility criteria were as follows: (a) histologically confirmed esophageal SCC; (b) age 20–75 years, (c) Eastern Clinical Oncology Group performance status score ≤2; (d) life expectancy of at least 8 weeks; (e) provision of written informed consent; (f) adequate bone marrow function (white blood cell count ≥3000/$mm^3$, platelet count ≥100 000/$mm^3$); (g) adequate hepatic function (total serum bilirubin level ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase levels less than or equal to twice the upper limit of the normal ranges); and (h) adequate renal function (serum creatinine ≤1.5 mg/dl). Exclusion criteria included concomitant uncontrolled diabetes mellitus, hypertension, severe heart disease, active infection, active double cancer, massive ascites, massive pleural effusion, massive pericardial effusion, active gastrointestinal tract bleeding, possible pregnancy, brain metastases with any symptoms, severe psychological disease, and tracheoesophageal fistula formation.

### *2.2. Treatment plan*

On day 1, an intravenous (i.v.) infusion of a mixture of 5-hydroxytryptamine-3 receptor antagonist and dexamethasone (8 mg/kg body weight) diluted with 100 ml of normal saline was administered over 30 min. Subsequently, docetaxel was diluted with 250 ml of normal saline and administered as a 90-min i.v. infusion. Nedaplatin was then diluted with 250 ml of normal saline and administered as a 90-min i.v. infusion; 1000 ml of lactated Ringer's solution was also administered for hydration.

### *2.3. Study design*

Five incremental dose levels were planned (Table 1). Level 1 was the starting dose level, but level 0 was also prepared, because level 1 could have constituted the maximum tolerated dose (MTD). At least three patients were treated at each dose level. MTD was defined as follows: if two or three of three patients experienced a dose-limiting toxicity (DLT), then the particular dose level was defined as MTD; if one of three

patients experienced DLT, three additional patients were added at the same dose level. If more than three of these six patients experienced DLT, then the dose level was defined as MTD; if fewer than three of the six patients experienced DLT, subsequent patients were treated at the next higher dose level. The recommended dose was defined as the dose just below MTD.

The definition of DLT was as follows: (a) grade 4 neutropenia lasting for 5 or more days; (b) grade 4 neutropenia with fever of 38°C or more; (c) grade 3 or 4 nonhematological toxicity except nausea, vomiting, anorexia, and transient electrolyte abnormalities; and (d) initiation of the second cycle of chemotherapy delayed by more than 8 days because of failure to meet the criteria.

The study protocol was approved by the Institutional Review Board of Toyama University, Japan. All patients provided their written informed consent before entering the study.

### *2.4. Evaluation of toxicity and response*

The US National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0) were used to evaluate toxicity. Standard clinical measurements and radiological examinations were used to assess tumor response according to the Response Evaluation Criteria in Solid Tumors version 1.0.[9] Progression-free and overall survival were analyzed using the Kaplan–Meier method. Survival was measured from the date of registration to the date of death or the last confirmed date of survival. Survival time was censored at the last confirmation date if the patient remained alive.

## 3. Results

### *3.1. Patient characteristics*

In total, nine patients were enrolled in the trial between February 2009 and November 2011 (Table 2). These included eight males and one female and their median age was 62 years (range, 58–72 years). Two, six, and one patient had a performance status score of 0, 1, and 2, respectively. All patients had histologically confirmed esophageal SCC and all had previously been treated with cisplatin plus 5-fluorouracil. Six patients had undergone radiotherapy and four had undergone surgical resection of the primary lesions. Metastatic lesions were detected in the lymph nodes (n = 9), lungs (n = 5), liver (n = 3), and bone (n = 3). All patients failed prior therapy because of disease progression.

### *3.2.DLT and the recommended dose*

The number of patients who were enrolled in and experienced DLT at each dose level is shown in Table 1. DLT occurred in two of three patients at dose level 1 (60 mg/m$^2$ docetaxel, 70 mg/m$^2$ nedaplatin). One patient had grade 4 leucopenia lasting for 7 days without fever, whereas in the other, initiation of the second cycle of chemotherapy was delayed by more than 15 days because the criteria had not been met. Three patients were enrolled at dose level 0 (50 mg/m$^2$ docetaxel, 70 mg/m$^2$ nedaplatin). No DLT was observed. Hence, three additional patients were enrolled, giving a total of six patients at this dose level. One patient experienced grade 4 neutropenia for 4 days without fever, whereas another had grade 3 neutropenia with fever. However, no DLT was observed at this dose level. Therefore, 50 mg/m$^2$ docetaxel plus 70 mg/m$^2$ nedaplatin was considered as the recommended dose.

### *3.3.Toxicity*

The hematological and nonhematological adverse events that occurred after the first cycle are summarized in Tables 3. Grade 3 anemia was observed in one and two patients at dose levels 1 and 0, respectively. Grade 3/4 nonhematological toxicity was not observed at either dose level.

*3.4. Response and survival*

No patient achieved complete response, although two patients (22%; 95% confidence interval, 0%–49%) achieved partial response and three patients had stable disease. Disease control rate (response plus stable disease) was thus 56% (95% confidence interval, 23%–88%). Median progression-free and overall survival times were 2.1 months and 9.5 months, respectively (Figure 1).

## 4. Discussion

Our study findings suggest that a recommended dose of 50 mg/m$^2$ docetaxel plus 70 mg/m$^2$ nedaplatin administered on day 1 every 4 weeks should be used in patients with metastatic or recurrent esophageal SCC pretreated with cisplatin plus 5-fluorouracil. There is no consensus as to the ideal second-line chemotherapy regimen for patients with esophageal SCC.[5] Docetaxel monotherapy is currently the most common treatment option in Japan despite its overall response rate of 0%–18%.[8,10,11] In a Japanese phase II trial, the response rate to docetaxel monotherapy (70 mg/m$^2$ docetaxel every 3 weeks) in patients undergoing second-line treatment for esophageal SCC was 16%, which is moderate.[8] Paclitaxel (Bristol-Myers Squibb, New York, USA) is a taxane, similar to docetaxel. A phase II trial with paclitaxel has been reported. This phase II trial showed promising efficacy, 44.2% of response rate, although it included not only recurrent patients but also progression patients to previous platinum-based chemotherapy. The rate of patients who failed prior platinum-based chemotherapy due to disease progression was 48.1%.[12]

In contrast, a phase II study of nedaplatin in gastrointestinal cancer demonstrated a response rate of 55.6% in esophageal cancer patients with prior chemotherapy, including two partial response in four patients previously treated with cisplatin.[13] To improve the outcome of chemotherapy, the administration of docetaxel in combination with nedaplatin has been suggested as a second-line chemotherapy regimen for patients with esophageal SCC. To decrease toxicity, fractionated administration of docetaxel has been considered. In patients with metastatic breast cancer, weekly docetaxel was associated with low hematological toxicity. There was no grade 4 toxicity and only 28% of patients had grade 3 toxicity.[14] In addition, two dose-finding studies on fractionated docetaxel plus nedaplatin as second-line chemotherapy for esophageal SCC have been conducted. Yoshioka et al. recommended a dosage regimen of 30 mg/m$^2$ docetaxel (days 1 and 15) plus 80 mg/m$^2$ nedaplatin (day 1) every 4 weeks; the response rate was 25%, and 25% of patients had grade 4 neutropenia and 17% of patients had grade 3 anorexia and nausea.[15] Akutsu et al. recommended a dosage regimen of 50 mg/m$^2$ docetaxel (days 1 and 8) plus 50 mg/m$^2$ nedaplatin (day 1) every 4 weeks; the response rate was 0% and

median overall survival time was 7.8 months (Table 4). Only 8% of patients had grade 4 leukopenia and 25% of patients had grade 3 nonhematological toxicity.[16]

On the other hand, fractionated administration of docetaxel has been reported to be associated with a higher incidence of adverse pulmonary events compared with conventional administration. Weekly administration of docetaxel and gemcitabine in patients with advanced non-small-cell lung cancer (NSCLC) was associated with a high incidence of severe interstitial pneumonitis.[17] This study was prematurely terminated because 23% of patients developed fever and pulmonary dysfunction with diffuse interstitial pneumonitis. In addition, concurrent weekly administration of docetaxel with radiotherapy for NSCLC was associated with radiation pneumonitis.[18] Moreover, fractionated administration of docetaxel has been reported to be associated with decreased efficacy compared with conventional administration every 3 weeks. For example, treatment with docetaxel every 3 weeks was associated with superior survival and improved response rates compared with weekly docetaxel in patients with metastatic hormone-refractory prostate cancer.[19]

Therefore, in our study, we chose a regimen of docetaxel plus nedaplatin administered every 4 weeks. This is the first report, to our knowledge, of a dose-finding study for non-fractionated administration of docetaxel plus nedaplatin for the second-line treatment of metastatic esophageal SCC, although a pilot trial of 60 mg/m$^2$ docetaxel plus 80 mg/m$^2$ nedaplatin administered every 4 weeks has been reported previously.[20] In that trial, the dose of the drugs was determined according to a phase I/II study of first-line treatment of unresectable NSCLC, and the dose used was higher than our recommended dose. Their response rate was 25% and median overall survival time was 26 weeks (Table 4). The efficacy in their study was similar to that in our study, but severe neutropenia occurred in 60% of patients severe febrile neutropenia necessitating the use of prophylactic granulocyte colony-stimulating factor to avoid severe hematological toxicity occurred in 25% patients. In contrast, in our study, no febrile neutropenia occurred. The recommended dose for first-line chemotherapy may differ from that for second-line chemotherapy and also according to the type of cancer. We therefore conducted this phase I study to determine the recommended dose for esophageal SCC.

In conclusion, docetaxel plus nedaplatin chemotherapy administered according to our recommended dose appears to be a safe and feasible regimen for the second-line treatment of esophageal SCC. We recommend that 50 mg/m$^2$ docetaxel (day 1) plus 70 mg/m$^2$ nedaplatin (day 1) be administered every 4 weeks in a phase II study.

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Table1. Dose-escalation scheme and prevalence of dose-limiting toxicity (DLT)

| Level | Docetaxel(mg/m$^2$) | Nedaplatin(mg/m$^2$) | No. of patients | Patients with DLT |
|---|---|---|---|---|
| 0 | 50 | 70 | 6 | 0 |
| 1 | 60 | 70 | 3 | 2 |
| 2 | 60 | 80 | Not enrolled | |
| 3 | 60 | 90 | Not enrolled | |
| 4 | 70 | 90 | Not enrolled | |

Table 2. Patient characteristics

| | Number of patients |
|---|---|
| Sex | |
| Male | 8 |
| Female | 1 |
| Age (median) | 62 (58-72) |
| ECOG PS* | |
| 0 | 2 |
| 1 | 6 |
| 2 | 1 |
| Location of primary site | |
| Mt | 2 |
| Lt | 7 |
| Prior chemotherapy | |
| Cisplatin + 5-FU | 3 |
| Cisplatin + 5-FU + radiation therapy | 6 |
| Prior site | |
| Operated | 4 |
| Remained | 5 |
| Site of metastasis | |
| Lymph nodes | 9 |
| Lung | 5 |
| Bone | 3 |
| Liver | 3 |
| Others | 2 |
| Clinical stage (UICC$^{+}$) | |
| IIa | 2 |
| III | 3 |
| IVb | 4 |

*ECOG PS, Eastern Cooperative Oncology Performance Status

$^{+}$Union for International Cancer Control TMN classification of malignant tumor 6$^{th}$ Edition

Table 3. Adverse events after the first cycle (Common Terminology Criteria for Adverse Events ver. 3.0)

| Toxicity | Dose level 1 (n=3) | | | | Dose level 0 (n=6) | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| Hematological | | | | | | | | |
| Leucocytopenia | 1 | 0 | 1 | 1 | 2 | 3 | 0 | 0 |
| Neutropenia | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Thrombocytopenia | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Anemia | 0 | 2 | 1 | 0 | 2 | 1 | 2 | 0 |
| Nonhematological | | | | | | | | |
| Nausea/vomiting | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| Vomiting | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Anorexia | 2 | 0 | 0 | 0 | 3 | 2 | 0 | 0 |
| Fatigue | 3 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| Diarrhea | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Stomatitis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Alopecia | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Creatinine | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 4. Docetaxel plus nedaplatin treatment in patients with metastatic or recurrent esophageal squamous cell carcinoma pretreated with cisplatin plus 5-fluorouracil.

| Docetaxel every 4 weeks | Nedaplatin every 4 weeks | No. of Patients | ORR (%) | PFS (Months) | OS (Months) | Reference |
|---|---|---|---|---|---|---|
| 30mg/m$^2$ (days 1 and 15) | 80 mg/m$^2$ (day 1) | 6 | 16.6 | N/S | N/S | Yoshioka et al.[15] |
| 50 mg/m$^2$ (days 1 and 8) | 50 mg/m$^2$ (day 1) | 12 | 0 | 2.0 | 7.8 | Akutsu et al.[16] |
| 60 mg/m$^2$ (day 1) | 80 mg/m$^2$ (day 1) | 20 | 25 | 3.2 | 6.0 | Nakajima et al.[20] |
| 50 mg/m$^2$ (day 1) | 70 mg/m$^2$ (day 1) | 6 | 33 | 4.4 | 9.5 | Our study (Recommend dose) |

Figure 1. Kaplan-Meier curve of nine patients.