Efficacy and Safety of Biweekly Docetaxel in Combination with Nedaplatin as Second-line Chemotherapy for Unresectable or Recurrent Esophageal Cancer

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Abstract. *Aim: In Japan, chemotherapeutic agents that have been approved for the treatment of esophageal cancer include cisplatin, nedaplatin, 5-fluorouracil, vindesine, and docetaxel. The aim of this study was to retrospectively investigate the efficacy and safety of docetaxel and nedaplatin combination chemotherapy for unresectable or recurrent esophageal cancer in an outpatient setting. Patients and Methods: In total, 33 patients with recurrent esophageal cancer after initial treatment (esophagectomy, chemotherapy, or chemoradiotherapy) were enrolled. Patients received docetaxel (30 mg/m^2 intravenously) and nedaplatin (30 mg/m^2 intravenously) on day 1 biweekly. The response rate (RR), time to treatment failure (TTF), overall survival time (OS), and toxicity were analyzed. Results: The median number of cycles of combination therapy was five (range=2-25 cycles). The RR was 21.2%, and the disease control rate was 60.6%. The median TTF was 71 days, and median OS was 211 days. The most frequent toxicities were leukopenia and anemia; non-hematological toxicities were generally mild. There were no treatment-related deaths. Conclusion: This outpatient combination chemotherapy was useful as second-line chemotherapy for unresectable or recurrent esophageal cancer.*

The incidence of esophageal cancer has been increasing in Japan; 23,119 new cases of esophageal cancer were diagnosed in 2011, and 11,543 patients died of this disease in 2013, accounting for 3.2% of all cancer deaths (1).

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Esophageal cancer has a poor prognosis and is well known for its aggressive invasiveness and metastasis to regional lymph nodes and distant organs. Therefore, combined-modality therapy, such as preoperative chemotherapy or chemoradiotherapy, is undertaken more frequently. Chemotherapeutic agents that have been approved for the treatment of esophageal cancer in Japan include cisplatin, nedaplatin, 5-fluorouracil (5-FU), vindesine, docetaxel, and paclitaxel. Among these agents, the combination of cisplatin with 5-FU is regarded as the reference chemotherapy regimen for metastatic or recurrent esophageal cancer, with a response rate (RR) of 30-40%. However, complete responses are rare, the median duration of response is generally short (4-6 months), and the median survival is only 6-10 months (2-7). Because an active regimen of second-line chemotherapy for esophageal cancer has not been developed, the prognosis of a patient who fails to respond to 5-FU plus platinum therapy remains poor.

Recent studies of combination chemotherapy using docetaxel and nedaplatin as second-line chemotherapy for patients with unresectable or recurrent esophageal cancer showed good results (8-10). However, a standard regimen for second-line chemotherapy is not yet established, and there is an urgent need for its development.

The aim of this study was to investigate the efficacy and toxicity of the combination of docetaxel and nedaplatin as second-line chemotherapy for patients with cisplatin-pretreated unresectable or recurrent esophageal cancer after surgery.

Patients and Methods

Patient eligibility. Eligibility criteria included histologically confirmed squamous cell carcinoma of the esophagus, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, and measurable lesions according to the Response Evaluation

Criteria in Solid Tumors (RECIST) criteria, version 1.1 (11). Inclusion also required either disease progression after one regimen of palliative chemotherapy with 5-FU plus cisplatin (FP) with or without radiation therapy, or disease recurrence within 12 months after neoadjuvant or adjuvant chemotherapy of a cisplatin-containing regimen. Patients had to have adequate bone marrow function (hemoglobin level ≥9 g/dl, white blood cell count ≥3,000/mm^3, neutrophil count ≥1,500/mm^3, and platelet count ≥100,000/mm^3), hepatic function (total bilirubin level ≤1.5 mg/dl and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤2.5-times the upper limit of normal), and renal function (serum creatinine level ≤1.5 mg/dl). Minimum patient age was 18 years, and minimum life expectancy was 12 weeks. Written, informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki.

Treatment schedule. The treatment was performed according to the following schedule: docetaxel (30 mg/m^2, intravenously) and nedaplatin (30 mg/m^2, intravenously) were administrated on day 1 every 2 weeks. The chemotherapy regimen was selected individually for each patient by the physician, who modified the dose of each agent according to the patient's medical condition and toxicity observed in first-line chemotherapy or previous courses. The initial dose was reduced by about 20% for older patients, those with poor PS, those with myelosuppression from first-line chemotherapy, or those recovering from infection. When grade 4 hematological toxicity, grade 3 or 4 nonhematological toxicity, or PS deterioration was seen, the dose was reduced by about 20% in the subsequent treatment course. The chemotherapy was continued until tumor progression or unacceptable toxicity, or until the patient refused to continue treatment.

Evaluation and statistical analysis. The pretreatment evaluation included a complete medical history, physical examination, and imaging of measurable disease. The complete blood cell count, serum chemistry, and physical condition were evaluated before each biweekly dose of chemotherapy. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.3.0 (12). The target lesions were measured using computed tomography (CT), which was performed every 4 weeks and at the end of treatment. Clinical response was evaluated in accordance with the RECIST, v.1.1. Definitions of response were: complete response (CR) – the disappearance of all target lesions; partial response (PR) – at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter; progressive disease (PD) – a 20% or greater increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesions; and stable disease (SD) – neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since the treatment started. The target lesions were determined from the measurable lesions outside the prior radiation field.

The overall survival time was calculated from the date of initiation of second-line chemotherapy to the date of death from any cause or confirmed survival. Progression-free survival was calculated from the date of the first administration of second-line chemotherapy to the date of disease progression or death from any cause. Overall and progression-free survival were analyzed using the Kaplan–Meier method.

Table I. *Patients' characteristics*.

	N
Total patients	33
Age, years	
Median (range)	67 (48-90)
Gender	
Male	27
Female	6
PS	
1	21
2	12
Histological type	
SCC	32
Other	1
Prior chemotherapy	
5-Fluorouracil+cisplatin (FP)	13
FP+radiation	20
Patient status	
Unresectable	18
Recurrence	15
Cycles of administration	
Median (range)	5 (2-25)

PS, Performance status; SCC, squamous cell carcinoma.

Table II. *Tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1. 1.(11).*

No. of patients	Response						
	CR	PR	SD	PD	NE	RR	DCR
33	3	4	13	12	1	21.2%	60.6%

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; RR, response rate; DCR, desease control rate.

Results

Patients' characteristics. From April 2007 to March 2012, 33 patients were enrolled in this study from the Department of Gastroenterological Surgery, Yamaguchi University Hospital (Yamaguchi, Japan).

The characteristics of the patients are summarized in Table I. The median age was 68 years (range=48-90 years), with 27 men and six women. The majority of the patients (63.6%) had ECOG PS of either 0 or 1. The histology of most cases (97.0%) was squamous cell carcinoma.

There were 15 cases (45.5%) of postoperative recurrence and 18 (54.5%) of unresectable disease. As a result, all cases were far-advanced cases. With regard to prior therapies, most cases (20/33, 60.6%) had undergone concurrent chemoradiotherapy with FP.

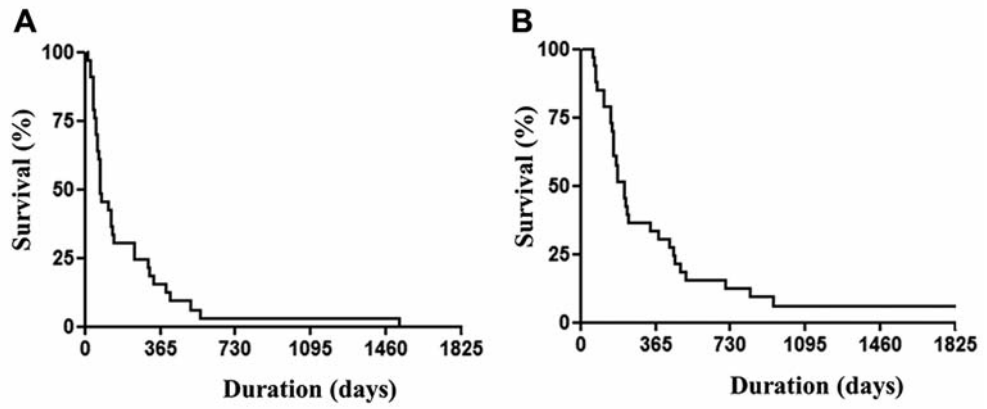

Figure 1. *Time to treatment failure (TTF) (A) and overall survival (OS) rate (B). In this study, the median TTF was 71 days, and median OS was 211 days.*

Response and survival. Thirty-two out of the 33 patients (97.0%) were assessable for response; the one patient not assessable discontinued the study because of side-effects. All efficacy data are reported using the intention-to-treat principle. Three patients had CR. The RR (defined as the percentage of patients who achieved CR and PR due to a therapeutic intervention) was 21.2%, and the disease control rate (DCR; defined as the percentage of patients who achieved CR, PR, and SD due to a therapeutic intervention) was 60.6% (Table II). In this study, median time to treatment failure (TTF) was 71 days, and median overall survival time was 211 days (Figure 1).

Toxicity. The toxicities associated with the treatment are shown in Tables III and IV. All cases were assessable for safety. The treatment was well tolerated, and no deaths occurred due to toxicity. The most common toxic effects were anemia, leukopenia, neutropenia, thrombocytopenia, nausea, anorexia, fatigue, and alopecia. The hematological toxicities of grade 3 or higher were as follows: four cases (12.1%) of leukopenia, four cases (12.1%) of neutropenia, four cases (12.1%) of anemia, and three cases (9.0%) of thrombocytopenia. In all of four cases, the therapeutic intervention was not necessary. Anaphylaxis occurred in one case (3.0%), and other non-hematological toxicities of grade 3 or higher were not seen.

Table III. *Hematotoxicity evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.3.0 (12).*

Adverse event	Cases		Grade, n				>G3 (%)
Total patients (n=33)	n	%	1	2	3	4	
Leukopenia	25	75.8	6	15	4	0	12.1
Neutropenia	24	72.7	7	13	4	0	12.1
Anemia	30	90.9	12	14	4	0	12.1
Thrombocytopenia	14	50	7	3	3	0	9

Table IV. *Non-hematological toxicity evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.3.0 (12).*

Adverse event	Cases		Grade, n				>G3 (%)
Total patients (n=33)	n	%	1	2	3	4	
Nausea	9	27.3	7	2	0	0	0
Anorexia	14	42.4	11	3	0	0	0
Fatigue	21	63.6	12	9	0	0	0
Alopecia	4	12.1	4	0	0	0	0
Anaphylaxis	1	3	0	0	0	1	3

Discussion

For patients with esophageal cancer who have failed to respond to FP as first-line chemotherapy, there are few drugs that are recommended for use as second-line therapy. However, docetaxel and nedaplatin have recently been recommended for use in such patients.

In this study, the efficacy and toxicity of the combination of docetaxel and nedaplatin were investigated as second-line chemotherapy for patients with cisplatin-pretreated unresectable or recurrent esophageal cancer after surgery in the outpatient setting. There are few reports of combination antitumor activity with docetaxel and nedaplatin as a second-line regimen for advanced esophageal cancer in previous studies. The RR was 11-36.3%, and the median survival time was 5.9-8.5 months (8, 9, 13-15). This study was performed in the outpatient setting because this combination chemotherapy seemed to be not only effective but also favorable in maintaining a high quality of life.

This regimen showed a RR of 21.2% and a DCR of 60.6%, with a median TTP and overall survival of 71 and 211 days, respectively. This combination therapy seems to be a useful regimen as second-line chemotherapy in cisplatin-pretreated refractory esophageal cancer.

In this study, nephrotoxicity and non-hematological toxicities such as nausea of grade 3 or higher were not seen. Although the most common toxicities were anemia, leukopenia, neutropenia, and thrombocytopenia, all cases were well controllable. Nedaplatin is a second-generation platinum agent that does not require hydration, and several *in vitro* studies have demonstrated that nedaplatin has equivalent antitumor activity to cisplatin, with less nephrotoxicity (16, 17). Consistent with the results of the *in vitro* studies, nedaplatin in combination with other agents (*e.g.* docetaxel) has shown modest antitumor activity for several human tumor types, with less nephrotoxicity and gastrointestinal toxicity (18-21). Because pre-treated patients have poorer tolerance to second-line chemotherapy, a less toxic treatment is desirable, and the present regimen was well tolerated.

Although esophageal cancer has an especially poor prognosis, few drugs have been developed for its treatment. One of the candidate new drugs was S-1, which led to a good response for squamous cell carcinoma of the head and neck (22, 23). Molecular targeting drugs such as cetuximab represent other potentially effective agents (24-27). Incorporating these newly-developed drugs as part of additional new regimens should be considered.

In conclusion, docetaxel and nedaplatin combination chemotherapy in the outpatient setting is safe and effective as second-line chemotherapy for cisplatin-pretreated unresectable or recurrent esophageal cancer. However, the development of more effective therapy is required to improve the prognosis of esophageal cancer patients.

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