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Original Article

Randomized Phase II Study to Comparing Docetaxel/Nedaplatin versus Docetaxel for 5-Fluorouracil/Cisplatin Resistant Esophageal Squamous Cell Carcinoma

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Purpose: To compare efficacy and safety of dual docetaxel/nedaplatin treatment versus docetaxel alone as second-line chemotherapy for advanced esophageal cancer.
Methods: In all, 36 patients with metastatic and/or recurrent esophagus squamous cell carcinoma resistant to first-line chemotherapy (fluorouracil/cisplatin) were recruited from 2011 to 2018 and randomized into two groups. Treatment response and survival were compared between the docetaxel/nedaplatin (60/80 mg/m^2/day) group and docetaxel (70 mg/m^2/day) group. Treatment was repeated every 3 weeks until tumor progression. Patients were followed up until March 2019 or death.
Results: The frequency of Grade 3 or higher adverse events in the docetaxel/nedaplatin group (58.8%) was higher compared with the docetaxel group (26.3%) (P = 0.090). We found a treatment response rate of 52.9% and 36.8% and a median survival of 8.9 and 7.0 months in the docetaxel/nedaplatin-treated and docetaxel-treated group, respectively (P = 0.544).
Conclusion: No significant survival advantage was found for docetaxel/nedaplatin-treated patients, although there was an increased frequency of high-grade adverse events compared to docetaxel-treated patients. Because of the limited cohort size, a Phase III study based on our findings is not warranted to assess the clinical impact of docetaxel/nedaplatin treatment. This trial is registered with the University Hospital Medical Information Network (UMIN 000005877).

Keywords: docetaxel, nedaplatin, esophageal squamous cell carcinoma, second-line treatment, Phase II study

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Introduction

Despite improvements to approaches and techniques for early diagnosis and minimally invasive surgery, the 5-year overall survival of patients with recurrent esophageal cancer remains approximately 30%–40% in Japan.[1–6] In fact, survival from recurrent esophageal cancer is worse than that of other gastrointestinal cancers, such as gastric and colorectal cancer.[7–10] Therefore, development of a standard chemotherapy for treatment of such resistant cases is vital to improve overall survival for patients with advanced esophageal cancer.

Treatment response of first-line chemotherapy, consisting of fluorouracil plus cisplatin (FP), is favorable[11,12];

however, a standard, effective second-line chemotherapy has not yet been established. As docetaxel is a key drug for second-line chemotherapy, several combination regimens have been developed using docetaxel in the last 10 years.[13,14] In addition, studies have reported that regimens consisting of docetaxel plus nedaplatin confer a survival advantage for patients with recurrent and/or metastatic esophageal cancer.[15–23]

Therefore, the purpose of this study was to determine whether there are clinical advantages of a dual docetaxel plus nedaplatin regimen. We compared the effects of a docetaxel/nedaplatin regimen versus a regimen of docetaxel alone through a prospective randomized Phase II study in a Japanese cohort.

Materials and Methods

Patients

Patients with determinable histologically proven squamous cell carcinoma of the esophagus were enrolled in this study. Recruitment eligibility was based on the following: (i) between 20 and 80 years of age; (ii) an Eastern Cooperative Oncology Group Performance Status Grade of 0–2; (iii) adequate bone marrow function as determined by hemoglobin level (>9 g/dL), neutrophil count (>1500/mm^3) and platelet count (>100000/mm^3); (iv) adequate hepatic function as defined by total bilirubin level (<1.5 mg/dL) and aspartate aminotransferase and alanine aminotransferase levels (<2.5× the upper limit of normal); (v) adequate renal function as determined by serum creatinine level (<1.5 mg/dL); and (vi) the absence of other active cancers. The present study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Toho University in Japan (23004, 2610723004, M1905618002). We obtained informed consent from all patients prior to their participation in our study, and recruitment ran from 2011 to 2018. Originally, a total of 43 patients were planned to be enrolled for each treatment group; however, the study was ended in March 2019 because of the very low pace of enrollment. We recruited a total of 36 patients for our study.

Treatment Regimens and Evaluation of Clinical Course

Enrolled patients were randomized to receive a dual docetaxel plus nedaplatin regimen or a regimen consisting of docetaxel alone though cluster randomization.[24] As a second-line treatment from day 1, patients in the docetaxel/nedaplatin group were treated with 60 mg/m^2/day docetaxel combined with 80 mg/m^2/day nedaplatin, whereas patients from the docetaxel group received 70 mg/m^2/day docetaxel. Treatment cycles were repeated every 3 weeks (**Fig. 1**) for as many cycles as possible, after which efficacy was evaluated. All patients were evaluated either monthly or bimonthly. If the tumor showed progressive disease and/or development of a severe adverse event greater than Grade 4, chemotherapy ceased. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (v4.0), and effects were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Overall survival was measured from the first day of initial treatment to date of patient death. Time to progression was measured from the first day of initial treatment to the date of estimated progression according to RECIST criteria. All patients in our study were followed up until March 2019 or death.

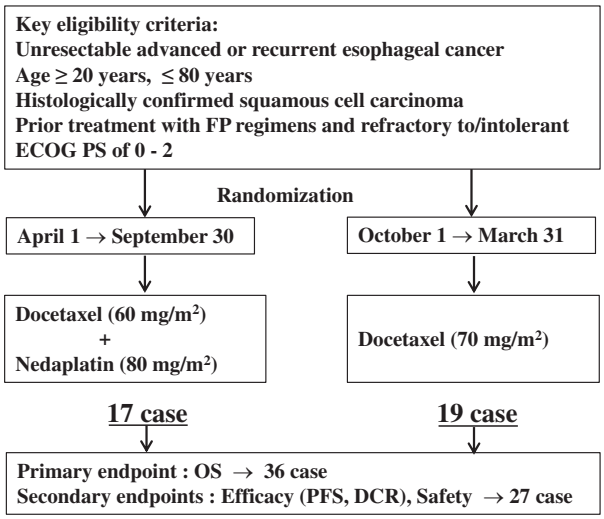
Statistical Analyses

Paired groups were compared using Fisher's exact probability test, and survival curves were calculated by Kaplan–Meier product limit estimate. Survival differences between groups were analyzed by log-rank test. Statistical calculations were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A P value less than 0.05 was considered significant.

Results

Patient characteristics and treatment randomization

Study design and algorithm for cluster randomization and assignation of patients with metastatic and/or recurrent esophageal squamous cell carcinoma to one of two chemotherapy groups are shown in **Fig. 1**. Between May 2011 and March 2018, 36 patients with relapsed and/or metastatic esophageal squamous cell carcinoma were enrolled in this randomized study (**Supplement 1**, All Supplements are available online.). All patients received FP therapy before enrollment, after which they were assigned to one of two groups based on treatment regimen; 17 patients received a dual docetaxel/nedaplatin regimen, whereas 19 patients received a regimen consisting of docetaxel alone. Our study cohort consisted of 32 men and 4 women with a median age of 64.3 years (range: 42–78 years) (**Table 1**). Among the 36 patients, 24 patients (67%) were classified as recurrent after



ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; DCR, disease control rate;

Fig. 1 Design study and cluster randomization of patients with metastatic and/or recurrent esophageal squamous cell carcinoma to two second-line chemotherapy groups, a docetaxel plus nedaplatin group and a docetaxel group.

standard esophagectomy and 12 patients (33%) were considered to have initially unresectable cases. Sites of relapse or metastasis were lymph node (n = 23), esophagus (n = 9), pleura (n = 3), liver (n = 3), lung (n = 3), and bone (n= 3) (**Table 1**). Of the 36 enrolled patients, treatment response was assessed in 27 patients (**Fig. 1**).

Treatment response and adverse events

The median number of treatment cycles for both regimen groups was three, ranging from 1 to 8 cycles in the docetaxel plus nedaplatin group and 2–21 cycles in the docetaxel group (**Table 1**). Of the 27 patients evaluated for treatment response (75% of total cohort), 13 patients were from the docetaxel/nedaplatin-treated group and 14 patients were from the docetaxel-treated group. The other nine patients of our study were not adequately treated because of the progression of subjective symptoms and/or side effects.

Treatment response is shown in **Table 2**. In the docetaxel/nedaplatin group, we found that one patient showed a complete response and two exhibited a partial response; furthermore, the disease was unchanged in six patients and there was evidence of disease progression in four patients. In this dual-treatment group, the response rate was 18% and the disease control rate was 53% (**Table 2**). In the docetaxel group, one patient exhibited a complete response, whereas no change was found in six patients and disease progression occurred in the remaining seven patients. In this group, we found that the response rate was 5.3% and the disease control rate was 37%. The median duration of survival was 271 days for patients in the docetaxel/nedaplatin-treated group and 213 days for patients in the docetaxel-treated group.

Survival comparison between groups

As shown in **Fig. 2**, survival curves were generated for the two groups and compared. We found that 1-year survival was 41.2% for the docetaxel/nedaplatin group and 31.5% for the docetaxel group. Importantly, there was no significant difference between the two groups regarding patient survival (P = 0.544). In the docetaxel/nedaplatin group, two patients survived for over 3 years. Both patients underwent a radical metastasectomy after confirmation of partial treatment response, and no recurrence has been observed to date.

We next assessed adverse events in our groups (**Table 3**), and found that the frequency of Grade 3 and Grade 4 adverse events was higher in the docetaxel/nedaplatin-treated group compared with that found in the docetaxel group (59% versus 26%, respectively; P = 0.090). Grade 3 or Grade 4 neutropenia was also more frequently observed in the docetaxel/nedaplatin group compared with the docetaxel group (47% versus 26%, respectively; P = 0.299); however, we found no evidence of statistically significant differences in the frequency of adverse events between our two groups.

Discussion

The purpose of this prospective randomized study was to compare treatment response, adverse events, and prognosis in a dual-treatment docetaxel/nedaplatin group versus a docetaxel-treated group as second-line treatment in patients with advanced/recurrent esophageal squamous cell carcinoma. We found that patients in the docetaxel/nedaplatin group showed better treatment response and a slightly better overall survival compared with patients in the docetaxel group; however, the differences were not statistically significant.

A number of previous reports evaluated docetaxel plus nedaplatin combination therapy as second-line chemotherapy for esophageal cancer (**Supplement 2**).[15–23] It was found that docetaxel alone or in combination chemotherapy, consisting of docetaxel plus nedaplatin, is an effective and safe regimen for patients with relapsed or metastatic esophageal cancer. In these previous studies,

Table 1 Characteristics of the patients of the two groups, chemotherapy cycles, and response

	Docetaxel + nedaplatin group (n = 17)	Docetaxel group (n = 19)	P-value
Age (years)	63.9 (42–78)	64.7 (44–76)	
Sex			NS
Male:female	16:1	16:3	
Prior treatment			
Resected cases	12	12	
Unresected cases	5	7	
Site of relapse/metastasis			NS
Esophagus	5	4	
Lymph node	11	12	
Pleura	3		
Liver	2	1	
Lung	2	1	
Bone	2	1	
Chemotherapy cycles			NS
1	2	0	
2–4	11	13	
>5	4	6	

Fisher's exact test was used for the statistical analysis. NS: not significant

Table 2 Comparison of treatment response in the two groups

	Docetaxel + nedaplatin group (n = 13)	Docetaxel group (n = 14)	P-value
CR	1 (5.9%)	1 (5.3%)	0.934
PR	2 (11.8%)	0 (0%)	0.124
SD	6 (35.3%)	6 (31.6%)	0.813
PD	4 (23.5%)	7 (36.8%)	0.387
CR + PR + SD	9 (52.9%)	7 (36.8%)	0.332
NE	4 (23.5%)	5 (26.3%)	0.847

Fisher's exact test was used for the statistical analysis. CR: complete response; NE: not evaluated; PD: progressive disease; PR: partial response; SD: stable disease

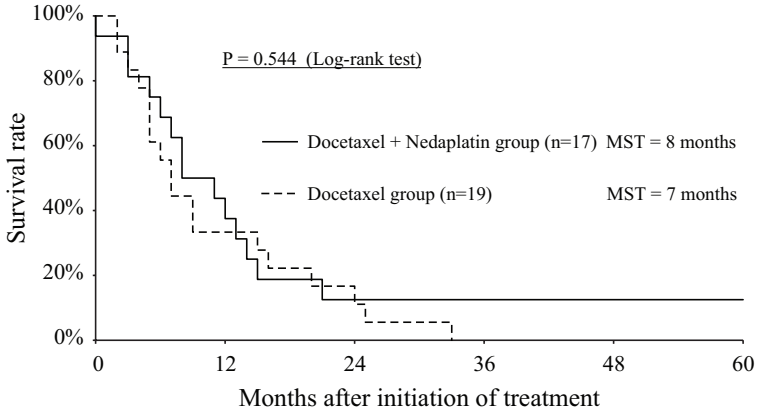


Fig. 2 Patient survival after treatment with docetaxel and nedaplatin or docetaxel alone.

it was found that a regimen consisting of docetaxel alone had a response rate of 20.0% and a disease control rate of 51–59%, with a median overall survival of 4.7–5.2 months.[13,14] For comparison, a dual-treatment regimen using docetaxel/nedaplatin showed a response rate of 21–27% and a disease control rate of 52–80%, with a

Table 3 Adverse events of the treatments

	Docetaxel + nedaplatin group (n = 17)				Docetaxel group (n = 19)				P-value
	G1	G2	G3	G4	G1	G2	G3	G4	
Neutrophils			5	3			1	4	
Hemoglobin			1						
Febrile neutropenia			3				2		
Nausea	3		1		1				
Diarrhea	2	1	2		3				
Anorexia			1						
Allergic reaction			1						
Grades 3–4 adverse events			10 (58.8%)				5 (26.3%)		0.0895

Fisher's exact test was used for the statistical analysis.

median overall survival of 5.9–11.4 months.[15–23] Our current study also showed a similar response rate and median survival in both groups, although the docetaxel/nedaplatin regimen had a slightly better clinical impact compared with treatment using docetaxel alone. Nevertheless, both regimens are useful as second-line chemotherapies in cisplatin-pretreated refractory esophageal cancer.

In the current study, nephrotoxicity was not seen in either group, but we had cases of Grade 3 and Grade 4 neutropenia and febrile neutropenia. Non-hematological toxicities of Grade 3 or higher were also seen. Although the most common toxicities in our patients were anemia, nausea, diarrhea, anorexia, and allergic reaction, all cases were effectively managed. It should be noted that because a docetaxel/nedaplatin regimen has a high probability of adverse events, patient monitoring and evaluation are important. In addition, we report two long-term survivors in the docetaxel/nedaplatin group, both of whom received surgery. Although the possibility of long-term survival is limited, a combination of chemotherapy and surgery for metastatic lesions confers the best possible chance to achieve long-term survival in patients.[25]

Another new drug candidate for second-line chemotherapy for esophageal cancer is nivolumab. Recently, the Japanese Ministry of Health, Labor and Welfare has approved nivolumab for use in second-line chemotherapy for patients with unresectable advanced and/or recurrent esophageal cancer. Because nivolumab has shown a better prognostic impact compared with taxane in second-line chemotherapy,[26] at least in FP-resistant cases, we predict a revised treatment approach consisting of nivolumab for second-line chemotherapy, followed by docetaxel or paclitaxel for use in third-line treatment. As we found a greater number of adverse events in patients receiving docetaxel/nedaplatin combination chemotherapy as well as no statistically significant improvement in prognosis compared with that found in patients receiving docetaxel alone, the findings from our study do not warrant the need to conduct a Phase III trial.

Conclusion

Although our current randomized study had a limited number of patients, we found that treatment with docetaxel plus nedaplatin resulted in a slight clinical difference compared with treatment using docetaxel alone. With the emergence of nivolumab and its potential use in second-line treatment, docetaxel-only treatment may be relegated as a third-line regimen for cases with unresectable advanced and/or recurrent esophageal squamous cell carcinoma after treatment failure with FP and nivolumab.

Compliance with Ethical Standards

The present study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Toho University (23004, 2610723004, M1905618002). We obtained informed consent from all participants.

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Disclosure Statement

The authors have no conflict of interest to declare.

References

1) Watanabe M. Recent topics and perspectives on esophageal cancer in Japan. JMA J 2018; **1**: 30–9.
2) Cancer statistics in Japan, Cancer Information Service. Center of cancer control and information services NCC. [cited 2018 Apr 10]. Available from:. Available from https:// ganjoho.jp/en/professional/statistics/table_download.html.
3) Ozawa S. Minimally invasive surgery for esophageal cancer in Japan. Ann Thorac Cardiovasc Surg 2020; **26**:179–183.
4) Udagawa H. Past, present, and future of three-field lymphadenectomy for thoracic esophageal cancer. Ann Gastroenterol Surg 2020; **4**: 324–30.
5) Matsubara H. Advances in the surgical treatment of esophageal cancer since 1965. Ann Gastroenterol Surg 2020; **4**: 243–49.
6) Suzuki T, Yajima S, Okamura A, et al. Clinical impact of preoperative serum p53 antibody titers in 1487 patients with surgically treated esophageal squamous cell carcinoma: a multi-institutional study. Esophagus 2020; [Epub ahead of print, July 26, 2020.
7) Parry K, Visser E, van Rossum PSN, et al. Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent. Ann Surg Oncol 2015; **22**: 1292–1300.
8) Ito S, Ohashi Y, Sasako M. Survival after recurrence in patients with gastric cancer who receive S-1 adjuvant chemotherapy: exploratory analysis of the ACTS-GC trial. BMC Cancer 2018; **18**: 449.
9) Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020; **25**: 1–42.
10) Su XD, Zhang DK, Zhang X, et al. Prognostic factors in patients with recurrence after complete resection of esophageal squamous cell carcinoma. J Thorac Dis 2014; **6**: 949–57.
11) Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. J Clin Oncol 2003; **21**: 4592–6.
12) Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012; **19**: 68–74.
13) Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 2004; **15**: 955–9.
14) Song Z, Zhang Y. Second-line docetaxel-based chemotherapy after failure of fluorouracil-based first-line treatment for advanced esophageal squamous cell carcinoma. Onco Targets Ther 2014; **7**: 1875–81.
15) Osaka Y, Takagi Y, Hoshino S, et al. Combination chemotherapy with docetaxel and nedaplatin for recurrent esophageal cancer in an outpatient setting. Dis Esophagus 2006; **19**: 473–6.
16) Yoshioka T, Sakayori M, Kato S, et al. Dose escalation study of docetaxel and nedaplatin in patients with relapsed or refractory squamous cell carcinoma of the esophagus pretreated using cisplatin, 5-fluorouracil, and radiation. Int J Clin Oncol 2006; **11**: 454–60.
17) Kanai M, Matsumoto S, Nishimura T, et al. Retrospective analysis of 27 consecutive patients treated with docetaxel/nedaplatin combination therapy as a second-line regimen for advanced esophageal cancer. Int J Clin Oncol 2007; **12**: 224–7.
18) Fujita Y, Hiramatsu M, Kawai M, et al. Evaluation of combined docetaxel and nedaplatin chemotherapy for recurrent esophageal cancer compared with conventional chemotherapy using cisplatin and 5-fluorouracil: a retrospective study. Dis Esophagus 2008; **21**: 496–501.
19) Nakajima Y, Suzuki T, Haruki S, et al. A pilot trial of docetaxel and nedaplatin in cisplatin-pretreated relapsed or refractory esophageal squamous cell cancer. Hepatogastroenterology 2008; **55**: 1631–5.
20) Jin J, Xu X, Wang F, et al. Second-line combination chemotherapy with docetaxel and nedaplatin for Cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma. J Thorac Oncol 2009; **4**: 1017–21.
21) Akutsu Y, Shuto K, Kono T, et al. A phase 1/11 study of second-line chemotherapy with fractionated docetaxel and nedaplatin for 5-FU/cisplatin-resistant esophageal squamous cell carcinoma. Hepatogastroenterology 2012; **59**: 2095–8.
22) Matsumoto H, Hirabayashi Y, Kubota H, et al. A combined therapy with docetaxel and nedaplatin for relapsed and metastatic esophageal carcinoma. Anticancer Res 2012; **32**: 1827–31.
23) Kanekiyo S, Takeda S, Nakajima M, et al. Efficacy and safety of biweekly docetaxel in combination with nedaplatin as second-line chemotherapy for unresectable or recurrent esophageal cancer. Anticancer Res 2016; **36**: 1923–7.
24) https://en.wikipedia.org/wiki/Cluster_randomised_controlled_trial.
25) Komatsu H, Izumi N, Tsukioka T, et al. Impact of perioperative chemotherapy on prognosis of patients with esophageal carcinoma undergoing pulmonary metastasectomy. Ann Thorac Cardiovasc Surg 2019; **25**: 253–9.
26) Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019; **20**: 1506–17.