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/m²/day) group and docetaxel (70 mg/m²/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 (UMIN000005877).

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

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. In fact, survival from recurrent esophageal cancer is worse than that of other gastrointestinal cancers, such as gastric and colorectal cancer. 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;
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/mm³) and platelet count (>100000/mm³); (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/m²/day docetaxel combined with 80 mg/m²/day nedaplatin, whereas patients from the docetaxel group received 70 mg/m²/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 the 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 assignment 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
October 1- In the case Supplement 2 complete response, whereas no change was found in six (rate was 18% and the disease control rate was 53%). In this dual-treatment group, the response in four 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). 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,
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.\textsuperscript{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
median overall survival of 5.9–11.4 months. 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.

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, 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.
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