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ORIGINAL ARTICLE

A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer

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Abstract
Objective The objective of this study was to evaluate the efficacy and toxicity of docetaxel and cisplatin combination chemotherapy in patients with metastatic esophageal cancer.
Methods Patients with untreated metastatic squamous cell esophageal cancer, which was histologically proven with at least one measurable lesion, were eligible for the study. Docetaxel 70 mg/m^2 and cisplatin 70 mg/m^2 were intravenously given on day 1 of 21 days schedule.
Results From December 2004 to December 2007, total of 39 patients (M/F = 39/0) were enrolled. The median age was 65 years. Thirty-four patients were evaluable for response. There were 3 (7.7%) complete remission, 10 (25.6%) partial remission, 11 (28.2%) stable disease, and 10 (25.6%) progression disease. The objective tumor response rate was 33.3% in intention-to-treat (ITT). Median PFS was 5.0 months and median survival was 8.3 months. Median number of cycles administered was 3. The relative dose intensity of docetaxel and cisplatin was 92 and 91%, respectively. This treatment was comparatively tolerated with grade 3/4 neutropenia in 20.5%/10.3%, grade 3 infection in 2.6% of patients.
Conclusion Docetaxel plus cisplatin combination chemotherapy showed promising antitumor activity with manageable toxicities in patients with metastatic squamous esophageal cancer.

Keywords Esophageal cancer · Docetaxel · Cisplatin · Combination chemotherapy

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Introduction

Esophageal cancer is the ninth most common cancer in male population in Korea [1]. It was estimated that 1,864 new cases of esophageal cancer were reported and 1,434 deaths occurred in Korea in 2005 [1]. Although half of the patients with esophageal cancer initially present with locoregional disease amenable to radical surgery or radiation-based therapy, most patients eventually develop metastatic disease with or without local recurrence [2]. Chemotherapy plays a major role in palliative therapy and remains to be the primary mode of treatment for the recurrent or metastatic esophageal cancer. Most of the chemotherapeutic agents, such as cisplatin, 5-fluorouracil (FU), bleomycin, and etoposide have been evaluated previously in esophageal cancer. The majority of the trials performed were in small numbers of patients with reported response rates from 15 to 40% [3]. The response was usually of short duration and there was no survival benefit with single-agent chemotherapy. Combination chemotherapy has slightly improved the results in terms of duration of response (3–6 months), but still there was little improvement in overall survival. Therefore, the identification of new active agents is essential to prolong the survival.

The search for more active agents has prompted trials of taxanes in esophageal cancer. Ajani et al. [4] reported a 34 and 28% response rate in paclitaxel-treated patients with adenocarcinoma and squamous cell carcinoma of the esophagus, respectively. Polee et al. [5] also reported a 51% response rate in patients with esophageal cancer treated with weekly paclitaxel and cisplatin. The response rate with a single-agent docetaxel is about 18–25%, and is similar to the single-agent activity observed with the most active conventional drugs used in this disease, such as 5-FU, cisplatin, and paclitaxel [6–8]. Korean data of cisplatin and 5-FU combination chemotherapy in advanced squamous esophageal cancer suggested that the responser rate was 39% and the median time of survival was 9 months [9]. Bleiberg et al. [10] reported randomized phases II trial of 5-fluorouracil and cisplatin versus cisplatin alone in advanced esophageal cancer. The response rate was 61% and enrolled patients was 142.

Docetaxel has shown antitumor activity against various common cancers in clinical studies [11]. Clinical trials of single-agent docetaxel have been reported in patients with esophageal cancer [12, 13]. However, there are few studies of combination chemotherapy with docetaxel and cisplatin. Therefore, we evaluated the efficacy of docetaxel and cisplatin combination chemotherapy in Korean patients with squamous cell esophageal cancer.

Patients and methods

This study was multicenter, single arm, open-labeled phase II study. Totally four centers participated to this study (Dongsan Medical Center, Yeungnam University Hospital, Daegu Catholic University Hospital, Ulsan University Hospital).

Patients

All patients involved in the current study had histologically confirmed squamous cell carcinoma of the esophagus. Eligible patient had to have metastatic, or recurrent disease after curative surgical therapy with unidimensionally measurable disease (i.e., at least 2 cm as the longest diameter on CT scan, chest X-ray, or physical examination). Patients were required to be 18–75 years of age, with a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, and have adequate bone marrow function (absolute neutrophil count $\geq$2,000 per μL, and platelet count $\geq$100,000 per μL), liver function (total bilirubin higher that the upper limit of the normal, AST, ALT $\leq$2.5 times upper limit of the normal range, ALP $\leq$5 times upper limit of the normal range), and renal function (serum creatinine less than the upper limit of the normal or creatinine clearance $\geq$60 mL/min). Prior chemotherapy was not allowed. The patients were able to understand the study and provide the written informed consent.

The exclusion criteria were: recent congestive heart failure, angina, arrhythmia and acute myocardial infarction within 6 months, severe neurologic impairment or mental disorder, active infection; uncontrolled diabetes mellitus, pregnancy or lactation, women of childbearing age unless using effective contraception, brain metastasis, and second primary malignancy within 5 years except skin cancer or cervix carcinoma in situ.

Treatment

Docetaxel (Taxotere®, sanofi-aventis, Korea) 70 mg/m^2 was given as a 1-h intravenous infusion on day 1 of each cycle, beginning 3 h before cisplatin. Cisplatin 70 mg/m^2 was also given by intravenous infusion over 1 h. The chemotherapy was given every 21 days and continued until disease progression, patient refusal, or unacceptable toxicity, to a maximum of six cycles. All patients were premedicated with dexamethasone 8 mg orally twice a day for 1 day, starting 1 day prior to docetaxel administration to prevent hypersensitivity reactions. To induce forced diuresis, the patients received at least 3,000 mL hydration (mannitol infusion with magnesium sulfate and potassium chloride). Antiemetic treatment was routinely given before each cycle of chemotherapy.

Dose modifications

On the first day of each cycle, patients were required to have an absolute neutrophil count (ANC) $\geq$1,500 per μL, and platelet count $\geq$75,000 per μL to start chemotherapy. If the treatment was to be delayed due to hematologic toxicity, both drugs were held until the recovery of the toxicity. If hematologic adverse events did not recover to the level of neutrophil count $\geq$1,500 per μL, and platelet count $\geq$75,000 per μL after 2 weeks of delayed treatment, patients were excluded from the study.

Dose modifications were made for treatment-related adverse events, for grade 2 and higher. Docetaxel and cisplatin treatments were delayed in the case of grade 2 or higher hematologic toxicity. The dose of docetaxel was reduced by 25% for grade 4, neutropenia lasting $\geq$7 days, febrile neutropenia $\geq$grade 3, neutropenic sepsis or for thrombocytopenia (<25,000 per μL) requiring platelet transfusion. If the toxicity reappeared with more than a 50% reduction from the starting dose in consecutive cycles, treatment will be stopped. We permitted to use of G-CSF in the case of febrile neutropenia.

In the case of renal toxicity, treatment was continued at the same dose when patients experienced creatinine level

<1.5 mg/dL. If the creatinine level was 1.5–2.5 mg/dL and recovered within 2 weeks, cisplatin was restarted at the dose of 50%. If the creatinine level was over 2.5 mg/dL and recovered within 2 weeks, cisplatin was discontinued. For patients with grade 2 neurologic toxicities which recovered to ≤grade 1 within 2 weeks, drugs were administered as full dose. In patients with grade 3 and recovered to ≤grade 1 toxicities, both drugs were given at 75% of the planned dose. For patients with grade 4 neuropathy, no further therapy was administered. If a patient developed a bilirubin level above the upper limit of normal (ULN), treatment was delayed up to 2 weeks; if recovery did not occur within 2 weeks, the patient was withdrawn from the study. Abnormal elevations in AST/ALT or ALP should result in dose modification of docetaxel as: AST/ALT $\leq 1.5 \times$ ULN and ALP ≤ 5, 100% of docetaxel; $1.5 <$ AST/ALT ≤ 5 and $2.5 <$ ALP ≤ 5, 75%; AST/ALT > 5 or ALP > 5, delayed to ≤grade 1 toxicities and treatment was delayed up to 2 weeks.

Study assessments

The base line screening assessments included a medical history, physical examination, CBC, serum chemistry, electrolytes, LDH, coagulation battery, pregnancy test, ECG, chest X-ray, and CT scan of the chest and abdomen within 2 weeks prior to entry onto the study. All patients were reviewed prior to the commencement of each cycle of chemotherapy. For the first cycle of chemotherapy, assessments were performed on days 1, 8, and 15 of the chemotherapy, which included physical examination, CBC, chemistry, electrolytes, and chest X-ray. Tumors were measured every two cycles until tumor progression. The tumor responses were evaluated according to RECIST [14]. We confirmed responses 4 weeks after a previous response evaluation. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical analysis

A Simon's two stage phase II design was used. The treatment program was designed to reject response rates of 20% and to provide a significance level of 0.05 with a statistical power of 80% to assess the activity of the regimen at a 40% response rate [15]. The upper limit for a first-stage treatment rejection was 4 responses among 18 evaluable patients; the upper limit of second-stage rejection was 10 responses among 33 evaluable patients. Assuming a drop-out rate of 20%, a total of 39 patients were required. All enrolled patients were included in the intention-to-treat (ITT) analysis of efficacy. Analysis of time to progression (TTP) and survival analysis were performed by the Kaplan–Meier method. The TTP was calculated from the initiation of chemotherapy to the date of the disease progression, while overall survival was measured from the initiation of chemotherapy to the date of the last follow-up or death. Statistical data were obtained using an SPSS 11.0 software package (SPSS Inc. Chicago, IL, USA).

Results

From December 2004 to December 2007, a total of 39 patients were enrolled from four centers. The characteristics of the patients are summarized in the Table 1. All the thirty-nine patients enrolled were males. The median age was 65 years. The most common metastatic lesions were lymph nodes (51.3%), lung (15.4%), liver (5.1%), and bone (5.1%). No patients had received prior chemotherapy or radiotherapy.

Thirty-nine patients were assessable for toxicity and 34 for the tumor response. At the time of last analysis, 29 patients had died and eight patients were still being treated. The median follow-up time for all patients was 7.5 months (95% CI: SD ± 9.82 months).

Delivered treatment

A total of 133 cycles were delivered to patients. Median cycle was 3.0 (range 1–6). The median dose of docetaxel and cisplatin was 67.9 mg/m^2/cycle, which was 91.8% of planned dose intensity of the protocol (Table 2). Calculation of actual or received dose intensity was done according to the method by Longo et al. [16].

Table 1 Patients characteristics ($n = 39$)

Characteristics	Number of patients (%)
Median age in years (range)	65 (75–46)
Male/female	39/0
ECOG performance status	
0	2 (5)
1	35 (90)
2	2 (5)
Metastatic sites[a]	
Lymph node	21 (54)
Lung	6 (15)
Stomach	5 (13)
Liver	2 (5)
Bone	2 (5)
Superior vena cava	1 (3)
Thyroid	1 (3)

[a] Sites are overlapping

Table 2 Duration of administration and dose intensity

Treatment variables	
Number of cycles	
Total	133
Median (range)	3.0 (0–6)
Dose intensity of docetaxel (mg/m^2/cycle)	
Median (%)	67.9 (91.8)
Dose intensity of cisplatin (mg/m^2/cycle)	
Median (%)	67.9 (91.8)

In 13 patients, treatment was discontinued due to disease progression, and treatment was discontinued in one patient due to toxicity (pneumonia). Moreover, four patients refused further treatment (intolerance to treatment in two patients and cause not defined in two patients).

Response to treatment and survival

Thirty-four (87.1%) of the enrolled patients were assessable for response. The remaining five patients refused further treatment prior to response evaluation because treatment was stopped due to toxicity (1 patient) or patient's refusal to further treatment (4 patients). We used 5-fluorouracil/cisplatin (8 patients), irinotecan/cisplatin (6 patients), capecitabine/cisplatin (1 patient) for second-line regimens.

There were 3 complete responses (CR, 7.7%), 10 partial responses (PR, 25.6%), 11 cases of stable diseases (SD, 28.2%), and 10 progressive diseases (PD, 25.6%). The objective tumor response rate was 33.3% in ITT population (95% CI: 21.9–54.6%) (Table 3). The median progression-free survival was 5.0 months (95% CI 2.7–7.3 months) and median overall survival was 8.3 months (95% CI: 7.3–9.4 months) (Fig. 1a, b).

Toxicity

The hematologic and non-hematologic toxicities are summarized in Table 3. A total of 113 cycles (median 3, range 1–6 cycles) in 39 patients were assessed for safety. The most frequent hematologic adverse event was neutropenia, which occurred with a grade 3 in 8 patients (20.5%) and grade 4 in 4 patients (10.3%). Anemia grade 2 and grade 3 occurred in 13 patients (33.3%) and 1 patient (2.6%), respectively. One patient (2.6%) had a grade 3 infection. Hematologic toxicities per cycles delivered are described in Table 4.

Nausea was the most common non-hematologic toxicity. Nausea grades 2 and 3 occurred in 15.4 and 2.6% of patients, respectively, and rates of grade 2 fatigue and dysphagia were 7.7% for both, grade 2 vomiting was 5.1%, and grade 2 anorexia and diarrhea were 2.6%.

Table 3 Efficacy result

Response	Number of patients
Complete response	3 (7.7%)
Partial response	10 (25.6%)
Stable disease	11 (28.2%)
Progressive disease	10 (25.6%)
Objective tumor response	33.3%

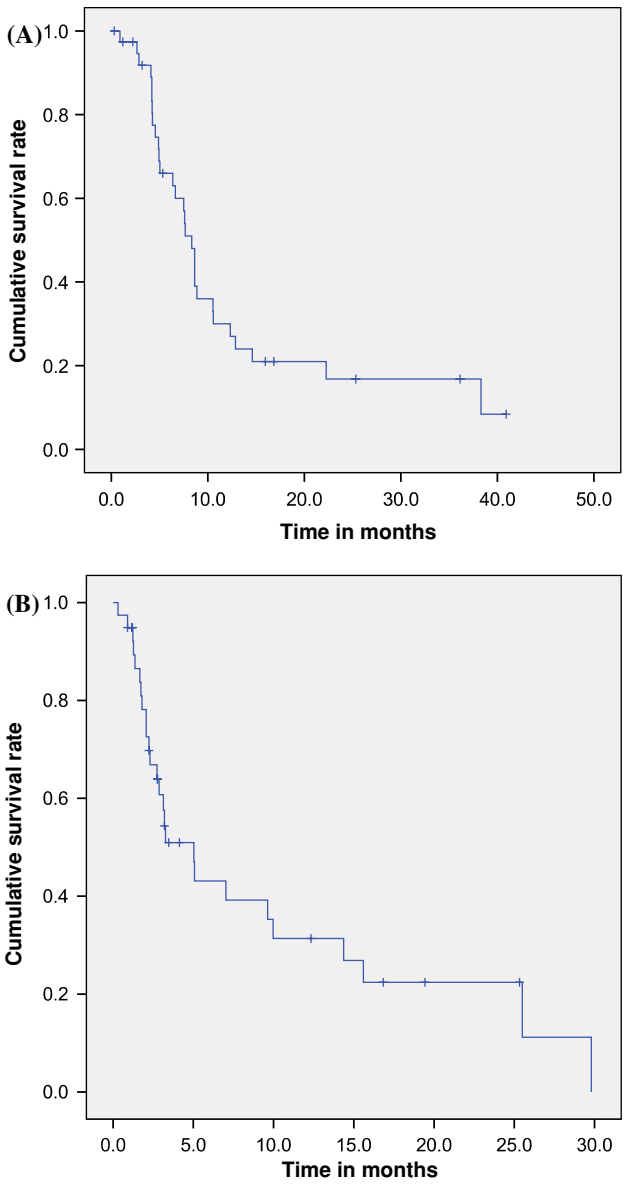

Fig. 1 Kaplan–Meier curves for time to disease progression (**a**) and overall survival (**b**) for intention-to-treat population ($n = 39$). The median time to progression and median overall survival were 5.0 and 8.3 months, respectively

Table 4 Adverse reactions according to NCI-CTC grade

	Grade (% of patients, $n = 39$)[a]			
	1	2	3	4
Hematologic				
Leukopenia	12 (30.8)	4 (10.3)	4 (10.3)	
Neutropenia	4 (10.3)	2 (5.1)	8 (20.5)	4 (10.3)
Anemia	12 (30.8)	13 (33.3)	1 (2.6)	
Thrombocytopenia	1 (2.6)			
Non-hematologic				
Nausea	3 (7.7)	6 (15.4)	1 (2.6)	
Vomiting	3 (7.7)	2 (5.1)		
Fatigue	1 (2.6)	3 (7.7)		
Dysphagia	3 (7.7)	3 (7.7)		
Anorexia	2 (5.1%)	1 (2.6)		
Diarrhea	2 (5.1)	1 (2.6)		
Infection		1 (2.6)	1 (2.6)	
Pain	1 (2.6)	1 (2.6)		
Edema	1 (2.6)			

[a] NCI-CTCAE v 2.0

Discussion

For many years, there was no standard treatment regimen for advanced esophageal cancer and the objective response and median overall survival of several study was low and still unsatisfactory.

Several phase II studies of taxane monotherapy or taxane-combination chemotherapy have been published [6–8, 17–20]. The results show that the response rate to single-agent docetaxel in esophageal cancer is about 18–25% [6–8], and is similar to the single-agent activity observed with the most active conventional drugs use in this disease, such as 5-FU, capecitabine, cisplatin, paclitaxel, docetaxel, oxaliplatin, irinotecan, and tyrosine kinase inhibitor.

Phase II study in Korea, using 5-FU, 1,000 mg/m^2/day in 12-h continuous infusion on day 1–5 and cisplatin, 60 mg/m^2/day on day 1, showed a response rate of 39% and overall survival of 9 months in advanced squamous cell esophageal cancer [9]. Up till now, many Korean esophageal cancer patients treated with 5-FU and cisplatin combination regimen.

Docetaxel has shown extensive cytotoxic activity in animal models as well as antitumor activity against a variety of common cancers in clinical studies [21]. The mechanism of action and side effect profile of docetaxel are different from cisplatin. Myelosuppression is a dose-limiting toxicity of docetaxel, whereas myelotoxicity with cisplatin is mild. The activity of combination docetaxel and cisplatin in gastric cancer, non-small cell lung cancer, and head/neck squamous cell carcinoma is well known [22]. Although these report, the combination of docetaxel and cisplatin has not been investigated in patients with esophageal cancer.

Laack et al. [22] treated patients with metastatic esophageal cancer or cancer of the gastroesophageal junction with docetaxel 75 mg/m^2 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. This study showed overall response rate of 31.3%, a median survival of 7.4 months, and a median progression-free survival of 4.7 months. The most common hematologic toxicity was leucopenia, with a grade 3/4 incidence of 42.9%. The most common non-hematologic toxicity was alopecia and neurotoxicity (grade 2 neurotoxicity was 14.3%). Even though they used the dosing schedule similar to our trial (70 mg/m^2 of docetaxel and cisplatin on day 1, repeated every 21 days), the efficacy of our study seem to be similar. In our study, the combination chemotherapy of docetaxel and cisplatin as a first-line treatment resulted in an overall response rate of 33.3%, disease control rate of 61.5%, a median survival of 8.3 months, and a median progression-free survival of 5.0 months. This treatment was relatively tolerated with grade 3/4 neutropenia in 30.8%, grade 2/3 anemia in 35.9%, grade 2/3 infection in 5.2%, grade 2/3 nausea in 18.0%, grade 2 diarrhea was in 2.6% of patients.

In another docetaxel-based combination study, they used the capecitabine (1,000 mg/m^2 twice daily on days 1–14) and docetaxel (75 mg/m^2 on day 1) every 3 weeks as first- ($n = 16$) or second-line ($n = 8$) in patients with metastatic adeno- or squamous esophageal cancer [23]. In the above study of Lorenzen et al. [23], the objective response rate was 46% and disease control rate was 63%, while the median progression-free survival and overall survival was 6.1 and 15.8 months. The clinical efficacy was superior to that of our present study. But this study included adenocarcinoma and the toxicity grade was higher than our study. The incidence of grade 3/4 neutropenia and febrile neutropenia was 42%/8%, grade 3/4 anemia was 8%.

Conclusion

In conclusion, docetaxel plus cisplatin combination chemotherapy showed a significant antitumor effect and was well tolerated with manageable toxicities in patients with metastatic squamous esophageal cancer.

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