Phase I Study of Docetaxel, Cisplatin, and 5-Fluorouracil Chemoradiotherapy for Local or Metastatic Esophageal Cancer

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Abstract. *Background/Aim: Chemoradiotherapy outcomes for unresectable esophageal cancer remain poor. We designed a phase I study of docetaxel, cisplatin (CDDP), and 5-fluorouracil (5-FU) chemoradiotherapy. Patients and Methods: Patients with T4 or M1 esophageal squamous cell carcinoma were enrolled. They received 2 chemotherapy cycles every 4 weeks with these initial doses (Phase I): docetaxel and CDDP (50 mg/m^2, days 1 and 29) with continuous 5-FU infusion (600 mg/m^2/day, days 1-5 and 29-33). Concurrent radiotherapy (60 Gy) was initiated on day 1. Docetaxel and CDDP plus 5-FU doses were increased to 60 mg/m^2 plus 800 mg/m^2/day. Results: Out of the 15 patients enrolled, 13 completed the treatment. The MTDs were as follows: docetaxel (60 mg/m^2), CDDP (60 mg/m^2), and 5-FU (800 mg/m^2/day). The overall response rate was 73%, with 27% achieving complete responses. Conclusion: In this phase I trial, docetaxel (60 mg/m^2), CDDP (60 mg/m^2), and 5-FU (600 mg/m^2/day) were considered as the tolerable and active doses. These are the recommended doses for a future phase II trial.*

Esophageal cancer is the 8th most frequently diagnosed cancer and the 6th most common cause of cancer-related death worldwide. Owing to advances in surgical techniques, perioperative management, and treatment, the outcome of esophageal cancer has slowly improved over the past 3 decades. However, the outcome of advanced esophageal cancer remains very poor. More than 50% of patients have either unresectable tumors or radiographically visible metastases at the time of esophageal cancer diagnosis (1). Combined chemotherapy of CDDP and 5-FU with or without radiotherapy has been used as standard treatment for advanced esophageal cancer. In spite of multidisciplinary treatments, the median survival time of stage IV patients with chemotherapy is reportedly less than one year (2). Moreover, the 3-year survival rate for esophageal cancer with distant organ metastasis was previously shown to be only 0.3%. (3). Therefore, the establishment of effective treatments for these patients is an urgent issue.

Docetaxel is a new taxane with a cytotoxic mechanism of action based on the promotion of tubule polymerization and inhibition of microtubule de-polymerization (4). Several phase II trials have proven the safety and efficacy of docetaxel alone for advanced esophageal cancer (5, 6).

Treatment with CDDP, 5-FU, and docetaxel was found to be superior to conventional treatment with CDDP and 5-FU for advanced gastric cancers (7). The addition of docetaxel to the CDDP and 5-FU combination resulted in better survival for patients with head and neck cancer (8). These findings indicate that docetaxel addition to the CDDP and 5-FU combination is feasible and a potentially promising treatment for esophageal cancer. Therefore, we conducted a phase I study on the combination of docetaxel, CDDP, and 5-FU with concurrent radiotherapy for patients with unresectable locally advanced or metastatic esophageal cancer. The aims of this study were i) to determine the maximum tolerated dose (MTD) and recommended dose (RD), and ii) to evaluate the toxicities of this treatment regimen.

Patients and Methods

Eligibility. Out of the 15 patients enrolled, 13 patients aged 20-80 years who had untreated histologically confirmed squamous cell carcinoma of the thoracic esophagus with T4 and/or M1b (6th edition of UICC Classification) (9), that includes nodal and distant metastases, were eligible to participate in the study.

Patients were required to have an Eastern Cooperative Oncology Group performance status (10) 0-1, measurable target lesions, a total white blood cell count ≥4,000/mm^3 or a neutrophil count ≥2,000/mm^3, a hemoglobin value ≥9 g/dl, a platelet count ≥100,000/mm^3, a total serum bilirubin level within the upper normal limit, aspartate aminotransferase and alanine aminotransferase levels ≤1.5-fold the upper normal limit, an alkaline phosphatase level ≤2.5-fold the upper normal limit, a serum creatinine level ≤1.5-fold the upper normal limit, and a creatinine clearance level ≥50 ml/min.

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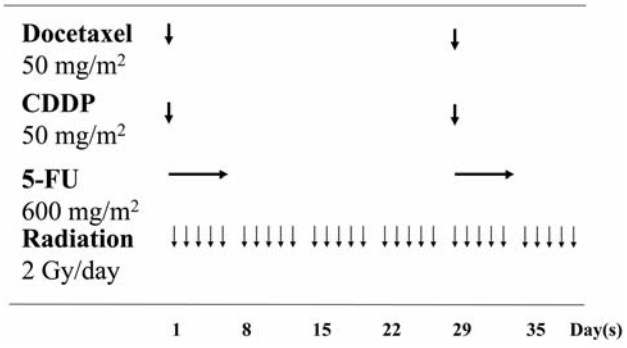

Figure 1. *Treatment schedule*.

Table I. *Dose levels used in the study.*

	Docetaxel (Day 1)	CDDP (Day 1)	5-FU (Days 1-5)	Radiation (/Day)
Level 0	40 mg/m^2	40 mg/m^2	600 mg/m^2	2 Gy
Level 1	50 mg/m^2	50 mg/m^2	600 mg/m^2	2 Gy
Level 2	60 mg/m^2	60 mg/m^2	600 mg/m^2	2 Gy
Level 3	60 mg/m^2	60 mg/m^2	800 mg/m^2	2 Gy
Level 4	70 mg/m^2	70 mg/m^2	800 mg/m^2	2 Gy

Patients were excluded if they had any of the following conditions: a history of serious allergic reactions to the chemotherapeutic agents used; severe general medical conditions that may prevent scheduled chemoradiotherapy; pregnancy, possible pregnancy, or breastfeeding; active febrile infections; any other conditions that the attending physicians decided that made the patient ineligible.

The study was approved by the Ethics Committee of the Tokyo Medical University. All patients provided written informed consent.

Pre-treatment evaluation. Patients were evaluated by history, physical examination, blood count, blood biochemistry, tumor markers, electrocardiography, chest radiography, barium esophagography, esophagoscopy, and contrast-enhanced computed tomographic (CT) scans of the neck, thorax, and abdomen. Ultrasonography of the neck or abdomen, bronchoscopy, bone scintigraphy, and endoscopic ultrasonography were optionally performed according to the tumor conditions. The clinical staging for tumors was defined according to the TNM classification for malignant tumors (6th edition) staging system.

Treatment plan. The treatment schedule is shown in Figure 1.

Chemotherapy. Docetaxel was administered intravenously for 1 h and CDDP for 2 h after the completion of the docetaxel infusion on day 1. 5-FU was administered as a protracted intravenous infusion on days 1 to 5. Two cycles of chemotherapy were administered every 4 weeks. The initial doses of docetaxel, CDDP, and 5-FU were 50 mg/m^2, 50 mg/m^2, and 600 mg/m^2, respectively. Each dose was increased as shown in Table I. The second cycle of chemotherapy was suspended when the total white blood cell count was <3,000/mm^3.

Radiotherapy. Treatment planning consisted of a computed tomography (CT) scan of the esophagus with 0.5-cm-thick slices obtained. Gross tumor volume (GTV) 1 and GTV 2 were defined as a primary tumor and lymph nodes with a maximum diameter of 1.5 cm or greater in the cervix, mediastinum, and abdomen, respectively. The clinical target volume (CTV) was determined as GTV 1 with a 3-cm expansion superiorly and inferiorly along the length of the esophagus and a 1.0- to 1.5-cm radical expansion plus GTV 2 with a 1.5-cm radical expansion in all directions. The planned treatment volume (PTV) was established by adding a 0.5- to 1.0-cm margin to CTV. Patients were treated daily 5-times per week. The PTV was irradiated using a parallel opposed field up to 40 Gy given in 20 sessions. The PTV was then irradiated a total dose of 60 Gy given in 30 sessions, using 2 or 3 ports to avoid the spinal cord. Radiotherapy was suspended if the patient developed grade 3 or 4 leukocytopenia.

Definition of DLT. Toxicities were evaluated weekly by physical examination, blood count, and blood chemistry. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). The following toxicities occurring during or within 2 weeks of the completion of chemoradiotherapy were defined as dose-limiting toxicity (DLT): (i) grade 3 febrile neutropenia for 5 days or longer; (ii) grade 4 neutropenia for 5 days or longer; (iii) grade 4 thrombocytopenia; (iv) grade 2 nephrotoxicity; (v) grade 4 mucositis; (vi) grade 4 diarrhea; (vii) grade 4 esophagitis; (viii) grade 3 or 4 non-hematological toxicity excluding anorexia, nausea, vomiting, fatigue, and alopecia.

Dose escalation and attenuation. Three patients were entered into the initial dose level (Level 1). If none of the 3 patients developed DLT, another 3 patients were treated at the next dose. If 1 of the 3 patients developed DLT, 3 additional patients were entered at that dose level. If 1 or 2 out of the 6 patients developed DLT, the dose was escalated to the next level. If 2 out of 3 or at least 3 out of the 6 patients developed DLT, further dose escalations were abandoned, and the previous dose level was defined as the MTD.

Response evaluation and monitoring. Four weeks after treatment completion, the clinical response of each patient was assessed by esophagoscopy and CT scans. Responses at the primary site were evaluated by esophagoscopy according to the response evaluation criteria of the Japanese Esophageal Society. Briefly, complete response (CR) was defined as complete tumor disappearance and absence of viable cells in biopsy samples. Incomplete response (IR)/stable disease (SD) was defined as incomplete tumor disappearance without tumor progression. Partial disease (PD) indicated incomplete tumor disappearance despite some tumor reduction. Partial response (PR) referred to 50% or more decrease in the tumor. Stable disease (SD) was defined as less than a 50% decrease or less than a 25% increase in the tumor. Progressive disease (PD) was defined as 25% or more increase in the primary tumor. The responses of metastatic lesions were evaluated according to the Response Evaluation Criteria in Solid Tumors.

After evaluation of the clinical response, the patients were subsequently evaluated every 3 months for the first 2 years and every 6 months for the next 3 years. This surveillance included

Table II. *Patients' characteristics*.

Level	Age	Gender	Tumor location	T	T4 organ	N	N4 Lymph	M	M1 organ
1									
1	70	M	Mt	4	Aorta Main br.	4	106pre	0	
2	55	F	Mt	4	Main br.	4	16	0	
3	80	M	Mt	3		2	1	1	Liver
4	57	M	Ut	4	Trachea	3		0	
5	66	M	Ut	4	Trachea	3		0	
6	67	M	Mt	4	Carotid artery	3		0	
2									
7	64	M	Mt	4	Aorta	2		1	Liver
8	80	M	Mt	3		2		1	Lung
9	61	M	Mt	2		4	16	1	Liver, Lung
10	67	M	Mt	3		4	9	1	Lung
11	32	M	Lt	4	Aorta	1		0	
12	68	M	Lt	3		0		1	Lung
3									
13	65	F	Mt	4	Trachea	2		0	
14	70	M	Mt	4	Trachea	2		0	
15	69	F	Lt	3		4	16	1	Liver, Lung

Ut: Upper thoracic esophagus, Mt: middle thoracic esophagus, Lt: lower thoracic esophagus, Br: bronchus.

physical examination, full blood examination, CT scan, and esophagoscopy. Late radiation toxicities were assessed using the RTOG/EORTC late radiation morbidity scoring scheme.

Results

Patients. In this phase I trial, 15 patients were enrolled between April 2007 and July 2008. The patients' characteristics are listed in Table II. There were 12 male patients (80%) and 3 female patients, and their median age was 67 years (range=32–80 years). All patients had squamous cell carcinoma, with the primary tumors mainly located in the middle third of the thoracic region (67%). Nine patients (60%) had T4, 14 patients (93%) had N1, and 12 patients (80%) had M1 disease. Of the 12 patients with M1 disease, 7 had metastases in distant organs. Fourteen patients (93%) completed the scheduled treatment. Although treatment was suspended in the 2nd cycle of chemotherapy in 1 patient because of liver dysfunction, radiotherapy was completed. Toxicities and responses were assessable in all patients.

Toxicity. The toxicities observed during this trial are listed in Table III. There was no treatment-related death during or after chemoradiotherapy. Leukocytopenia was the most common adverse effect. Grade 3-4 leukocytopenia was observed in 14 patients (93%). Seven patients (47%) developed grade 3 febrile neutropenia at dose levels 2 and 3. Grade 4 liver dysfunction was observed in 1 patient at dose level 3. Renal dysfunction occurred in 2 out of 6 patients at dose level 2, but not at dose level 3. At dose level 3, 3 out of 6 patients developed Grade 3-4 hyponatremia and 2 patients hypokalemia. Late radiation toxicity was not observed in any patient.

Treatment delivery. All patients completed the planned radiotherapy. Radiotherapy was interrupted in 14 out of the 15 patients (93%) because of leukocytopenia. The interrupted periods were within 5 days for all 14 patients.

All patients were treated with the planned chemotherapy dose for at least 1 course. Fourteen patients received the 2nd cycle of chemotherapy at the same dose, whereas 1 patient did not because of liver dysfunction.

Table IV shows the Grade 1-4 toxicities and DLTs that occurred at each dose level. At dose level 1, DLT was not observed in 3 patients. One out of the 3 patients developed grade 2 renal dysfunction, defined as a DLT; therefore, 3 additional patients were entered at dose level 2. Since 2 out of the 6 patients developed DLT at dose level 2, the dose

Table III. *Toxicities (worst Grade).*

	Level 1 (n=3)				Level 2 (n=6)				Level 3 (n=6)			
Toxicity/Grade	1	2	3	4	1	2	3	4	1	2	3	4
Leukocytopenia	0	0	3	0	0	1	2	3	0	0	4	2
Febrile neutropenia	0	0	0	0	0	0	2	0	0	0	5	0
Anemia	0	2	1	0	0	3	2	0	0	5	0	0
Thrombocytopenia	1	0	0	0	1	0	0	0	2	1	1	0
Esophagitis	1	0	1	0	0	1	1	0	0	0	1	0
Anorexia	1	0	1	0	1	1	3	0	1	3	1	0
Diarrhea	0	2	0	0	1	1	1	0	0	0	3	0
Mucositis	0	0	0	0	0	0	0	0	1	0	1	0
Liver dysfunction	1	0	0	0	0	0	0	0	1	0	0	1
Renal dysfunction	0	0	0	0	0	2	0	0	0	0	0	0
Hyponatremia	0	0	0	0	0	0	0	0	0	0	1	2
Hypokalemia	0	0	0	0	0	0	0	0	0	0	2	0
Hair loss	1	1	0	0	3	1	0	0	3	2	0	0

level was escalated to the next level. One out of the 3 patients developed Grade 3 hyponatremia, defined as a DLT, and 3 additional patients were entered at dose level 3. Since all additional patients had a DLT, a total of 4 DLTs were observed in 6 patients at dose level 3. Therefore, docetaxel at 60 mg/m^2, CDDP at 60 mg/m^2, and 5-FU at 600 mg/m^2/day were defined as the MTDs and recommended phase II doses.

Response. Clinical responses were assessable in all 15 patients by esophagoscopy and CT scans. The overall clinical response rate was 73% (11 out of 15). As shown in Table V, 4 patients had CR, 7 patients had PR, and 4 patients had PD. Although CR and PR were observed at all dose levels, PD was not seen at dose level 3. All PD patients had tumor progression out of the radiation fields, despite 3 out of 4 patients having CR or PR within the radiation fields. In the 7 patients who had metastases to distant organs, only 1 had CR at the metastatic site, whereas 8 out of 9 patients with T4 diseases had CR at the primary sites.

Additional treatment. Eight out of the 15 patients received 1 cycle of chemotherapy with the same regimen every 4 months after initial chemoradiotherapy. A total of 15 cycles of chemotherapy were administered to the 8 patients (average=1.9 cycles). Because of the patient's condition or refusal, 2 patients received other chemotherapies and 5 received best supportive care.

Survival. With a median follow-up of 41 months (range=22-48 months), 7 patients (47%) remained alive without evidence of recurrence. The median overall survival time was 18 months (range=4-48 months). The overall survival rates at 1 year and 3 years were 53% and 40%, respectively.

Table IV. *Dose-limiting toxicities (DLTs).*

Level	Tumor location	T	N	M	DLTs
1					
1	Mt	4	4	0	None
2	Mt	4	4	0	None
3	Mt	3	2	1	None
4	Ut	4	3	0	None
5	Ut	4	3	0	None
2					
6	Mt	4	3	0	G2 Renal dysfunction
7	Mt	4	2	1	G2 Renal dysfunction
8	Mt	3	2	1	None
9	Mt	2	4	1	None
10	Mt	3	4	1	None
11	Lt	4	1	0	G3 Hyponatremia
3					
12	Lt	3	0	1	None
13	Mt	4	2	0	G4 Liver dysfunction
14	Mt	4	2	0	G4 Hyponatremia, G3 Hypokalemia
15	Lt	3	4	1	G4 Hyponatremia, G3 Hypokalemia

DLTs: Dose-limiting toxicities, Ut: upper thoracic esophagus, Mt: middle thoracic esophagus, Lt: lower thoracic esophagus, Br: bronchus.

Table V. *Efficacy of treatments.*

	CR	PR	SD	PD	RR
Level 1 (n=3)	1	1	0	1	66%
Level 2 (n=6)	1	2	0	3	50%
Level 3 (n=6)	2	4	0	0	100%

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease, RR: response rate.

Discussion

Esophageal cancer is highly malignant and one of the gastrointestinal cancers that is associated with a poor prognosis. In approximately 50% of patients with this cancer, invasion of other organs and distant metastasis are already present at the time of cancer detection, and surgery is not indicated. In Western countries and Japan, resectable stage II/III esophageal cancer is currently treated by radical surgical resection, and long-term results have improved due to advances in surgical and lymph node dissection techniques, particularly in 3 regions (*i.e.*, neck, chest, and

abdomen). Although there have been no detailed studies on stage IVB cancer, the 3- and 5-year survival rates of patients with unresectable advanced esophageal cancer, as described above were 5-8% and 0%, respectively, and the median survival time was approximately 7-9 months, showing an extremely poor prognosis. Therefore, improvements in survival rates are urgently needed.

Radical chemoradiotherapy is mainly recommended as a treatment for patients with esophageal cancer accompanied by invasion of the surrounding organs, such as T4 cancer, and those with unresectable advanced cancer, with the expectation of improvements in symptoms such as dysphagia by high local control.

Radical chemoradiotherapy has been performed for esophageal cancer since the 1980s in Western countries. The Radiation Randomized Therapy Oncology Group (RTOG) previously performed a randomized controlled trial using radiotherapy alone or in combination with concurrent chemotherapy (RTOG8501) (11), and showed more favorable results using chemoradiotherapy. In Western countries, chemoradiotherapy is strongly recommended as a non-surgical method. In Japan, Ohtsu *et al*. were the first to perform a phase II trial on radical chemoradiotherapy for T4/M1 Lym cancer that could not be surgically treated (12). The indications of this therapy have since expanded to unresectable cases. Unresectable advanced esophageal cancer is currently treated using concurrent chemoradiotherapy consisting of radiotherapy at a dose of 60 Gy/fractions and FP therapy (5-FU, 700 mg/m^2/day, days 1-4 and 29-32; CDDP, 70 mg/m^2/day, days 1 and 29) (13). Previous studies performed in Japan have reported a 3-year survival rate of approximately 20% (12, 13, 15) and a mean survival time (MST) of 305.5 days. (14) Iwase *et al*. performed UFT/CDDP chemotherapy with radiotherapy (60/70 Gy) using regimens other than FP therapy for Stage IVB esophageal cancer and showed a response rate (RR) of 63% and an MST of 6.2 months (13). Cho *et al*. subsequently used S-1/CDDP with radiation (54 Gy), and reported an RR of 50% and an MST of 11.6 months (16), whereas Ikeda *et al*. used 5-FU/CDDP with radiation (40 Gy) and showed an RR of 55% and an MST of 10.3 months (17). Conroy *et al*. have recently performed a phase II trial to evaluate the superiority of chemoradiotherapy with FOLFOX over that with FP (ACCORD17 trial), but observed no superiority of oxaliplatin over CDDP (18). These treatment findings were not favorable; therefore, improvements through the development of new regimens are needed.

A regimen that is known to be effective against esophageal cancer is FP therapy with taxane anticancer drugs (paclitaxel/docetaxel). Both drugs act against microtubular polymerization and inhibit cell division, thereby exerting antitumor effects. An *in vitro* study using human esophageal cell strains demonstrated that docetaxel exerted more prominent effects than paclitaxel (19). Additionally, docetaxel was reported to show less nephrotoxicity and gastrointestinal toxicity, could be administered on an outpatient basis, and had enhanced radioresponses (30). Moreover, docetaxel with FP (DCF therapy) has been reported to have beneficial effects on head and neck cancer and advanced gastric cancer (7, 8, 21). Vermorken *et al*. performed a phase III trial comparing DCF therapy with FP therapy as induction therapy before chemoradiotherapy in patients with unresectable locally advanced squamous cell carcinoma of the head and neck (EORTC2491/TAX323 trial), and they observed significantly superior treatment results in the DCF therapy group than in the FP therapy group despite the development of ≥grade 3 neutropenia in 77% of the DCF group (22). Posner *et al*. performed a phase III trial comparing TPF (DOC+CDDP+5-FU) with PF (TAX324) for induction chemotherapy before chemoradiotherapy (CBDCA+RT) as standard treatment for patients with unresectable head and neck cancer tumors (23), and observed superior treatment results in the TPF group than in the PF group. On the other hand, Roth *et al*. performed a randomized phase II trial comparing EFG (Epirubicin+CDDP+5-FU), TC (DOC+CDDP), and TCF (DOC+CDDP+5-FU) in patients with unresectable/recurrent gastric cancer, and reported more favorable results in the TCF group than in the other groups despite marked hematotoxicity (24). In Japan, a phase I/II trial in which the safety and effectiveness of DCF therapy were evaluated in patients with unresectable/recurrent esophageal cancer (JCOG0807) showed that docetaxel administration once biweekly combined with CDDP+5-FU as a standard treatment (bi-weekly DCF therapy) was safe and effective (25). A phase III trial comparing bi-weekly DCF therapy with CF therapy is currently being planned based on these findings. With such a background, 3-drug (docetaxel added to 5-FU/CDDP) chemoradiotherapy may be a useful radical regimen for patients with T4/M1 Lym.

Only a limited number of patients have received 3-drug (DCF) chemoradiotherapy. Eisterer *et al*. performed chemoradiotherapy consisting of chemotherapy with docetaxel (15 mg/m^2, days 1, 8, 15, and 22) and 5-FU (300 mg/m^2, irradiation days) and radiotherapy (40 or 60 Gy) after induction chemotherapy with docetaxel (75 mg/m^2, days 1 and 29), CDDP (25 mg/m^2, days 1-5 and 29-34), and 5-FU (750 mg/m^2, days 1-5 and 29-34) in 24 patients with locally advanced esophageal cancer (26). They achieved down-staging to resectable cancer in 16 patients, 5 of whom showed pCR. As Grade 3 and 4 adverse events, leukopenia was observed in 41.7%, diarrhea in 16.7%, and hair loss in 8.3%. However, their subjects consisted of 16 patients with squamous cell carcinoma and 8 with adenocarcinoma. The effects of 3-drug (DCF) chemoradiotherapy in patients with squamous cell carcinoma have not yet been investigated. Therefore, we

performed this study to accumulate more data, including the optimal dose and adverse events.

The administered doses of docetaxel, CDDP, and 5-FU and the radiation dose were determined based on previous clinical trials. As described above, chemoradiotherapy for unresectable esophageal cancer in Japan consists of chemotherapy with 5-FU (700-800 mg/m^2, days 1-4 or 5) and CDDP (70-80 mg/m^2, day 1) and radiation at a total dose of 60 Gy (2 Gy×30 fractions) (12, 13, 27). Using docetaxel, a phase II trial for esophageal cancer was performed at a dose of 70 mg/m^2 in Japan. Although this dose was reduced to 60 mg/m^2 due to adverse effects in 37% of the subjects, beneficial effects were observed (6). Tamura *et al*. performed a joint multi-center phase II study on DCF therapy (OGSG 0403) using docetaxel at 60 mg/m^2 (day 1), CDDP at 70 mg/m^2 (day 1), and 5-FU at 600 mg/m^2 (days 1-5), and achieved CR in 3 out of 29 subjects (28). In patients with non-small cell lung cancer, gastric cancer, and head and neck cancer including squamous cell carcinoma, docetaxel was shown to exert beneficial effects at a dose of 60 mg/m^2 (29-36). Posner *et al*. (37) performed DPF therapy consisting of docetaxel at 75 mg/m^2 (day 1), CDDP at 75 or 100 mg/m^2 (day 1), and 5-FU at 1000 mg/m^2 (days 1-4) in 43 patients with head and neck cancer, and reported favorable treatment results (RR, 93%; CR rate, 40%). As adverse events, neutropenia was observed in 95% of patients and stomatitis in 30%. In 2 previous phase III randomized controlled trials that compared DPF therapy with FP therapy in patients with head and neck cancer or gastric cancer, the doses of docetaxel, CDDP, and 5-FU were 75 mg/m^2 (day 1), 75 mg/m^2, and 1000 mg/m^2 (days 1-5), respectively (7, 22).

We determined the dose levels (0-4 mg/m^2) of docetaxel, CDDP, and 5-FU based on these studies, and as a result, the regimen used was tolerable, there was no treatment-related death during or after the treatment, and the treatment completion rate was 100% (15/15). Leukopenia was the most frequently observed adverse event, and included Grade 3-4 leukopenia in 14 patients (93%). Febrile neutropenia was observed in 3 (47%) out of 7 patients at dose level 2 or 3. However, the treatment delay was ≤5 days, which may be a permissible range. In addition, Grade 3-4 hyponatremia was observed in 3 patients at dose level 3, Grade 3 hypokalemia in 2, and Grade 4 liver dysfunction in 1. There were no definite late complications.

Regarding treatment results, 4/15 patients (26.7%) achieved pCR, and the overall clinical RR was 73% (11/15). CR and PR were observed at all dose levels. There were no patients who showed PD at dose level 3. PD was observed in 4 patients, all of whom exhibited tumor enlargement in areas other than the irradiation field, whereas 3 showed CR or PR in the irradiation field, suggesting the favorable local control of unresectable esophageal cancer.

In the present clinical phase I trial, DLT was observed in 4 out of 6 patients at dose level 3. Therefore, the MTD in chemoradiotherapy with docetaxel, CDDP, and 5-FU for advanced esophageal cancer was Level 3 (docetaxel, 60 mg/m^2; CDDP, 60 mg/m^2; 5-FU, 800 mg/m^2; and radiation, 2 Gy/fraction×30 days). These were considered to be the RDs in the phase II clinical trial. Since there have only been a limited number of studies on chemoradiotherapy with docetaxel, CDDP, and 5-FU, comparisons with the results of the present study are difficult. However, this therapy exerted beneficial effects and is a promising treatment for unresectable advanced esophageal cancer. Leukopenia and electrolyte abnormalities frequently developed as adverse effects, requiring adequate attention to safety. A phase II trial is presently underway based on the results of this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest with regard to any parts of this study.

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