Phase I Study of Docetaxel (TXT) and 5-Fluorouracil (5-FU) with Concurrent Radiotherapy in Patients with Advanced Esophageal Cancer

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Abstract. *This phase I study was designed to determine the maximum-tolerated dose (MTD) of docetaxel (TXT) and toxicities of combining weekly administration of TXT and continuous infusion of 5-fluorouracil (5-FU) with concomitant radiotherapy for advanced esophageal cancer. Patients and Methods: Patients received TXT by i.v. infusion over 1 h on days 1, 8, 22 and 29. They were also given 5-FU 250 mg/m^2/day by continuous infusion for 24 h on days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40 and 43-45. Fractionated radiotherapy was performed on days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40 and 43-45, and a total dose of 60 to 66 Gy was delivered. The starting dose level (Level 1) of TXT was set at 7.5 mg/m^2. Dose escalation was conducted in increments of 2.5 mg/m^2, until the dose reached Level 4 (15 mg/m^2). At least three patients were enrolled at each level. Results: Seven patients (median age, 64 years) were enrolled. Six patients had stage III (T4N1M0) and one had stage IVb (T4N1M1b) esophageal cancer; six had squamous cell carcinoma and one had carcinosarcoma. No patient had received prior chemotherapy or radiotherapy, and two patients had undergone esophageal bypass surgery using a whole stomach tube without resection of primary or metastatic lesions. In the 7 patients, the regimen was well-tolerated, with esophagitis as the most common toxicity (grade 3: n=1; grade 4: n=3). In general, hematological toxicity was mild. Dose-limiting toxicity (DLT) was observed at Level 2 (TXT 10 mg/m^2) when three patients developed grade 4 esophagitis and this dose was deemed the MTD for this regimen. In the 7 assessable patients, the overall clinical response rate was 85.7%. Conclusion: The MTD of TXT in this regimen was 10 mg/m^2 and the recommended dose of TXT was 7.5 mg/m^2. Although esophagitis was the dose-limiting and the most frequent toxicity, the regimen was safe and well-tolerated, and demonstrated the possibility of good efficacy in patients with advanced esophageal cancer.*

The incidence of esophageal adenocarcinoma is rapidly increasing and is now more common than squamous cell carcinoma in the United States (1, 2), while more than 90% of patients still present with squamous cell carcinoma in Japan (3). Regardless of histology, local and systemic spread of esophageal cancer occurs early in the course of the disease (4). Although recent advances in endoscopic diagnosis enable the detection of increasing numbers of early-stage esophageal cancer (5), the overall survival of patients with esophageal cancer is dismal because most patients present with advanced disease (6, 7).

Definitive chemoradiotherapy and preoperative chemoradiotherapy followed by surgery have become frequently used treatment regimens for advanced esophageal cancer, since clinical trials have demonstrated the superiority of concurrent chemoradiotherapy over radiotherapy alone (8, 9). Although cisplatin and 5-fluorouracil (5-FU) are the most frequently used chemotherapeutic agents in esophageal cancer treatment, cisplatin plus 5-FU-based concurrent chemoradiotherapy programs have limited efficacy (10-12). In order to increase the therapeutic ratio over that of standard cisplatin and 5-FU-based chemoradiotherapy, attempts have been made to incorporate next-generation cytotoxic chemotherapeutic agents such as CPT-11, paclitaxel, docetaxel (TXT), and oxaliplatin (13).

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We have focused on an incorporation of TXT, which has been extensively used with radiation for the treatment of patients with non-small cell lung cancer and head and neck cancer (14). TXT is a novel semisynthetic agent of the taxoid class that acts by enhancing tubulin polymerization and inhibiting microtubule depolymerization (15, 16). This action leads to cell-cycle arrest in the G2/M-phase, which is known to be 2.5-fold more sensitive to radiation than the G1/S-phase (17). TXT has been shown to enhance response to radiation with induced mitotic arrest and apoptosis in murine tumor cells (18, 19).

On the other hand, 5-FU has been one of the key drugs in esophageal cancer treatment and also allows for an enhanced interaction with radiotherapy (1, 20, 21). We recently demonstrated the synergistic effect of TXT and 5-FU, which was explained by biochemical modulation of the expressions of thymidine synthetase (TS), dihydropyrimidine dehydrogenase (DPD), and orotate phosphorybosyl transferase (OPRT), the key enzymes in the functional activities of 5-FU (22). Furthermore, high antitumor activity was shown in our phase I/II study of combination therapy with TXT and S-1, a novel oral fluorouracil antitumor drug, for advanced or recurrent gastric cancer (23, 24). Thus, in addition to the radiosensitizing and cytotoxic effect of each drug, the synergistic effect of TXT and 5-FU constitutes the rationale for combining these drugs with radiation.

Standing on the basis of the above, we conducted the current phase I clinical trial, combining continuous infusion of 5-FU and escalating doses of weekly administration of TXT with concomitant radiotherapy for advanced esophageal cancer. The primary objective was to define the maximum-tolerated dose (MTD) of TXT and the recommended dose (RD) for the phase II trial.

Patients and Methods

Patient eligibility. Patients were considered eligible for this study based on the following criteria: a histologically confirmed diagnosis of unresectable malignant neoplasm of the esophagus; prior chemotherapy was permitted, provided it had been completed at least 4 weeks earlier; prior esophageal bypass operation was permitted if performed at least 2 weeks before the study; no prior radiotherapy to the sites planned for irradiation in the present study; evaluable or measurable disease; age 18 to 75 years; a performance status under 2 according to the World Health Organization (WHO) scale; life expectancy of 3 months or more; adequate bone marrow function (white blood cell (WBC) count between 3000/mm^3 and 12000/mm^3, absolute neutrophil count of >2000/mm^3, platelet count of >100000/mm^3, Hb >9.5 g/dl); adequate renal function (serum creatinine <1.5 mg/dl); adequate liver function (serum bilirubin level <1.5 mg/dl, serum AST and ALT within 1.5 times the upper limit of normal for the institution, serum alkaline phosphatase within 2.5 times the upper limit of normal for the institution). Written informed consent was obtained from each patient.

Patients were excluded from the trial if any of the following exclusion criteria were fulfilled: symptomatic infectious disease, pulmonary fibrosis, interstitial pneumonia, malignant hypertension, congestive heart failure, severe coronary artery disease, severe liver cirrhosis, uncontrolled diabetes mellitus, bleeding tendency, preexisting symptomatic peripheral neuropathy or edema of more than grade 2 severity according to the common toxicity criteria of the National Cancer Institute (NCI-CTC), active double cancer, symptomatic pleural effusion or pericardial effusion, past history of allergic reaction to polysorbate 80, and pregnancy or breast feeding. The patient enrollment was started on April 21, 2004 and completed on April 7, 2005.

Evaluation. Pretreatment evaluation included a complete history and physical examination, a complete blood count, a biochemical screening profile including liver function studies and electrolytes, a urinalysis, and electrocardiogram (ECG). Radiological assessment included a chest X-ray, barium esophagram, and computed tomography (CT) scan of the neck, chest, and abdomen. Patients were required to undergo endoscopy with biopsy of the primary tumor, with review of the pathology at the Hiroshima University Hospital. Endoscopic ultrasonography (EUS) was required if it had not been performed during the initial endoscopy. Bronchoscopy was performed in patients with T3/T4 tumors of the proximal thoracic esophagus. Additional imaging examinations were performed if there was a clinical indication, or to measure the extent of the known disease. The clinical tumor staging was defined according to the TNM classification of the International Union Against Cancer (UICC) (25).

During the study period, all the patients were reviewed weekly for symptoms of toxicity and underwent clinical examinations, including determination of body weight and performance status, a weekly complete blood count and a biochemical screening profile. The barium esophagram was repeated when deemed necessary. At the end of therapy and 4 weeks after completion of therapy, an upper endoscopy with biopsy, a barium esophagram and a CT scan were repeated to assess response.

Toxicity due to the treatment was evaluated according to NCI-CTC, version 2. Dose limiting toxicity (DLT) that required additional patient enrollment was defined in advance as one or more of the following: Grade 4 neutropenia, thrombocytopenia, vasculitis, otitis of the external ear, fatigue, infection, nonmalignant ascites, constipation, central nervous system (CNS) hemorrhage, hyponatremia, esophagitis and dysphagia, or other Grade 3 nonhematological toxicity, except weight loss, anorexia, dyspepsia, heartburn, nausea, vomiting, incontinence, or urinary frequency/urgency. No dose modification for toxicity was allowed in this study.

Treatment plan. The treatment schedule is outlined in Figure 1. All treatment was delivered in the inpatient setting. TXT was diluted in 100 ml of 0.9% saline and infused over 1 h on days 1, 8, 22 and 29. Patients were premedicated with dexamethasone (8 mg intravenously) 30 min prior to infusion of TXT. 5-FU 250 mg/m^2/day was administered by continuous infusion for 24 h on the days shown in Figure 1. Fractionated radiotherapy was performed as shown with a total dose of 60 to 66 Gy was delivered in 2 Gy per fraction. Administration of TXT was suspended for 7 days when the WBC count decreased to <2000/mm^3, the absolute neutrophil count decreased to <1000/mm^3, or the platelet count decreased to

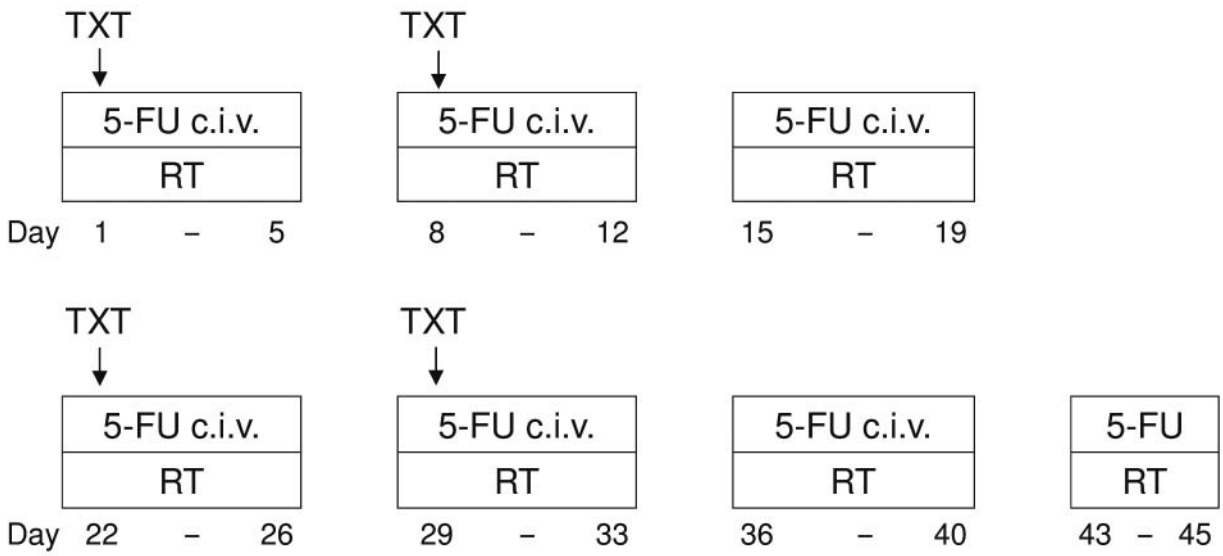

Figure 1. *Treatment schedule of docetaxel and 5-fluorouracil with concurrent radiotherapy.*

<100000/mm^3. Administration of TXT and 5-FU was suspended for 7 days when serum bilirubin levels were >1.7 mg/dl, serum AST and ALT were >1.7 times the upper limit of normal for the institution, serum alkaline phosphatase within 2.8 times the upper limit of normal for the institution, or serum creatinine >1.7 mg/dl. Chemoradiotherapy was suspended until the resolution of toxicity to Grade 1, or less when dose-limiting toxicity (DLT) was observed. Chemoradiotherapy was cancelled when the therapy was delayed more than 2 weeks.

The study protocol was approved by the institutional ethics committee. The protocol was discontinued at any time that the patient expressed the desire to discontinue it.

Dose level. The trial used a conventional dose-escalation schema with the primary end-point of defining the MTD of TXT that can be delivered with 5-FU and radiotherapy. The starting dose level (level 1) of TXT was set at 7.5 mg/m^2. Dose escalation was conducted in increments of 2.5 mg/m^2 until the dose reached level 4 (15 mg/m^2). Patients were not allowed to escalate or reduce the dose of 5-FU and radiation.

At least three patients were enrolled at each level. If no DLT was observed, the next dose level was opened for enrollment. If DLT was observed in one or two patients, then up to three additional patients were enrolled. If a total of three or more patients experienced DLT, escalation was stopped and the dose at this level was regarded as the MTD. The RD for the phase II study of TXT was determined to be one dose level below the level of MTD.

Assessment of response. The responses to treatment of the primary and metastatic lesions were assessed independently. Complete response (CR) was defined as the disappearance of all evidence of cancer for a minimum of 4 weeks. Partial response (PR) was defined as an at least 50% reduction in the sum of products of the perpendicular diameters of measurable lesions for a minimum of 4 weeks. Stable disease (SD) was defined as the failure to observe a PR, CR, or progressive disease (PD) for at least 4 weeks. PD was defined as a more than 25% increase in the sum of the products of the perpendicular diameter of measurable disease or the appearance of new lesions. Response of the primary tumor was evaluated by modified criteria of the Japanese Society for Esophageal Diseases (26, 27). CR for primary tumors was determined when all visible tumors, including ulcerations, disappeared for a minimum of 4 weeks. PR was assigned if the primary tumor was observed on esophagography as being reduced in area by at least 50%. Progressive disease was considered to be an increase of more than 25% in the tumor area. Response was evaluated using esophagram and chest and abdominal CT scans. The overall survival rate was calculated by the Kaplan-Meier method, from the date of initiation of treatment.

Results

Patient characteristics. Seven patients were enrolled in the study; the patient characteristics are summarized in Table I. There were 5 males and two females, ranging in age from 58 to 74 years (median, 64 years). The patient performance status (PS) was evaluated as 0 in all cases. Six patients had stage III (T4N1M0) and one stage IVb (T4N1M1b) esophageal cancer. Six cases had squamous cell carcinoma and one had carcinosarcoma. Target lesions were primary tumors in all patients and metastatic lymph nodes in six patients. In the case of stage IVb, distant metastatic lesions in bilateral lung were excluded from the radiation field. No patient had received prior chemotherapy and/or radiotherapy, while two patients had undergone esophageal bypass surgery using a whole stomach tube without resection of primary or metastatic lesions.

Toxicity. All patients were assessable for toxicity; the adverse effects are summarized in Table II A and B. None of the

Table I. *Patient characteristics.*

Patients number	7
Gender	
Male	5
Female	2
Age (years)	58-74
(median)	(64)
PS	
0	7
1	0
UICC TNM stage	
T4N1M0 stage III	6
T4N1M1b stage IVb (lung metastases)	1
Location of primary tumor	
Cervical	2
Upper thoracic	3
Middle thoracic	2
dLower thoracic	0
Histology	
SCC	6
Carcinosarcoma	1
Target lesion	
Primary tumor	7
Lymph node	6
Previous therapy	
None	5
Esophageal bypass surgery	2
Chemotherapy and/or radiotherapy	0

Table IIA. *Hematological toxicities experienced by patients.*

Level	Item	Grade			
		1	2	3	4
Level 1 (TXT 7.5 mg/m^2) n=3	Leukopenia	0	1	0	0
	Anemia	0	0	0	0
	Thrombocytopenia	0	0	0	0
Level 2 (TXT 10 mg/m^2) n=4	Leukopenia	0	0	0	0
	Anemia	0	0	0	0
	Thrombocytopenia	0	0	0	0

Table IIB. *Nonhematological toxicities experienced by patients.*

Level	Item	Grade			
		1	2	3	4
Level 1 (TXT 7.5 mg/m^2) n=3	Esophagitis	0	2	1	0
	Anorexia	0	2	0	0
	Diarrhea	0	0	0	0
	Fever	2	1	0	0
	Nausea	0	0	0	0
	Vomiting	0	0	0	0
	Pneumonitis	0	1	0	0
Level 2 (TXT 10 mg/m^2) n=4	Esophagitis	0	1	0	3
	Anorexia	0	1	3	0
	Diarrhea	2	0	0	0
	Fever	3	1	0	0
	Nausea	3	0	0	0
	Vomiting	2	0	0	0
	Pneumonitis	0	0	0	0

patients entered into Level 1 developed DLT, while three of four patients in Level 2 experienced Grade 4 esophagitis. They could not swallow a fluid diet or water and finally spit saliva due to the sensation of obstruction or pain of esophagitis. The symptoms were relieved by morphine or transdermal fentanyl. It took 1 or 2 months for them to recover completely from esophagitis; one patient required an esophageal dilatation procedure for esophageal stricture 2 months after completion of chemoradiotherapy. Level 2 was regarded as the MTD and the RD of TXT for the phase II trial was determined to be 7.5 mg/m^2. In general, hematological toxicity was mild; only one patient had Grade 2 leukopenia. As for non-hematological adverse effects, Grade 3 or Grade 4 toxicities were limited to esophagitis and anorexia attributed to esophagitis. Diarrhea, fever elevation, nausea, and vomiting were observed, but of Grade 2 or less severity. One patient in Level 1 had Grade 2 radiation pneumonitis and recovered after withdrawal of chemoradiotherapy for 6 scheduled days and steroid administration.

Treatment response. The characteristics of the evaluable lesions in each patient and the response status are summarized in Table III. The evaluable lesions were 7 primary lesions, 6 lymph node metastasis, and 1 lung metastasis. Overall, PR was observed in 6 patients. The response rate was therefore 85.7%. One patient had SD, and no PD was observed. The response rates in the target sites were 85.7% (6 of 7) in primary lesions of the esophagus and 66.7% (4 of 6) in lymph nodes, while lung metastasis did not respond to treatment, as shown in Table IV.

Survival. The median follow-up for the 7 patients who were treated on this protocol was 19 months, with a range of 10-23 months. Currently, a total of 4 patients are alive, and 3 patients died of disease. The overall 1-year survival rate was 57%. Of the living patients, one patient has lung and bone metastases and is alive 20 months after the date of initiation of treatment, one patient has a lung metastasis and is alive at 10 months. Two patients have no evidence of disease relapse and are alive at 23 months and 17 months respectively, after the date of initiation of treatment.

Table III. *Response of each patient treated with docetaxel (TXT)-5-FU with concurrent radiotherapy.*

Level 1 (TXT 7.5 mg/m^2)					
	Response	Lesions	RT(Gy)	Outcome	Duration (months)
1.	SD	Primary: SD	66	D	6
2.	PR	Primary: PR, LN: PR	66	A	23
3.	PR	Primary: PR, LN: SD	64	D	9
Level 2 (TXT 10 mg/m^2)					
	Response	Lesions	RT(Gy)	Outcome	Duration (months)
1.	PR	Primary: PR, LN: PR	60	A	20
2.	PR	Primary: CR, LN: PR, Lung: SD	66	D	7
3.	PR	Primary: PR, LN: SD	66	A	17
4.	PR	Primary: PR, LN: PR	66	A	10

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LN: lymph node metastasis; RT: radiotherapy.

Table IV. *Response rate of patients treated with docetaxel (TXT)-5-FU concurrent with radiotherapy.*

	CR	PR	SD	PD	Response rate (%)
Overall (n=7)	0	6	1	0	85.7
Local response rate					
Site of tumor	CR	PR	SD	PD	Response Rate (%)
Primary lesion (n=7)	0	6	1	0	85.7
Metastatic site					
Lymph nodes (n=6)	0	4	2	0	66.7
Lung (n=1)	0	0	1	0	0.0

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Discussion

Since clinical trials have demonstrated the superiority of concurrent chemoradiotherapy over radiotherapy alone for esophageal cancer (9, 11, 12, 28), the current standard of care for patients who are not suitable candidates for surgery, or who do not wish to have surgery, is definitive chemoradiotherapy (29). With regard to far advanced T4 and/or distant lymph node metastasis (M1 Lym) esophageal cancer, a few studies using definitive chemoradiotherapy of 60 Gy combined with cisplatin and 5-FU have been reported. Ohtsu *et al.* (27) reported an overall response rate of 87%, including a CR rate of 33% and a 3-year survival rate of 23%. In the Japanese phase II study, the overall response rate was 68.3%, including a CR rate of 15%, and a 2-year survival rate of 31.5% (30). In the study of Nishimura *et al.* (31), participants were limited to T4 or T4M1 Lym esophageal cancer patients, and the overall response rate was 88%, including a CR rate of 32% and a 2-year survival rate for T4M0 tumor of 27%.

In preoperative chemoradiotherapy, the achievement of a pathologically complete response (pCR) identifies patients with an improved chance of 5-year survival in nearly all trials reported (32). This finding indicates that achievement of a pCR to chemoradiotherapy will lead to further improvement in survival either in the preoperative setting or as definitive local therapy without surgery.

To overcome the therapeutic ratio of standard cisplatin plus 5-FU concurrent chemoradiotherapy, we have focused on an incorporation of TXT into the therapy, which has been extensively used with radiation for the treatment of patients with non-small cell lung cancer and head and neck cancer (14). As a single agent, TXT has demonstrated efficacy against esophageal cancer. Muro *et al.* (33) have demonstrated a response rate of 20% for metastatic esophageal cancer using tri-weekly TXT alone. In addition to cytotoxic activity, TXT acts as an excellent radiation sensitizer, arresting cell-cycles in G2/M-phase, the most radiation-sensitive phase of the cell-cycle (17, 34). In general, the radiation-sensitizing effects of taxanes are seen at very low drug levels, well below the levels required for cytotoxic effects (18). With regard to the administration schedule of TXT with radiation, frequent administration is considered to offer potential for maximizing the drug-radiation interaction by long duration of exposure (14). Weekly TXT has been the most widely investigated schedule in combination with radiation, because weekly administration of TXT demonstrated the most effective cytotoxic dosing (14, 35).

We have considered that 5-FU is a promising partner of TXT. The combination of TXT and 5-FU has been shown to have synergistic anticancer effects both *in vitro* and *in vivo* (36). We demonstrated that the cotreatment with TXT and 5-FU increased the expression of orotate phosphorybosyl transferase (OPRT) and decreased thymidine synthetase (TS) and dihydropyrimidine dehydrogenase (DPD) activity, which can explain why the combination of TXT and 5-FU enhances the antitumor activity of 5-FU (22). Continuous infusion of 5-FU also exhibits an enhanced interaction with

radiotherapy (20, 21). For these reasons, we conducted the current phase I clinical trial, combining weekly administration of TXT and continuous infusion of 5-FU.

Based on our results, the RD for Phase II studies of TXT and 5-FU (in continuous *i.v.* infusion) are 7.5 mg/m^2 and 250 mg/m^2/day, respectively. Esophagitis was dose-limiting and the most frequent toxicity. Three of four patients at Level 2 experienced Grade 4 esophagitis. Mauer *et al.* (37) have reported a phase I study of TXT with concomitant thoracic radiation for lung and esophageal cancer. They observed Grade 4 esophagitis in two of six patients at 20 mg/m^2 weekly TXT with radiation. Fujii *et al.* (38) reported a phase I/II study of weekly TXT and concomitant radiotherapy for head and neck squamous cell carcinoma. The RD of TXT was determined to be 10 mg/m^2, but a high incidence of mucositis was also noted. Thus the radiosensitizing effects of TXT are considered to lead to more severe mucosal toxicity. In our protocol, it was determined that weekly TXT should be paused on the third and sixth week (day 15 and 36) to avoid an excess progression of esophagitis. Other nonhematological and hematological adverse effects were mild in our study. Alopecia, neuropathy, fluid retention, and nail change, which are frequently observed in high-dose administration of TXT, did not occur with our treatment doses.

Conclusion

Weekly administration of TXT combining continuous infusion of 5-FU with concurrent radiotherapy is feasible and safe. The response rates were 85.7% in primary lesions and 66.7% in metastatic lymph nodes; these data are encouraging. A phase II clinical study of this regimen in patients with locally advanced esophageal cancer is now underway.

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