Docetaxel/ TS-1 with Radiation for Unresectable Squamous Cell Carcinoma of the Esophagus - A Phase II Trial

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Abstract. *Background: We tried a new regimen of docetaxel / TS-1 (tegafur-gimestat-otastat potassium) combined with radiation for squamous cell carcinoma of the esophagus in a phase II trial. Patients and Methods: The patients, whose tumor invaded other organs without other organ metastasis, were given TS-1 (60 mg/m^2/day) from days 1 to 14, and docetaxel (20-30 mg/m^2) on days 1 and 8. They received radiation in 2.0 Gy from days 1 to 21. Patients were given a seven-day rest after the first course, and then were treated with the same regimen from days 28 to 49. Results: Seventeen cases were enrolled in the study. The response rate was 76.4% (13/17). The overall 5-year survival rate was 29.6% (5/17) and median survival time was 15.2 months. Adverse events more than grade 3 occurred in 10 cases. Conclusion: This combination therapy may be one of the most effective treatments because of its lower rate of non-hematological adverse events and higher response rate. Three cases also underwent salvage surgery when the tumor recurred, and in one case, chemoradiation to a metastatic nodule on the thoracic wall was added.*

Esophageal cancer is the sixth-most common cause of cancer-related death worldwide (1). Although significant improvements have been achieved in both the diagnosis, and treatment of patients with esophageal cancer, their prognosis remains poor, with 5-year survival of 17% during the period 1996-2004 (2).

Surgery might be a most effective treatment for patients with esophageal cancer. However, chemoradiotherapy is another effective therapy when curative resection is difficult because of advanced stage invading to other organs.

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Chemoradiotherapy has been reported to significantly increase the survival rate of patients with esophageal cancer (3, 4). The standard regimen of the chemoradiation has consisted of 5-fluorouracil (5-FU) and cisplatin concomitant with 50-60 Gy radiation for over 20 years from the 1990s. This regimen is effective and safe, but needs hospitalization as it requires a large amount of hydration and for the control of the severe digestive symptoms; *e.g.* nausea, and appetite loss.

We tried a combination regimen consisting of docetaxel and TS-1 (a drug comprising tegafur, gimeracil and oteracil) concomitant with radiation to assess the possibility of achieving the same efficacy without hospitalization and with reduction of severe digestive symptoms.

Docetaxel has been extensively used with radiation for the treatment of patients with non-small cell lung cancer and head and neck cancer (5, 6). Docetaxel is a novel semi-synthetic taxane and has been shown to enhance response to radiation, with induced mitotic arrest and apoptosis in murine tumor cells (7, 8).

TS-1 was introduced as a novel oral anticancer drug. TS-1 is now considered to be a key treatment modality in the control of head and neck cancer (8, 9) and advanced gastric cancer (10, 11) in Japan. Moreover, it has recently been reported that gimeracil might enhance the efficacy of radiotherapy through suppression of homologous recombination-mediated DNA repair pathways (12, 13).

This combination of docetaxel and TS-1 has been demonstrated to have a synergistic effect which was explained by biochemical modulation of the expression of thymidine synthetase, dihydropyrimidine dehydrogenase, and orotate phosphorybosyl transferase, the components of TS-1 (14, 15). This combination has a synergistic effect on cancer in addition to the radio sensitizing and cytotoxic effect of each drug.

For these reasons, we started this study in 2006 at a single Institute. The recommended dose of docetaxel was determined by dose-escalation phase I study as 30mg/m^2 (16). The degree of dose-escalation was level 3. TS-1 was fixed at 60 mg/m^2.

However, we reduced the dose of docetaxel from 30 mg/m^2 to 20 mg/m^2 according to the recommendation of the Safety Review Committee due to treatment-related death in March, 2010, because it was considered that the dose of level 1 was sufficiently effective for reducing the occurrence of pneumonitis. Three patients were treated at the decreased dose.

Patients and Methods

Eligibility was as follows: The patients were required to have histologically-proven squamous cell carcinoma of the esophagus. The tumor was T4 without other organ metastasis or recurrent cancer. The tumor was a measurable lesion. All areas of the disease were to be encompassed in the radiation port. The patient's Eastern Cooperative Oncology Group (ECOG) performance status had to be 0 to 1. The patient's age was over 20 and under 80 years. Life expectancy was more than 12 weeks. Patients with esophagobronchial fistulas were excluded. Adequate organ function was required: adequate bone marrow function (hemoglobin level >9.5 g/dl, white blood cell count >4,000 mm^3, neutrophil count >2,000/mm^3 and platelet count >100,000/mm^3), adequate hepatic function (total bilirubin level <1.5 mg/dl, asparate aminotransferase and alanine aminotransferase levels <2× the upper limit of normal), adequate renal function (serum creatinin level <1.5 mg/dl). Patients were required to have no other active cancer. The patients provided their written informed consent to receive this chemoradiotherapy at our Hospital.

Seventeen patients were enrolled from April, 2006 to December 2012. In this period, 230 patients with esophageal cancer were treated at our hospital. One hundred and forty-five patients underwent esophagectomy and 55 patients were treated by chemoradiation.

Patients were given TS-1 (60 mg/m^2/day) orally from days 1 to 14, and Docetaxel (20-30 mg/m^2) intravenously on days 1 and 8. Megavoltage radiotherapy was performed with standard fractionation (1.8-2.0 Gy per fraction, five days per week) concurrently with chemotherapy. Patients were given a one-week rest at the fourth week, and then treated with the same regimen from day 29. Radiation fields included gross tumor volumes (primary tumor and involved lymph nodes) and regional lymph nodes (supraclavicular and mediastinal nodes) with adequate margins in all patients. Prescribed dose to gross tumor volumes was aimed at 60 Gy. When the prescription dose conflicted with normal tissue tolerance, altered prescription dose of 54 Gy (in five patients) or 50.4 Gy (in two patients) was applied.

The primary end-point was overall response and secondary endpoints were overall survival, progression-free survival, local control rate and toxicities.

All patients were evaluated every one to two months. The effect of therapy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) (17). Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE v 4.0) (18).

TS-1 has not yet received approval for esophageal cancer in Japan but this study was approved by the Institutional Review Board of Kawasaki Medical School (approval No.204, 204-1).

Statistical analysis. Overall survival was measured from the treatment start date to the date of the patient's death. Time-to-progression (TTP) was measured from the start of treatment to the date of estimated progression according to RECIST. The Kaplan Meier method was used to estimate the overall survival time. Estimated survival times were based on the confirmation date of final survival. Statistical calculations were performed with the JMP® 8 statistical software produced by SAS Institute Inc. (Cary, NC, USA).

Table I. *Patients' characteristics*.

Characteristics		n=17
Gender	Male	15
	Female	2
Age, years	Median	64±8.5
	Range	40-79
Target lesion		
	Esophagus	16
	Cervical lymph node	11
	Mediastinal lymph node	1
T4 organ	Trachea	12
	Aorta	8

Results

Of the 17 measurable cases, 15 patients were males and two patients were females. Their median age was 64 (range 40-79) years old. Target lesions were esophagus in 16 cases, cervical lymph nodes in 11 cases, mediastinal lymph nodes in one case. T4 organs were trachea in 10 cases, aorta in 8 cases (Table I). Some cases were included more than once due to the presence of more than one lesion.

There were three CR, 10 showed PR, one showed SD and three showed PD. The response rate was 76.4% (13/17) and disease control rate was 82.4% (14/17). Four patients underwent salvage esophagectomy and one patient underwent additional chemoradiation for a metastatic pleural nodule of docetaxel/nedaplatin with RT (19). Five-year overall survival was 29.6% (5/17) and the median overall survival time was 15.2 months (Figure 1). Five-year progression-free survival rate of the effectively-treated patients was 41.4% (5/14) and the median progression-free survival time was 26.8 months (Figure 2).

Unfortunately, one case suffered treatment-related death due to cytomegalovirus infection followed by grade 4 pneumonitis. Major toxicities included myelosuppression and esophagitis. Most toxicities were grade 3 or less (Table II). One patient was treated as an outpatient using this regimen.

Discussion

Chemoradiotherapy using docetaxel plus TS-1 concomitant radiation led to a high response rate and high survival rate. In this regimen, patients were free from the need for large amounts of hydration and continuous infusion of anti-cancer drug.

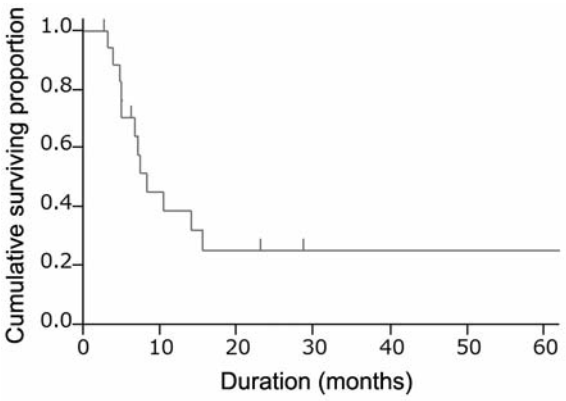

Figure 1. *Overall survival in 17 cases 5-year survival rate was 29.6% (13/17) and the median survival time was 15.2 months.*

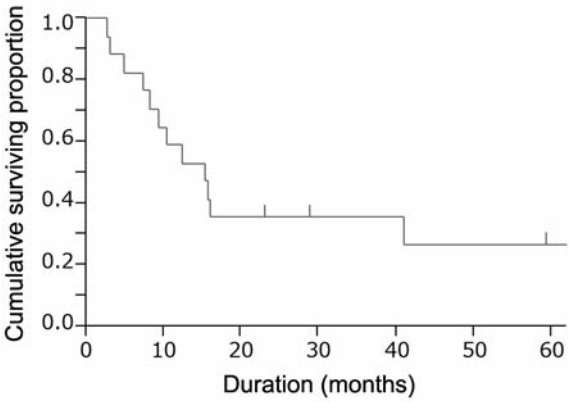

Figure 2. *Progression-free survival in response 14 cases 5-year survival rate was 41.4% (5/14) and the median survival time was 26.8 months.*

There have been some reports of chemoradiation for T4 esophageal cancer using 5-FU plus cisplatin. Ohtsu *et al*. reported in a trial of 21 patients that the 3-years survival rate was 23% and the median survival time was nine months; there were four treatment-related deaths (20). The Japan Clinical Oncology Group (JCOG) reported that the median survival time was 305.5 days, and the 2-year survival rate was 31.5% in a trial with 60 patients. As far as toxicity was concerned, one toxicity-related death occurred. The major form of toxicity exceeding grade 2 was found to be myelosuppression; grade 4 toxicity was observed in five patients (21). In our study, the recurrent cases received second-line chemotherapy with/without salvage surgery. Although our study can not be compared with the study described above, it was a good outcome that five-year overall survival was 29.6%, median survival time was 15.2 months, response rate was 76.4% and disease control rate was 82.4%.

TS-1 has not yet received approval for esophageal cancer by the Ministry of Health, Labor and Welfare in Japan. However, TS-1 has had favorable effects for many kinds of cancers, as mentioned above. A phase I/II study of definitive chemoradiotherapy for esophageal cancer using TS-1 plus cisplatin and concurrent radiation has finished the registration phase and the data have been analyzed by JCOG (22).

When the treatment-related death occurred, the case was valuated by the Safety Review Committee in this trial. The recommendation was that the dose of docetaxel recommended should be reduced from 30 mg/m^2 to 20 mg/m^2, because the response did not differ among each dosage in phase I but there was a possibility that radiation-induced pneumonitis was related to docetaxel (23, 24).

The incidence of severe acute/late radiation-induced pneumonitis was approximately 10% with cisplatin-based second-generation chemotherapy and with radiation (23, 24).

Table II. *Adverse events. (CTCAEv4.0).*

	Grade (n)					
	1	2	3	4	5	Grade 3-5 (%)
Leukocytopenia	0	4	2	1	0	17.6
Neutrophilia	1	4	2	0	0	11.7
Ttronbocytopenia	0	1	1	0	0	5.8
Hemoglobin	0	2	1	0	0	5.8
General fatigue	2	4	0	0	0	0
Esophagitis	2	5	2	0	0	11.7
Fever	1	1	0	0	0	0
Pneumonitis	0	2	0	1	0	5.8
Sepsis	0	0	0	0	1	5.8

Segawa *et al*. reported radiation-induced pneumonitis was severe in the group using docetaxel plus cisplatin with concurrent radiation compared with the group using mitomycin, vindesine and cisplatin in non-small-cell lung cancer (25). Moreover, some studies reported that the incidence of pneumonitis tended to be higher in elderly patients (70 years or older) (26-28). In our study, the treatment-related death was the oldest patient was 79 years - old. Other toxicities including myelosuppression and esophagitis might be reported to increase in elder patients (26, 27), therefore when treating elderly patients, great care should be taken if using this regimen.

TS-1 is the useful anticancer drug which is possible to be administered by oral intake. The response rate in a single-agent for gastric cancer was 44% in phase II study (29). Gimeracil, one component of TS-1, is a dihydropyrimidine dehydrogenase inhibitor used to maintain the concentration

of 5-FU in the blood. This is convenient to be administered and to be effective as same as infusion of 5-FU (10).

Recently, there have been some reports that gimeracil enhanced the efficacy of radiation for cancer by inhibiting rapid repair of X-ray-induced DNA damage in tumors. From this point of view, chemoradiotherapy using TS-1 may be useful in treating patients with locally advanced cancers whose disease progression is difficult to control (12, 13).

In conclusion, chemoradiation using docetaxel plus TS-1 concomitant radiation leads to a high response rate and high local disease control rate. This method has the benefit of no need for high volume hydration and continuous infusion of anti-cancer drug. However, elderly patients must be carefully-monitored to avoid toxicity such as pneumonitis.

Conflicts of Interest

All Authors have nothing to declare.

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