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Phase I Study of Combination Therapy with S-1 and Docetaxel (TXT) for Advanced or Recurrent Gastric Cancer

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Abstract. *Background: S-1, an oral fluorouracil antitumor drug, and docetaxel have both been identified as effective agents for the treatment of gastric cancer. The two drugs have incompletely overlapping principal toxicities, which constitute the rationale for evaluating the effects of a combination of S-1 and docetaxel in this phase I study. The aim of this phase I study was to determine the maximum-tolerated dose (MTD) and the recommended dose of docetaxel with a fixed dose of S-1 in patients with advanced or recurrent gastric cancer. Patients and Methods: The pharmacokinetics of both drugs were evaluated on Day 1 of treatment. Patients with a performance status (PS) of 0 to 2 received docetaxel at the starting dose of 40 mg/m^2 by i.v. infusion over 1 hour on Day 1 and S-1 at the full dose of 80 mg/m^2 daily for two weeks every three weeks. Nine patients were treated with increasing dose levels of docetaxel as follows: (docetaxel/S-1, mg/m^2): 40/80 (Level 1), 50/80 (Level 2) and 60/80 (Level 3) and all the cases were found to be assessable for drug safety, while 7 were assessable for response. Colony-stimulating factor (CSF) was not used in this study. The adverse effects of the treatment were analyzed according to NCI-CTC, version 2, and the response was assessed according to the Japanese Classification of Gastric Cancer, 13th Ed. Results: The MTD was reached at the 50/80 mg/m^2 dose level in three patients out of six, who experienced a dose-limiting toxicity (DLT). The DLTs were neutropenia and allergic reactions. No hematological or non-hematological adverse effects (more severe than Grade 2) were observed in any of the Level 1 patients. However, among the Level 2 patients, 50% developed neutropenia (more severe than Grade 2), 33% developed loss of appetite, 17% developed diarrhea, 33% developed stomatitis and 17% developed allergic reactions. On the other hand, partial response was achieved in 5 (71.4%) of the 7 patients with evaluable lesions. The pharmacokinetics of docetaxel were not altered as compared to that in the historical controls by the administration of S-1. These results indicate that the recommended doses of the two drugs in the combination therapy would be 40 mg/m^2 for docetaxel and 80 mg/m^2 for S-1. Conclusion: The drug combination showed a good safety profile, with neutropenia being a common but manageable adverse reaction. Moreover, the responses observed in the study suggest that the drug combination shows a high degree of efficacy in patients with advanced and or recurrent gastric cancer.*

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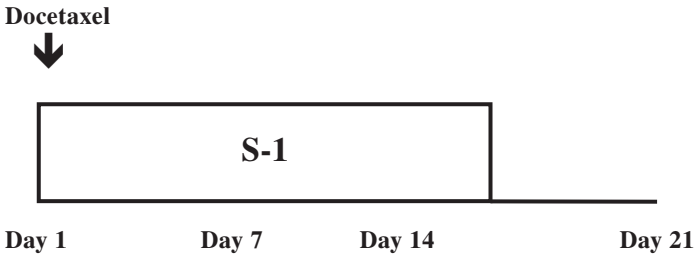
Recent advances in diagnostic and surgical treatment techniques have led to much improvement in the prognosis of gastric carcinoma patients. However, many patients are still diagnosed only in the late stages of the disease and recurrent disease is often found even after the performance of curative surgery. Until recently, gastric cancer was regarded as a poorly chemo-responsive cancer, however several clinical trials have revealed that some chemotherapeutic agents are quite effective against gastric cancer (1,2). FAM was reported to show a short-lived effect in 20-40% of patients (3). EAP (1), FAMTX (4) and ECF (5) were developed as second-generation chemotherapeutic regimens for gastric cancer, however the response rates were not as high as expected and, furthermore, severe adverse reactions were observed. For these reasons, these

Administration of S-1
80mg/m^2/day orally twice daily, from Day1 – Day 14
(Drug-free interval, Day15 – Day21)
Administration of docetaxel
Drip infusion within 60min on Day 1

level	Docetaxel	S-1
1	40mg/m^2	80mg/m^2
2	50mg/m^2	80mg/m^2
3	60mg/m^2	80mg/m^2
4	70mg/m^2	80mg/m^2



***At all dose levels, the administration cycle was repeated every 3 weeks**

Figure 1. *Treatment schedule of combination therapy with S-1 and docetaxel.*

drug regimens have not come to be widely accepted. The standard chemotherapy for gastric cancer has thus not yet been established, although there is a consensus that the prognosis of non-resectable or recurrent gastric cancer patients is better with than without chemotherapy.

Oral fluorouracil antitumor drugs were first developed in 1971 in Japan, leading to the establishment of UFT (6). S-1 is a novel oral fluorouracil antitumor drug that contains a combination of three pharmacological agents: tegafur (FT), which is a prodrug of 5-fluorouracil (5-FU); 5-chloro-2,4-dihydroxypyridine (CDHP), which inhibits the activity of dihydropyrimidine dehydrogenase (DPD) activity; and potassium oxonate (Oxo), which reduces the gastrointestinal toxicity of 5-FU. Phase II studies have demonstrated that S-1 is active against gastric carcinomas (7-13) and this drug has gradually come to be accepted as the front-line regimen for the chemotherapy of gastric cancer in Japan.

Docetaxel (Taxotere; Aventis Pharma Ltd, France) (N-debenzoyl-N-tert- butoxycarbonyl-10-deacetyl baccatin) is a semi-synthetic toxoid with a broad spectrum of preclinical activity against transplanted tumors *in vivo* (14-17). Phase I trials using various schedules identified neutropenia as the dose-limiting toxicity (DLT) of this drug, with non-hematological adverse effects that included mucositis, fatigue and peripheral neuropathy (18-23). A schedule using a 1-hour infusion every 3 weeks produced the highest dose intensity and, since no significant schedule dependency was observed in preclinical studies, this schedule was chosen for a phase II study as a recommended single agent. The phase II study was conducted in Japan and the response rate to the drug was found to be about 20%; however, the noteworthy finding in this study was that there was no cross-resistance with other treatments (24-28). As reported previously (29), TXT and 5-FU have been shown to be synergistic both *in vitro* and *in vivo*, which constitutes the rationale for combining S-1 and docetaxel. However, little is known about the effects of this drug combination in gastric cancer patients.

The aims of the present study were to determine the maximum-tolerated dose (MTD) of docetaxel in combined S-1 and docetaxel therapy administered in 3-week cycles, to establish the recommended dose for phase II studies, to describe the toxicities of the drug combination and to determine their pharmacokinetic profiles.

Patients and Methods

Patient eligibility. The subjects of the study comprised patients with histologically or cytologically proven metastatic or recurrent, or unresectable locally advanced gastric cancer. Prior chemotherapy or adjuvant chemotherapy was permitted, provided it had been completed at least 4 weeks or 2 weeks, respectively, prior to the patient's entry into this study. The inclusion criteria were: age 20 to 75 years, performance status (World Health Organization: WHO) 0 to 2 and an estimated life expectancy of more than 3 months.

Other eligibility criteria included a white blood cell count between 4,000/mm^3 and 12,000/mm^3, absolute neutrophil count of over 2,000/mm^3, platelet count of over 100,000/mm^3, Hb over 9.5g/dl, serum bilirubin level under 1.5 mg/dl, AST and ALT within two times the upper limit of normal for the institution, BUN under 25mg/dl, serum creatinine within the upper limit of normal for the institution and the measured 24-hour creatinine clearance over 50 ml/min. Written informed consent was obtained from all the patients and the protocol was approved by the institutional ethics committees of the participating centers.

Patients were excluded from the trial if any of the following exclusion criteria were present: symptomatic infectious disease, pulmonary fibrosis, interstitial pneumonia, 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 ascites, past history of allergic reaction to polysorbate 80, pregnancy or breast feeding, obstructive bowel disease, other concomitant anticancer therapy drug administration, including flucytocine and a past history of drug allergy. Patients were not permitted to receive corticosteroids or granulocyte colony-stimulating factor (G-CSF) during the study period, except as outlined later. The patient enrolment was started on July 1, 2001 and completed on January 31, 2002. The patient progress was observed until August 31, 2003.

Evaluations. All the patients underwent clinical examinations, including evaluation of the performance status, complete blood cell count (CBC), liver function tests, renal function tests, creatinine clearance determination and urinalysis, before they were enrolled in the study . ECG, chest X-ray and computed tomography, upper GI series, gastrointestinal fiberscopy (GIF) and/or barium enema were performed when judged necessary. Additional imaging examinations were performed if there was a clinical indication, or to measure the extent of the known disease.

During the study period, all the patients were reviewed weekly for symptoms of toxicity and underwent clinical examinations, including determination of weight and performance status, while CBC was performed twice each week. Liver and renal function tests were performed every three weeks. CT scanning and imaging of measurable disease were done in every cycle or once in every two cycles until death. Tumor markers, including CEA and Ca19-9, were monitored once each month.

Toxicity due to the treatment was evaluated according to NCI-CTC, version 2. DLT that required additional patient enrolment was defined in advance as one or more of the following, based on the toxicity criteria of NCI-CTC, version 2: Grade 4 neutropenia, Grade 4 thrombocytopenia or any Grade 3 nonhematological toxicity, except general fatigue, emesis/nausea and alopecia. The subjects were monitored during the first cycle for evaluation of drug toxicity and pharmacokinetics. No dose modification for toxicity was allowed in this study.

Although patients were not required to have measurable or assessable disease for this phase I study, in those patients in whom the disease was measurable or assessable at study entry the response was evaluated according to the Japanese criteria for gastric cancer. All responses were subjected to independent verification. For the patients showing good response to the treatment, the response duration was defined as the time from the commencement of the treatment protocol until the first documentation of progression or relapse. Overall survival was estimated using the Kaplan-Meier product-limit method and the 95% confidence interval for median survival was estimated by the Brookmeyer-Crowley method.

Table I. *Background of the patients.*

Patient number	9	Histology	
Sex: Male	6	Differentiated	3
Female	3	Poorly-diff	6
Age	47-75	Target lesion	
(median)	(59)	Primary tumor	6
PS 0	6	Lymph node	6
1	3	Liver	2
		Peritoneum	3
Previous therapy		(Ascites)	(2)
none	6	Total cycles	4-16
op+adjuvant chemo	3	(median)	(7)

Drug administration. S-1 was administered orally at a dose of 80 mg/m^2 within 30 minutes of the morning and evening meals for two weeks, followed by a drug-free interval of a week (one cycle). Docetaxel was diluted in 100 ml of 0.9% saline and infused over one hour on the morning of Day 1; the infusion was started at the same time as the S-1 administration. No steroids or G-CSF administration was permitted, except in an emergency. Antiemetic treatment with ondansetron and diuretic treatment for edema were allowed as deemed necessary.

Dose level. The starting dose level (level 1) of docetaxel was set at 40 mg/m^2. This level was two-thirds of the recommended dose for a single-agent phase II study of docetaxel and the dose escalation was conducted in increments of 10 mg/m^2, until a dose of 70 mg/m^2 was reached at Level 4 (Figure 1). At all the levels, the administration cycle was repeated every 3 weeks. Patients were not allowed to escalate or reduce the dose of S-1, or receive the drug for longer or shorter periods of time. Patients who showed response continued to receive treatment until detection of disease progression or development of serious toxicity. The protocol was discontinued at any time that the patient expressed the desire to discontinue it.

At least three patients were enrolled at each level. If DLT was observed following the first cycle in one or two patients, then an additional three patients were enrolled. If three or more patients developed DLT, then enrolment was discontinued and the dose at this level was regarded as the MTD. The maximal-acceptable dose (MAD) was defined as the highest dose that produced tolerable, manageable and reversible toxicity. DLT that required additional patient enrolment was defined in advance, as mentioned above, based on the toxicity criteria of NCI-CTC, version 2. The patients were monitored during the first cycle for evaluation of drug toxicity and pharmacokinetics. No dose modification because of toxicity was allowed in this study.

Assessment of response. The responses to treatment of the primary and metastatic lesions were assessed according to the World Health Organization (WHO) criteria. The primary and metastatic lesions

Table IIA. *Hematological toxicities (first cycle).*

	NCI-CTC grade				
	1	2	3	4	Grade 3 and 4 (%)
Level 1 (n=3)					
leukocytopenia	1	0	0	0	0
neutropenia	1	0	0	0	0
anemia	0	0	0	0	0
thrombocytopenia	0	0	0	0	0
Level 2 (n=6)					
leukocytopenia	1	2	2	0	33
neutropenia	0	1	1	2	50
anemia	3	0	0	0	0
thrombocytopenia	0	0	0	0	0

Table IIB. *Non-hematological toxicities (first cycle).*

	NCI-CTC grade				
	1	2	3	4	Grade 2,3 and 4 (%)
Level 1 (n=3)					
appetite loss	1	0	0	0	0
nausea/vomiting	1	0	0	0	0
diarrhea	0	0	0	0	0
stomatitis	1	0	0	0	0
fever elevation	0	0	0	0	0
hypersensitivity	0	0	0	0	0
Level 2 (n=6)					
appetite loss	0	2	0	0	33
nausea/vomiting	1	0	0	0	0
diarrhea	3	1	0	0	0
stomatitis	0	2	0	0	33
fever elevation	1	0	0	0	0
hypersensitivity	0	0	1	0	17

were evaluated by gastrointestinal fiberscopy, computed tomography, ultrasonography and other radiographic examinations. Complete response was defined as the disappearance of all evidence of cancer for more than 4 weeks. Partial response (PR) was defined as at least 50% reduction in the sum of the products of the perpendicular diameters of all the lesions for more than 4 weeks, without any evidence of new lesions or progression of the lesions. No change (NC) was defined as less than 50% reduction, or less than a 25% increase in the sum of the products of the perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as more than a 25% increase in more than one lesion, or the appearance of new lesions.

The response to treatment of the primary lesion was assessed according to the criteria for response assessment of chemotherapy for gastric carcinoma established by the Japanese Research Society for Gastric Cancer (30).

Pharmacokinetics. The pharmacokinetics of docetaxel and S-1(tegafur) were studied during the first cycle of therapy. For assays, 10-ml blood samples were taken from the control arm of the docetaxel infusion group at the following time-points: prior to the start of the drug infusion, the end of docetaxel infusion and 2 hours, 4 hours and 8 hours after starting both the medications on the first day of therapy. All the blood samples were centrifuged immediately and the separated plasma samples were frozen at -20˚C until use.

The frozen plasma samples were thawed at ambient temperature, then vortexed and centrifuged for 5 minutes at 3,000 rpm to remove fibrous materials that can clog extraction columns.

Docetaxel concentrations in the plasma were determined by high-performance liquid chromatography (HPLC, reverse-phase) using the Inertsil® ODS 2 column (5 μm, 4.6 x 250 mm, GL Sciences, Tokyo, Japan) with UV detection (31); this method involves a solid-phase extraction (Bond Elut® C2, Varian, Harbor, CA, USA). Docetaxel and the internal standard were determined by an UV detector adjusted to 225 nm and the peak height was used for the quantification. The lower limit of detection in the assay was 10.0 ng/ml and linearity was confirmed up to 4,000 ng/ml in the plasma. Pharmacokinetic parameters were calculated using the software WinNonlin (Ver.3.1, Pharsight Co., North Carolina, USA). The peak plasma concentration (Cmax) was taken from the actual value . The area under the plasma concentration-time curve from time 0 to T, AUC (0 – T), where T represents the time-point of the last measurable concentration, was calculated by the trapezoidal method (11).

Results

Patient characteristics. Nine patients were enrolled in the study and the patient characteristics are summarized in Table I. There were 6 males and three females, ranging in age from 47 to 75 years old (median, 59 years). The patient performance status (PS) was evaluated to be 0 in six cases and 1 in three cases. Six patients had stage IV gastric cancer and three had recurrent gastric cancer and had undergone adjuvant chemotherapy with UFT and PSK. Six of the nine cases had poorly- differentiated adenocarcinoma and three had well-differentiated adenocarcinoma. The target lesions in these cases are listed in the tables. The total number of chemotherapy cycles completed in the patients ranged from 4 to 16 cycles (median 7 cycles).

Toxicity. All the patients were assessable for toxicity and the adverse effects are summarized in Tables IIA and IIB. None of the patients entered into Level 1 developed DLT, while three of the six patients in Level 2 developed DLT during the very first treatment cycle. These DLT's included neutropenia in two patients and hypersensitivity reaction in one patient. No hematological or non-hematological adverse effects (more severe than Grade 2) were observed in any of the Level 1 patients. However, among the patients at Level 2, two developed Grade 4 neutropenia and one developed Grade 3 neutropenia. With respect to

Table III. *Response of each case.*

	Response	PS	Lesions	Cycles	Outcome	** Duration
Level 1						
1.	NC	0	Primary: NC, Liver : PR, LN: NC	4	A	762
2.	PR	0	LN: PR	10	D	352
3.	PR	0	Primary: PR, Liver: PR, LN: PR	9	D	344
Level 2						
1.	ND	0	Ascites: ND	1	A	696
2.	PR	1	Primary: PR, LN: PR	16	A	678
* 3.	PR	0	LN: PR	7	D	627
4.	PR	1	Primary: PR, Peritoneum: PR	5	A	654
5.	NC	1	Primary: NC, LN: NC, Ascites: CR	12	D	388
6.	ND	0	Primary: ND	–	D	327

* One DLT case of Level 2 was continued with Level 1 dose
** Until Aug. 31. 2003

leucopenia, one each of the first 2 patients had Grade 3 and Grade 2 leucopenia, and the third patient had Grade 1 leucopenia. In most of these patients, the neutrophil count reached its nadir on Day 6 or Day 7 of chemotherapy and returned to its previous level by Day 21.

As for non-hematological adverse effects, no apparent adverse effects were observed in any of the Level 1 patients. Among the Level 2 patients, Grade 2 loss of appetite and stomatitis occurred in two patients each, while Grade 2 diarrhea was reported in one patient; Grade 1 nausea/vomiting occurred in two patients, Grade 1 diarrhea in one patient and Grade 1 pyrexia in one patient. One patient (patient No 6 in Level 2) experienced a flushing and choking sensation immediately after the commencement of docetaxel infusion during the first cycle of Level 2 and the drug infusion was stopped immediately. This phenomenon was completely reversed without any medication, except oxygen administration. No decrease in the blood pressure or loss of consciousness occurred, presumably because of the prompt action of the attending medical staff. However, according to the NCI-CTC, version 2, we regarded this as a Grade 3 hypersensitivity reaction and abandoned the protocol in this patient. In one Level 2 patient who developed Grade 4 neutropenia (patient No. 3 in Level 2), the second cycle of treatment was administered with the Level 1 dose of docetaxel. Interestingly, the patient did not develop any hematological or non-hematological toxicities and 7 cycles of treatment were completed, until progressive disease was detected, as described later.

Treatment response. The characteristics of the evaluable lesions in each patient and the response status are summarized in Table III. Overall, 4 to 16 cycles (median 7 cycles) of the S-1 and docetaxel combination therapy could be completed in the patients.

Table IVA. *Response rate.*

	CR	PR	NC	PD	Response rate (%)
Overall (n=7)	0	5	2	0	71.4%
Level 1 (n=4) (TXT; 40mg/m^2)	0	3*	1	0	75.0%
Level 2 (n=3) (TXT; 50mg/m^2)	0	2	1	0	66.7%

* One DLT case of Level 2 was continued with Level 1 dose.

Table IVB. *Local response rate.*

Site of tumor	CR	PR	NC	PD	Response rate (%)
Primary lesion (n=5)	0	3	2	0	60.0%
Metastatic site					
Liver (n=2)	1	1	0	0	100.0%
Lymph nodes					
Abdominal (n=6)	0	4	2	0	66.7%
Peritoneum (n=2) (Ascites)	0	1	1	0	50.0%

The evaluable lesions were 5 primary lesions, 2 liver metastasis, 6 distant lymph node metastasis and 2 peritoneal lesions, including one ascites and one disseminated disease evaluated at the second look operation.

Among the 7 cases with evaluable lesions, 5 (71.4%) showed PR, while 2 showed NC and no progressive disease after 4 cycles of the treatment, as summarized in Table

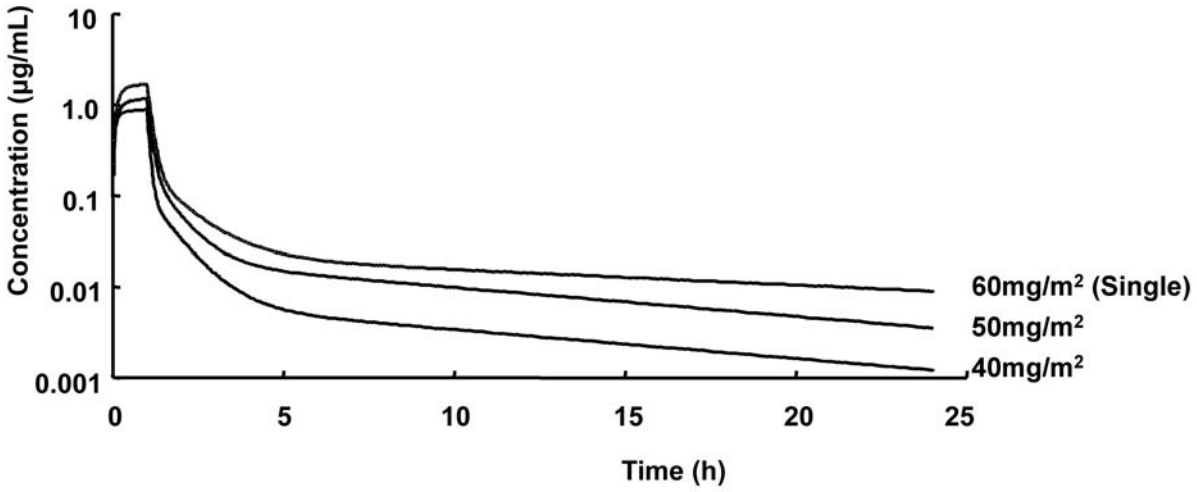


Figure 2. *Docetaxel concentration- time curves.*

Table V. *Pharmacokinetic parameters of TXT, FT and 5-FU.*

	TXT		FT		5-FU	
	$AUC_{(0-\infty)}$ (μg h/mL)	C_{max} (μg /mL)	$AUC_{(0-8)}$ (ng h/mL)	C_{max} (ng /mL)	$AUC_{(0-8)}$ (ng h/mL)	C_{max} (ng /mL)
Level 1	1.13	1.12	15593.2	2890.5	536.3	92.5
(n=2)	1.09	1.03	9817.1	1537.5	508.7	108.1
mean	1.11	1.08	12705.2	2214.0	522.5	100.3
	1.34	1.10	9583.7	2092.1	783.9	143.1
Level 2	1.33	1.10	11262.5	2148.2	965.7	185.1
(n=3)	2.06	1.45	12546.9	3141.8	821.9	139.5
mean	1.57	1.22	11131.0	2460.7	857.2	155.9

IVA. The response rate to the treatment did not differ among the different docetaxel dose level groups. In this assessment, patient No. 3 was evaluated as a Level 1 case, because even the first cycle in Level 2 had not been completed in this patient. As shown in Table IVB, PR was achieved in 3 (60.0%) out of 5 cases with a primary advanced cancer of the stomach; PR was also noted in 1 patient with liver metastasis and 4 out of 6 patients (66.7%) with distant lymph node metastases. One patient with liver metastasis showed CR. Moreover, patient No.4 of Level 2, in whom marked peritoneal dissemination was observed at the time of initial operation, causing the operation to be abandoned, showed shrinkage of the tumor and disappearance of the peritoneal disease, except for one lesion 3mm in size, at the second-look operation after 4 cycles of treatment.

Survival of the patient. The survival of the patients was followed up until the end of August 2003; the outcome and survival times are summarized in Table III and the survival curves are presented in Figure 2. Four patients died and 5 patients are still alive. The survival time of the patients who completed the treatment ranged from 344 days to 762 days and the median survival time of the patients (excluding Cases No. 1 and 6 of Level 2) was determined to be 627 days, which indicated that this combination regimen is promising for the treatment of gastric cancer and that it would be worthwhile to proceed to a phase II study.

Pharmacokinetics of docetaxel, FT and 5-FU. The pharmacokinetic parameters of docetaxel and S-1 at each of the dose levels were examined in 5 patients, as shown in Table V. The time of disappearance of docetaxel from the plasma is shown in Figure 3. The values of the pharmacokinetic parameters of docetaxel in this combination study regimen were similar to those reported previously in the docetaxel-alone study (32). As for FT and 5-FU, their pharmacokinetic parameters at each dose level were similar to those reported previously (11). The occurrence of bone marrow suppression and the response of the tumor were not correlated with the Cmax or AUC of any of TXT, FT, or 5-FU.

Discussion

Docetaxel exerts its antineoplastic actions by promoting the assembly of tubulin and stabilizing the formed polymers against depolymerization, which causes inhibition of the G2-M-phases of the cell cycle (14). This mechanism of action is markedly different from that of 5-FU. 5-FU is widely

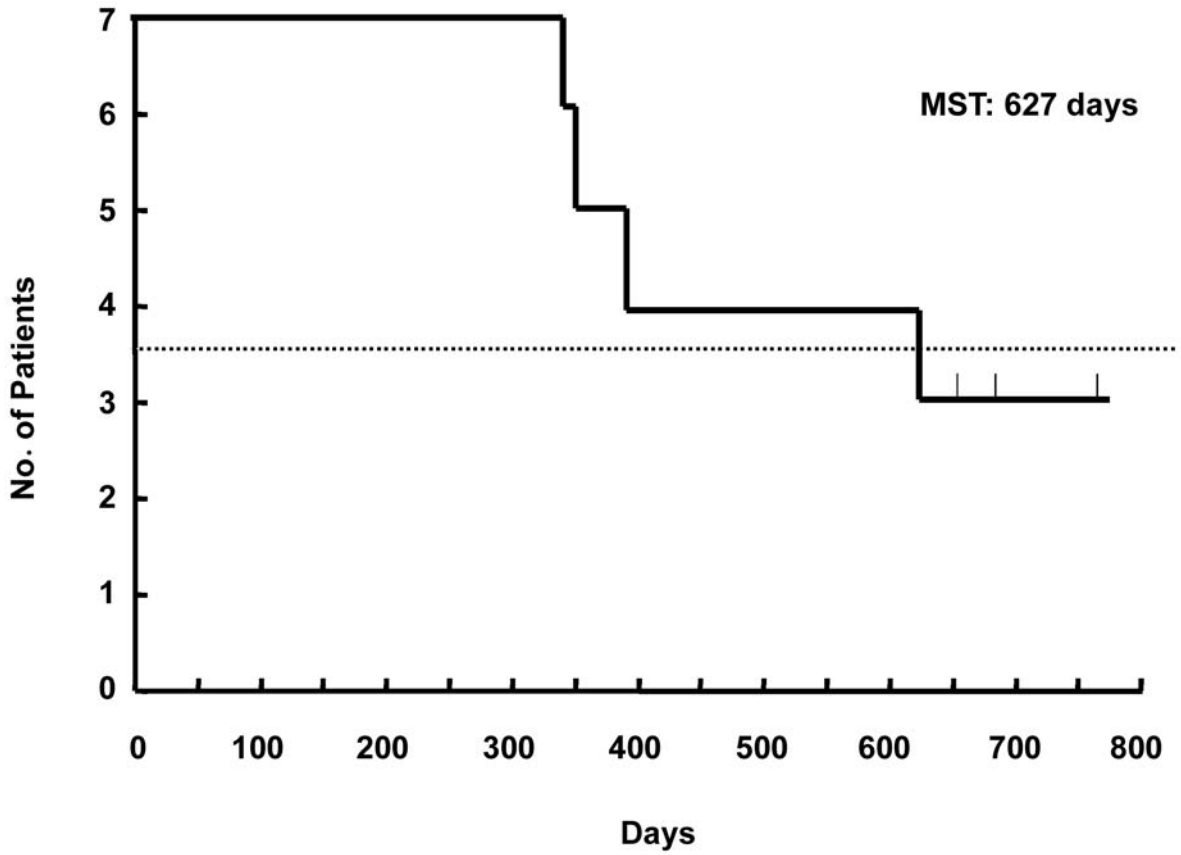


Figure 3. *Survival curve of the patients in the study. The median survival of the seven patients who received the combination drug therapy in this study was 627 days.*

accepted as a therapeutic agent for a variety of solid tumors, but the drug is rapidly degraded in the body (33). The activity of the degradation enzyme of 5-FU, namely DPD, has been demonstrated to play the key role in the anti-tumor effect of the drug against several solid tumors (34). A correlation has been reported to exist between the expression of DPD and the response to 5-FU for a variety of tumors (35,36). TS-1, a newly developed oral tegafur compound, contains CDHP which transiently, but strongly, inhibits DPD. The presence of this enzyme in the formulation allows the plasma concentration of 5-FU to be maintained at a high level for 8 hours, giving a high response rate for gastric cancer. A phase II study revealed a response rate to the drug of 45% and a median survival rate of the patients of 275 days. This response rate is equivalent to that for low-dose FP therapy, as reported by us elsewhere. However, S-1 treatment can be administered on an outpatient basis, which is the most striking difference from other intensive chemotherapies, including those with low-dose FP (37,38) and MTX/5FU (39). A high response rate coupled with maintenance of a high quality of life was achieved with this treatment. Another point that must be emphasized here is that S-1 is active even against disseminated peritoneal metastases in gastric carcinoma patients. This was confirmed by Mori *et al.* (40) using the mouse model of gastric cancer with disseminated peritoneal disease. A high concentration of 5-FU was confirmed in the intraperitoneal tumor lesions in the S-1 group and prolonged survival was observed. However, the mechanism by which the high concentration of 5-FU is maintained in the peritoneal cavity is not yet known.

TXT has been used clinically in combination with 5-FU for several reasons (41-43). First, TXT and the fluoropyrimidines have overlapping antitumor spectra, including against breast, esophageal and head and neck cancer; taxane-fluoropyrimidine regimes may become increasingly useful as first-line treatment in patients with metastatic breast cancer as anthracyclines are more frequently used in the adjuvant setting. Second, their principal toxicities do not overlap completely. Neutropenia is the principal toxicity of TXT, whereas stomatitis and diarrhea are the predominant toxicities of fluoropyrimidies in the most commonly used

regimens. Finally, the principal mechanisms of the antineoplastic activity of the taxanes and fluoropyrimidines are different. 5-FU arrests tumor cell proliferation in the G1- and S-phases of the cell cycle and prevents tumor cells from entering the G1/M-phase, whereas the latter is the phase at which the cells are most prone to taxane-induced cytotoxicity.

The basic rationale for the use of a combination of S-1 and TXT is as follows: 1) additive/synergistic effects of the drugs may be expected ; 2) the quality of life of the patient can be maintained because this therapy can be administered from the outpatient clinic. As demonstrated in the Results section, this was true for most of the patients enrolled in the study. Moreover, no unmanageable adverse effects occurred during the treatment. As for neutropenia, the nadir begins from 5 to 7 days after the start of a treatment cycle, but the neutrophil count recovers by 14 or 21 days: The WBC count was within normal limits in all the patients. In a preclinical study, Takahashi *et al.* demonstrated, using a rat model in the context of combined therapy with S-1 and TXT, that administration of TXT on Day 1 is better than administration of the drug on Day 8, in terms of both the efficacy of the regimen and the incidence of adverse effects. The results in our study support this contention.

Whether synergistic actions or biochemical modulation underlie the superior efficacy of the drug combination is not yet fully understood. However, since it has been reported that the activities of DPD, TS and OPRT are closely related to the effects of 5-fluorouracil, it is possible that these enzyme activities are modulated by TXT. Further studies and clinical trials are required to clearly elucidate the basic mechanisms and clinical benefits of the treatment and, additionally, to compare them to those of other intensive therapies (44). A phase II clinical trial of this regimen in patients with advanced and recurrent gastric cancer is now under way.

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