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ORIGINAL ARTICLE

Phase I and pharmacokinetic study of S-1 administered for 14 days in a 21-day cycle in patients with advanced upper gastrointestinal cancer

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Abstract
Purpose S-1 is a novel oral fluoropyrimidine that combines tegafur with CDHP and oxonic acid. To decrease the incidence of late onset, severe diarrhea observed in a previous study, a phase I study was conducted to determine the maximum tolerated dose (MTD) of S-1 utilizing a 14-day schedule, repeated every 21 days, in patients with chemotherapy–refractory upper gastrointestinal malignancies.
Methods S-1 was administered orally, twice-daily, at an initial dose level of 30 mg/m^2/dose; doses were escalated by 5 mg/m^2 at each level. A minimum of three patients were enrolled at each dose level. S-1 toxicity, antitumor activity, and pharmacokinetics were assessed. The MTD was based on the dose limiting toxicity (DLT) during the first treatment cycle.
Results At 30 mg/m^2 no DLT was observed in the first three evaluable patients. Two of the first three patients at the 35 mg/m^2 dose level developed DLTs (grade 3 rash and dehydration). An additional nine patients were subsequently treated at 30 mg/m^2 without DLT and this dose was established as the MTD. Common toxicities at 30 mg/m^2 included diarrhea, nausea, skin rash, anorexia, and fatigue. No grade 4 toxicities were observed. One partial response was seen in a patient with gemcitabine-refractory pancreatic adenocarcinoma and ten patients with pancreatic, gastric, or gallbladder carcinomas achieved stable disease as their best response to therapy. The $AUC_{(0–8)}$ of 5-FU at the 30 and 35 mg/m^2 dose levels were 875 ± 212 and 894 ± 151 h ng/ml, respectively.
Conclusions In a 14-day dosing schedule, the MTD of S-1 was 30 mg/m^2 and preliminary evidence of antitumor activity was seen in a North American population with refractory upper gastrointestinal malignancies.

Keywords S-1 · 5-Fluorouracil (5-FU) · Gastrointestinal malignancies · Antitumor activity · Phase I · Pharmacokinetics

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Introduction

5-Fluorouracil (5-FU) remains one of the most commonly used chemotherapeutic agents for upper gastro-

intestinal malignancies. Unfortunately, response rates associated with single agent 5-FU are low, and it is more commonly used in combination with other cytotoxic drugs for many of these malignancies. While such combination regimens have been associated with higher response rates, they have also been associated with more toxicity and only marginal improvements in overall survival [5, 23, 24, 39, 40].

S-1 is an oral fluoropyrimidine in which Tegafur (FT) [5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H) pyrimidinedione] is combined with two classes of modulators, Gimeracil (CDHP) [5-chloro-2,4-dihydroxypyridine] and oteracil potassium (Oxo) [monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate] [30]. Tegafur is converted to 5-FU in the liver by cytochrome P450 (CYP) 2A6 after oral administration [14, 16]. CDHP inhibits the dihydropyrimidine dehydrogenase (DPD)-dependent catabolism of 5-FU, resulting in enhanced and prolonged tumor concentrations of 5-FU in blood and tumor tissue [34]. Another component of S-1, Oxo, blocks phosphorylation of 5-FU and has been shown to reduce 5-FU-induced gastrointestinal toxicity [29, 33].

S-1 has demonstrated promising activity with gastric, colorectal, head and neck, and non-small cell lung and breast cancer in phase I and II studies performed in Japan [8, 13, 15, 17–19, 21, 25, 31, 32]. Subsequent studies have also suggested differences in S-1 metabolism and toxicity between Japanese and North American or European populations [4, 6, 12, 37, 38]. Specifically, late onset of diarrhea tended to occur more commonly in North American and European populations, whereas hematologic toxicity was more common in Japanese populations.

Most prior studies with S-1 have utilized a 28-day schedule of S-1, repeated every 35 days. To limit the potential toxicity of S-1 in a North American population, we explored a dosing schedule in which S-1 was given twice daily for 14 consecutive days every 21 days. The primary objective of this phase I clinical trial was to determine the maximum tolerated dose (MTD) of S-1 with this schedule. Secondary objectives were to characterize the pharmacokinetics of S-1 components (FT, CDHP, Oxo) and their metabolites, and to describe any evidence of antitumor activity in this population.

Patients and methods

Patient selection

The protocol for this clinical trial and the informed consent document were approved by the Dana-Farber/Partners Cancer Care Scientific Review Committee and Institutional Review Board. All patients were required to provide written, informed consent to participate in the trial. Eligibility criteria for this trial included histologically confirmed, advanced upper gastrointestinal malignancies, including esophageal, gastric, pancreatic and biliary tract cancers that were refractory to conventional treatment or for which no standard therapy exists. Patients at least 18 years of age with Karnofsky Performance Status $\geq 50\%$ and life expectance ≥ 12 weeks were included in the study. In addition, all patients had adequate bone marrow function (absolute neutrophil count $\geq 1{,}500$ cells/μl, hemoglobin > 9.0 g/dL, and platelet count $\geq 100{,}000$ cells/μl); adequate hepatic function (total bilirubin $\leq 1.5 \times$ the upper limit of normal, and alanine aminotransferase/aspartate aminotransferase $\leq 2.5 \times$ the upper limit of normal [ULN] or $\leq 5 \times$ the ULN if liver metastasis present); and, adequate renal function (serum creatinine $\leq 1.25 \times$ the ULN). Prior chemotherapy for advanced disease, including prior therapy with fluoropyrimidines, was allowed. Conditions resulting in exclusion from the study included the following: known brain metastasis, history of DPD deficiency, any serious uncontrolled medical disorder or active infection, uncontrolled or clinically significant cardiovascular disease (as indicated by a myocardial infarction within 6 months, atrial or ventricular arrhythmias), congestive heart failure, gastrointestinal disorders that would interfere with absorption, and females who were either pregnant or lactating. Adequate contraception was required for fertile patients.

Treatment plan

S-1 was supplied by Taiho Pharma USA Inc. (Princeton, NJ, USA) in capsules containing 20 or 25 mg Tegafur (FT). Individual doses were calculated based on body surface area and rounded as closely as possible to the calculated dose for the number of capsules to be dispensed. At each dose level, S-1 was administered orally, twice daily for 14 consecutive days followed by a 7-day recovery period in a 21-day cycle. Patients were instructed to take S-1 1 h before or at least 1 h after meals to avoid food effects [22].

Three dose levels were planned in the dose escalation schema. The initial dose level (Level 1) was started at 30 mg/m^2, based on our prior clinical experience with other schedules. At dose levels 2 and 3, the dose of S-1 was planned at 35 and 40 mg/m^2, respectively. Patients at each administered dose level continued to receive S-1 until disease progression, intolerable toxicity or withdrawal of consent.

S-1 dose was delayed if patients experienced unacceptable drug-related hematologic and non-hematologic toxicity. There was no replacement of a missed S-1 dose. No extension of S-1 treatment into the recovery period (day 15 to day 21) was allowed. If patients required more than 4 weeks to resume the next cycle of S-1, they were discontinued from the study. The lowest dose allowed for dose reduction was 25 mg/m^2/dose in 5 mg/m^2 steps. Supportive treatment such as antiemetics, antidiarrheals, analgesics, and blood products were permitted at the investigator's discretion.

Toxicity classifications

All toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 [3]. Dose limiting toxicity (DLT) was defined as the following during the first cycle: Grade 3 or worse nonhematologic toxicity excluding nausea/vomiting and diarrhea; Grade 3 or worse nausea/vomiting and diarrhea uncontrolled by antiemetic or antidiarrheal treatment; Grade 4 neutropenia lasting more than 3 days; Grade 4 thrombocytopenia (Grade 3 thrombocytopenia associated with bleeding and requiring transfusion); febrile neutropenia. Other DLT standards included a patient's inability to take more than 75% of the planned chemotherapy dose during the treatment cycle or toxicity which required more than a 14-day delay of a therapeutic cycle. The MTD of S-1 in this dosing regimen was defined as the highest dose level at which less than 33% of the patients experienced a DLT.

Evaluation of response

Computed tomography produced a baseline assessment of all measurable disease within a 28-day time frame before the first cycle of therapy. Over the course of the trial, therapeutic response was evaluated by computer tomography after the completion of every second cycle (6-week intervals). We performed response confirmation studies at least 4 weeks after documentation of initial response. Patient response was classified according to RECIST criteria [35].

Pharmacokinetic analysis

During the first cycle of therapy we studied blood samples in order to define the plasma pharmacokinetics (PK) of S-1. Samples (8 ml each) were drawn from a peripheral vein directly into EDTA coated Vacutainer before dosing, and at 0.5, 1.0, 2.0, 4.0, 6.0 and 8.0 h after S-1 dosing on Day 1, as well as prior to and 2 h after the S-1 morning dose on Days 8 and 14. Sample tubes were mixed by inversion and placed on wet ice until centrifuged (2,000*g*, 10 min, 4°C) within 15 min. The plasma was removed and stored at −70°C until assayed. The concentrations of FT, 5-FU, CDHP, cyanuric acid (CA), Oxo, α-fluoro-β-alanine (FBAL), and uracil were measured (at the designated laboratory, Tandem Lab, Ewing, NJ, USA) in plasma by validated bioanalytical methods using liquid chromatographic-tandem mass spectrometry (LC/MS/MS), based on Matsushima's method [20]. For the S-1 components (FT, CDHP, and Oxo) and 5-FU, FBAL, CA, and uracil plasma concentration, PK parameters ($AUC_{0-8\,h}$, C_{max}, and T_{max}) were derived for each analyte using noncompartmental methods with *WinNonlin Professional* Version 5.0 (Pharsight Corp, Mountain View, CA, USA). Since sample collection on Day 1 did not exceed 8 h, the terminal elimination rate constant was not studied in this protocol.

Results

Patient population and characteristics

A total of 16 patients, 12 (75%) men and 4 (25%) women, were enrolled in this study. The median age of the patient population was 58.5 years (range, 46–70 years). Thirteen (81%) patients were Caucasian, two (13%) were Hispanic and one (6%) was African American. The majority of patients ($n = 15$, 94%) had a Karnofsky performance status of 70% or above. Esophageal and gastric cancers ($n = 9$, 56%), as well as pancreatic cancer ($n = 5$, 31%) were the most common tumor types. All but one patient had received prior chemotherapy, five patients (31%) had received definitive surgery and nine (56%) had received prior radiotherapy. The characteristics of patients enrolled in this study are listed in Table 1.

Assessment of the maximum tolerated dose

One patient withdrew consent after receiving only 6 days of treatment at the first dose level, and was considered nonevaluable. Three patients completed treatment at the 30 mg/m^2 dose level. No dose limiting toxicities were observed in the first 3 DLT evaluable patients treated at the 30 mg/m^2 dose level. At the next dose level of 35 mg/m^2, 2 of the 3 patients developed dose-limiting toxicities. One patient experienced grade 3 skin rash and grade 3 dehydration during the first cycle of treatment, which resolved without sequelae. The second patient experienced grade 3 abdominal pain, nausea, anorexia, stomatitis and dehydration during the first cycle of treatment.

Table 1 Patient characteristics ($N = 16$)

Age (years)	
Median	58.5
Range	46–70
Gender *n* (%)	
Male	12 (75)
Female	4 (25)
Race *n* (%)	
Caucasian	13 (81.3)
African American	1 (6.3)
Hispanic	2 (12.5)
Karnofsky performance score *n* (%)	
100%	6 (37.8)
90%	3 (18.8)
80%	3 (18.8)
70%	3 (18.8)
50%	1 (6.3)
Primary tumor site *n* (%)	
Esophagus	4 (25.0)
G–E junction	1 (6.3)
Stomach	4 (25.0)
Pancreas	5 (31.3)
Biliary tract (extrahepatic)	2 (12.5)
Prior chemotherapy *n* (%)	
Yes	15 (93.8)
No	1 (6.3)
Prior surgery *n* (%)	
Yes (resected)	5 (31.3)
No	11(68.8)
Prior radiotherapy *n* (%)	
Yes	9 (56.3)
No	7 (43.8)

There were no grade 4 toxicities observed in the 35 mg/m^2 dose level. Because of these DLTs in the 35 mg/m^2 dose level, an additional nine patients were subsequently treated at the 30 mg/m^2 dose level. None of the additional patients experienced a DLT at the original dose level. Therefore, the MTD was defined as 30 mg/m^2.

Dose intensity

Dose intensity was summarized for 13 patients at the defined MTD (30 mg/m^2). An average of 5.3 cycles of S-1 were initiated at this dose level (range 1–17 cycles). Five of 13 (38.5%) patients received more than 4 cycles of treatment. At the 30 mg/m^2 dose level, S-1 administration was withheld in three patients during cycle 1. During the entire treatment period, S-1 dose was reduced in 4 (30.8%) patients at the 30 mg/m^2 dose level. Six of 13 (46.2%) patients received more than 75% of the target S-1 dose during the entire treatment period at this dose level.

Toxicity

A total of 13 patients were treated at the 30 mg/m^2 dose level, with the most common toxicities being diarrhea ($n = 9$, 69.2%), nausea, and skin rash (each $n = 8$, 61.5%). Less common toxicities included anorexia and fatigue, which occurred in six (46%) patients, and pyrexia and abdominal pain, which occurred in five (39%) patients. Vomiting occurred in four (31%) patients and stomatitis and hand–foot syndrome occurred in three (23%) patients as a result of the S-1 dosing. No patient developed neutropenia; however, four (31%) patients developed mild anemia and three (23%) patients developed thrombocytopenia. Toxicities reported in at least three patients in either dose level are summarized in Table 2.

No grade 4 toxicities were reported as adverse events at the 30 mg/m^2 dose level. At the 30 mg/m^2 dose level, grade 3 elevated transaminase levels were observed for two (15.4%) patients during treatment, grade 3 elevated creatinine was noted in one patient, and one patient experienced grade 3 decreased serum sodium. One patient in the 30 mg/m^2 cohort discontinued treatment due to grade 3 elevated serum creatinine that was considered by the investigator to be unrelated to S-1. No patients died due to an adverse event during study treatment. All other patients who discontinued the study treatment did so as a result of disease progression or withdrawal of consent.

Antitumor activity

One pancreatic cancer patient at the 30 mg/m^2 dose level experienced a confirmed partial response (PR) for 5 months. This patient had failed prior therapy with gemcitabine. Ten of the 15 evaluable patients experienced stable disease (by RECIST criteria) as their best response to therapy. Of these ten patients, five patients had minor responses with radiographic shrinkage of target lesions of 11–25%. The medium duration of stable disease was 3.8 months (range, 1.7–11.9 + months). Four of these patients had esophageal cancer, three gastric cancer, two pancreatic cancer, and one biliary tract cancer. Notably, the two patients with pancreatic cancer, both of whom had failed prior gemcitabine-based therapy, continued to experience stable disease for 10 months or more on S-1 treatment.

Pharmacokinetics

All 16 patients were evaluable for pharmacokinetics on day 1. The PK parameters, C_{max}, T_{max} and $AUC_{(0–8)}$ for FT, 5-FU, CDHP, Oxo, FBAL, CA, and uracil are summarized in Table 3 and are compared with S-1 PK data from other studies. The $AUC_{(0–8)}$ of 5-FU at the 30 and 35 mg/m^2 dose level were 875 ± 212 and 894 ± 151 h ng/ml, respectively. The predose and 2-h postdose plasma concentrations of 5-FU, CDHP and

Table 2 Common toxicities of any grade occurring in at least three patients in either dose group

Toxicity	Level 1: 30 mg/m^2 (n = 13)			Level 2: 35 mg/m^2 (n = 3)		
	Any grade (%)	Grade		Any grade (%)	Grade	
		3 (in Cycle 1)[a]	4		3 (in Cycle 1)[a]	4
Diarrhea	9 (69.2)	2 (1)	–	2 (66.7)	1	–
Nausea	8 (61.5)	1 (1)	–	2 (66.7)	1 (1)	–
Skin rash	8 (61.5)	1	–	1 (33.3)	1(1)	–
Anorexia	6 (46.2)	1 (1)	–	2 (66.7)	1(1)	–
Fatigue	6 (46.2)	1	–	2 (66.7)	–	–
Pyrexia	5 (38.5)	–	–	1 (33.3)	–	–
Abdominal pain	5 (38.5)	–	–	2 (66.7)	1(1)	–
Anemia	4 (30.8)	–	–	1 (33.3)	–	–
Vomiting	4 (30.8)	1	–	1 (33.3)	–	–
Constipation	4 (30.8)	–	–	3 (100.0)	–	–
Pruritus	4 (30.8)	–	–	2 (66.7)	–	–
Hand–foot syndrome	3 (23.1)	1	–	2 (66.7)	1	–
Stomatitis	3 (23.1)	–	–	2 (66.7)	1 (1)	–
Alanine aminotransferase increased	3 (23.1)	2 (1)	–	–	–	–
Aspartate aminotransferase increased	3 (23.1)	1	–	–	–	–
Weight decreased	3 (23.1)	–	–	1 (33.3)	–	–
Cough	3 (23.1)	–	–	–	–	–
Epistaxis	3 (23.1)	–	–	–	–	–
Thrombocytopenia	3 (23.1)	–	–	1 (33.3)	–	–
Hyponatraemia	3 (23.1)	1	–	–	–	–
Dizziness	3 (23.1)	1	–	1 (33.3)	–	–

[a] Grade 3 toxicity occurring in cycle 1 indicated in parenthesis

Oxo on days 8 and 14 of the first cycle at 30 mg/m^2 dose level were summarized in Table 4. The predose (trough) and 2-h postdose (C_{max} in steady-state) levels of 5-FU were similar on days 8 and 14, indicating that 5-FU concentration in plasma reached the steady-state on day 8. Comparably, the steady-state was reached on day 8 for CDHP and Oxo.

The plasma concentration–time relationship of 5-FU, CDHP and FBAL are plotted in Fig. 1. During a standard intravenous infusion of 5-FU, 5-FU is quickly degraded into metabolites, including FBAL. FBAL is believed to be the main source of 5-FU-related toxicity such as hand-foot syndrome as well as neurologic and cardiac toxicities. With the administration of S-1, 5-FU appears to be maintained at relatively high levels. CDHP increases initially, peaks at 2 h, and decreases afterwards following S-1 administration. FBAL levels slowly accumulate approximately 2 h after S-1 administration.

Discussion

This study demonstrates that S-1, when administered on a 14-day schedule every 21 days, is safe and associated with preliminary evidence of antitumor activity in patients with chemotherapy refractory upper gastrointestinal malignancies. The recommended dose of S-1 on this schedule is 30 mg/m^2. The common toxicities observed at this dose level were relatively mild, and included diarrhea, nausea and skin rash. One patient with gemcitabine-refractory pancreatic cancer achieved a partial response and an additional ten patients with upper gastrointestinal malignancies achieved stable disease as their best response to therapy.

Previous studies of S-1 in North America and Europe have utilized prolonged dosing regimens and have been associated with high rates of both diarrhea and hand–foot syndrome. In two phase I studies conducted in the United States, S-1 was given twice daily for 28 consecutive days in one study and once daily for 21 days in another, followed by a 1-week rest [6, 12]. The dose limiting toxicity in both of these studies was grade 3–4 diarrhea, observed at doses of 70 mg/m^2/day in one study and at 60 mg/m^2/day in the other study. In a European phase I study, S-1 was administered on a 28-day schedule for 3 weeks out of every four. The dose limiting toxicity was again diarrhea, which was observed at a dose of 45 mg/m^2/day [38].

Table 3 Pharmacokinetic parameters after a single oral dose of S-1

PK parameter	Zhu[a] $AUC_{(0–8)}$		Hoff[b] $AUC_{(0-t)}$		Ajani[c] $AUC_{(0–12)}$		Zhu[a] $AUC_{(0–8)}$		Hoff[b] $AUC_{(0-t)}$		Van Groeningen[d]		Hirata[e]	
	30 mg/m^2 $n = 13$		30 mg/m^2 $n = 7$		30 mg/m^2 $n = 6$		35 mg/m^2 $n = 3$		35 mg/m^2 $n = 4$		35 mg/m^2 $n = 5$		35.9 mg/m^2 Range (32–40 mg/m^2) $n = 12$	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5-FU														
C_{max} (ng/ml)	168	43	144	19.5	158	29	156	32	176	21.9	179.5[f]	32.5	128.5	41.5
AUC (ng h/ml)	875	211	782	135.9	872	137	894	151	1,004	56.7	1,133.0[f]	331.3	723.9	272.7
T_{max} (h)	2.5	1.0	2.6	0.98	–	–	2.7	1.2	2.5	1.0	2.85	1.1	3.5	1.7
FT														
C_{max} (ng/ml)	1,503	617	1,426	304.3	1,430	567	2,507	490	1,943	365.2	–	–	1,971	269
AUC (ng h/ml)	6,621	1,048	13,653	2,250.1	7,367	1,417	10,322	612	18,863	2,189.8	18,427.3[f]	7,577	28,216.9	7,771.4
T_{max} (h)	1.5	1.3	1.79	1.150	–	–	0.7	0.3	1.75	0.5	–	–	2.4	1.2
CDHP														
C_{max} (ng/ml)	309	133	298	79.1	328	145	539	66	398	196.3	–	–	284.6	116.6
AUC (ng h/ml)	1,163	376	1,583	459.7	1,168	183	1,898	206	1,784	590.6	1,562.5[f]	443	1,372.2	573.7
T_{max} (h)	1.9	1.1	1.57	0.535	–	–	1.3	0.6	2.25	1.258	–	–	2.1	1.2
Oxo														
C_{max} (ng/ml)	80	86	57.8	60.31	126	24	69	57	42.9	28.51	–	–	78.0	58.2
AUC (ng h/ml)	255	194	232	206.0	533	204	280	246	206	227.6	347.7[f]	219	365.7	248.6
T_{max} (h)	2.1	1.2	1.79	1.150	–	–	1.7	0.6	2.50	1.00	–	–	2.3	1.1
FBAL														
C_{max} (ng/ml)	82	21	–	–	–	–	65	19	–	–	–	–	–	
AUC (ng h/ml)	451	140	–	–	–	–	346	169	–	–	–	–	–	
T_{max} (h)	6.5	1.9	–	–	–	–	7.4	1.2	–	–	–	–	–	
Uracil														
C_{max} (ng/ml)	891	188	764	166	–	–	1,035	118	924	141	–	–	890	259
AUC (ng h/ml)	4,751	1,168	8,403	2,821	–	–	5,585	285	9,828	2,424	–	–	8,483	3,859
T_{max} (h)	5.4	1.3	6.3	2.1	–	–	6.7	1.2	6.0	2.3	–	–	5.3	1.8

t The last measurable plasma concentration

FT and CDHP: $AUC_{(0–18)}$; 5-FU: $AUC_{(0–14)}$; Oxo: $AUC_{(0–24)}$

[a] S-1 was administered 1 h before or at least 1 h after a meal. Data from the present study

[b] S-1 was administered within 1 h after a meal. Data from Hoff et al. [12]

[c] S-1 was administered 1 h before or after a meal. Data from Ajani et al. [1]

[d] S-1 was administered within 1 h after a meal. Data from Van Groeningen et al. [38]

[e] S-1 administered within 30 min following a meal. FT and CDHP: $AUC_{(0–48)}$; 5-FU: $AUC_{(0–14)}$; Oxo: $AUC_{(0–24)}$. Data from Hirata et al. [11]

[f] Units converted from original publication by Ajani et al. [1]

Table 4 Plasma concentrations of 5-FU, CDHP and Oxo on day 8 and day 14 at 30 mg/m^2 level

Analytes	Day 8 (ng/ml)				Day 14 (ng/ml)			
	Predose		2-h Postdose		Predose		2-h Postdose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5-FU	76.9	57.9	192.5	83.5	65.6	40.9	204.0	53.4
CDHP	69.9	73.4	256.7	148.1	54.4	57.0	261.1	68.6
Oxo	9.2	7.39	44.4	36.3	11.7	11.0	71.79	65.6

Two subsequent phase II studies [4, 37], which were conducted by the European Organization for Research and Treatment of Cancer (EORTC) in patients with gastric and colorectal cancer, evaluated an S-1 dose regimen of 35 mg/m^2 twice daily for 28 days every 5 weeks. Toxicity was a concern in both studies, with high rates of both diarrhea and hand–foot syndrome observed. The development of late diarrhea in these studies was a primary factor in our choice of a shortened, 2-week dosing schedule for the current phase I study. Despite our efforts to develop a new schedule with less dose intensity and decreased severe diarrhea, we were unable to escalate the dose further. The recommended MTD dose in this study at 30 mg/m^2 administered twice daily is consistent with prior studies.

In this study, nine patients, in addition to the initial four patients, were treated at the recommended MTD of 30 mg/m^2 BID, allowing us to obtain additional data on the potential toxicities of this regimen. Gastrointestinal toxicity was both mild and manageable at this dose level. Only two patients developed grade 3 diarrhea at this dose level, and all were subsequently managed without dose reduction with initiation of antidiarrheals and other supportive care. Hematologic toxicity was also mild: no patients developed grade 3–4 neutropenia and there were no instances of grade 3–4 anemia or thrombocytopenia. Skin rash, though relatively common, was generally effectively treated with topical steroids.

Pharmacokinetic data for this study are compared in Table 3 with data from three previous studies in which S-1 was administered at a dose of 30 or 35 mg/m^2. In Japanese studies, S-1 has routinely been administered at higher dose levels with less associated toxicity than in North American or European studies. These differences in toxicity profiles appear to be explained by differences in 5-FU PK profiles between the patient populations. In a Japanese PK study evaluating an average S-1 dose of 35.9 mg/m^2, the C_{max} and AUC for 5-FU derived from tegafur were 128.5 ± 41.5 ng/ml and 723.9 ± 272.7 ng h/ml, respectively [11]. In a US study, a corresponding dose of 35 mg/m^2 resulted in a higher C_{max} (176 ± 21.9 ng/ml) and a higher AUC ($1{,}004 \pm 56.7$ ng h/ml) [12]. In our study the three patients in the 35 mg/m^2 dose cohort had similarly elevated 5-FU levels, with a mean C_{max} of 156 ng/ml and a mean AUC of 894 ng h/ml.

An S-1 dose of 30 mg/m^2 was associated with a C_{max} of 168 ± 43 ng/ml and an $AUC_{(0-8)}$ of 875 ± 211 ng h/ml. These levels are in fact higher than levels obtained with a higher average dose of 35.9 mg/m^2 in a Japanese population (Table 3) [11]. Our pharmacokinetic data with the 30 mg/m^2 dose are comparable to two other US phase I studies in which S-1 was either administered alone or in combination with cisplatin [1, 12].

The differences in PK profile between Japanese and Western populations observed in these studies suggest significant ethnic variation in S-1 metabolism. These ethnic differences in 5-FU PK profiles appear to be related to genetic polymorphisms in the detoxifying enzyme CYP2A6, which mediates the conversion of tegafur to 5-FU. In one study, both CYP2A6 and coumarin

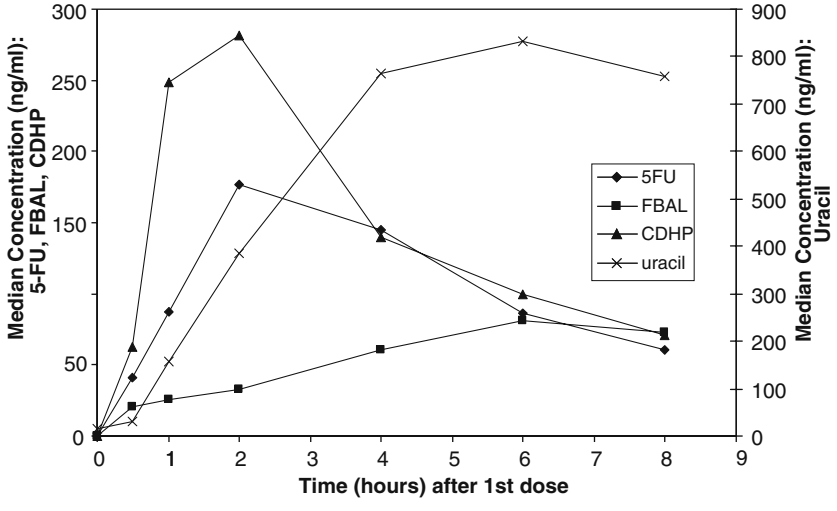

Fig. 1 Inhibitory effect of 5-chloro-2,4-dihydroxypyridine (*CDHP*) in S-1 (30 mg/m^2) on dihydropyrimidine dehydrogenase (*DPD*) activity as measured by median plasma levels of CDHP, 5-fluorouracil (*5-FU*), and its metabolites α-fluoro-β-alanine (*FBAL*) and uracil. $N = 13$

7-hydroxylation activity, an indicator of CYP2A6 activity, were found to be higher in Caucasian than in Japanese populations [27]. Conceivably, some of the PK parameters of S-1 may be related to the occurrence of toxicities, however, our study failed to establish this correlation (data not shown).

S-1 has previously been shown in Japanese studies to be active against a broad range of malignancies. In advanced gastric cancer, S-1 monotherapy has been associated with an overall response rate of 44%, leading to its current widespread use as a first line therapy for Japanese patients with advanced gastric cancer [18, 25]. Japanese studies have further demonstrated that S-1 monotherapy is associated with an overall response rate of 22% in non-small cell lung cancer and 37.5% in advanced pancreatic cancer [9, 17]. S-1 is also active in squamous cell carcinoma of the head and neck, colorectal cancer, cholangiocarcinoma, and breast cancer [7, 10, 26, 28, 36]. In a phase II study of S-1 in combination with cisplatin conducted in the US, it appeared that antitumor activity was associated with clinical benefit in patients with advanced gastric carcinoma [2]. Although assessment of antitumor activity was not a primary objective of this study, we did observe preliminary evidence of such activity. Among four patients with gemcitabine-refractory metastatic pancreatic cancer, one patient achieved a PR and two patients achieved stable disease. Other patients with stable disease included those with gastric, esophageal, or biliary tract cancer resistant to prior regimens.

We conclude that S-1 administered on 14-day schedule every 21 days is safe and is associated with preliminary evidence of antitumor activity in patients with advanced upper gastrointestinal cancer in North America. In these patients, the recommended dose level for this schedule is 30 mg/m^2, administered twice daily for 14 days every 21 days. We further note that the MTD in our study is lower than the MTD in similar Japanese studies; this difference appears to be related to differences in drug metabolism in different patient populations. Phase II studies with this regimen have already been initiated.

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