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Featured Article

Phase I and Pharmacokinetic Study of the Oral Fluoropyrimidine S-1 on a Once-Daily-for-28-Day Schedule in Patients with Advanced Malignancies

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ABSTRACT

Purpose: **The oral fluoropyrimidine S-1, which consists of a mixture of a 5-fluorouracil (5-FU) prodrug (tegafur), a dihydropyrimidine dehydrogenase inhibitor [5-chloro-2,4-dihydroxypyrimidine (CDHP)], and an inhibitor of orotate phosphoribosyltransferase [potassium oxonate (oxonic acid)], was developed to increase the feasibility and therapeutic index of 5-FU administered orally. The principal objective of this study was to assess the feasibility of administering S-1 on a once-daily-for-28-day schedule every 5 weeks, determine the maximum tolerated dose, characterize the pharmacokinetics of S-1, and seek evidence of anticancer activity.**

Experimental Design: **Patients with advanced solid malignancies were treated with escalating doses of S-1 on a once-daily oral schedule for 28 days every 5 weeks. The maximum tolerated dose was defined as the highest dose in which fewer than two of the first six new patients experienced dose-limiting toxicity. The pharmacokinetic profiles of the tegafur, CDHP, and oxonic acid constituents were characterized.**

Results: **Twenty patients were treated with 72 courses of S-1 at three dose levels ranging from 50 to 70 mg/m^2/day. Diarrhea, which was often associated with abdominal discomfort and cramping, was the principal dose-limiting toxicity of S-1 on this protracted schedule. Nausea, vomiting, mucositis, fatigue, and cutaneous effects were also observed but were rarely severe. Myelosuppression was modest and uncommon. A partial response and a 49% reduction in tumor size were observed in patients with fluoropyrimidine- and irinotecan-resistant colorectal carcinoma. The pharmacokinetic data suggested potent inhibition of 5-FU clearance by CHDP, with resultant 5-FU exposure at least 10-fold higher than that reported from equitoxic doses of tegafur modulated by uracil in the oral fluoropyrimidine UFT.**

Conclusions: **The recommended dose for Phase II studies of S-1 administered once daily for 28 consecutive days every 5 weeks is 50 mg/m^2/day. The pharmacokinetic data indicate substantial modulation of 5-FU clearance by CDHP. Based on these pharmacokinetic data, the predictable toxicity profile of S-1, and the low incidence of severe adverse effects at the recommended Phase II dose, evaluations of S-1 on this schedule are warranted in malignancies that are sensitive to the fluoropyrimidines.**

INTRODUCTION

The fluoropyrimidines have been the mainstay of therapy for the management of colorectal and other gastrointestinal malignancies since the introduction of 5-fluorouracil (5-FU) into practice in the 1950s (1). Over the last several decades, many methods of fluorpyrimidine administration and biochemical modulation strategies have been investigated to improve the overall efficacy and therapeutic index of this class of antimetabolites (1–11). In patients with advanced colorectal cancer, regimens that result in continuous fluoropyrimidine exposure, particularly protracted intravenous infusions, have consistently demonstrated higher response rates and more favorable toxicity profiles than intermittent bolus and short infusion schedules (1–9). Despite these results, protracted intravenous infusional methods have not been widely adopted because of the costs, cumbersomeness, and inconvenience associated with the requirements for central venous catheters and portable infusion pumps, as well as a the absence of a clear survival advantage. Furthermore, 5-FU itself is associated with large interpatient variability in pharmacokinetics and, in turn, pharmacodynamics, largely due to substantial interindividual variability in the principal catabolic enzyme of 5-FU, dihydropyrimidine dehydrogenase, which impedes the utility of 5-FU administered both parenterally and orally (12–17).

Although daily oral 5-FU administration represents an attractive alternate means of achieving protracted 5-FU exposure, the high dihydropyrimidine dehydrogenase activity in the liver results

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in low, variable, and unpredictable systemic bioavailability (12–16). The development of 5-FU prodrugs represents efforts directed at increasing oral bioavailability as well as developing oral schedules that simulate protracted intravenous 5-FU administration. The oral 5-FU prodrug tegafur (5-fluoro-1-[tetrahydro-2-furanyl]-2,4[1*H*,3*H*]pyrimidinedione) is metabolically activated to 5-FU by hepatic microsomes (18). UFT, a combination of tegafur and the dihydropyrimidine dehydrogenase inhibitor uracil, achieves relevant systemic 5-FU concentrations, achieves relevant antitumor activity in fluoropyrimidine-sensitive neoplasms, and has undergone regulatory approval in many countries worldwide for treatment of patients with colorectal cancer (18). S-1, which contains tegafur, 5-chloro-2,4-dihydropyridine (CDHP), and potassium oxonate (oxonic acid) in a fixed molar ratio of 1:0.4:1 based on cytotoxicity studies in Yoshida sarcoma-bearing rats and human gastric cancer xenografts, was developed to further enhance the therapeutic index of tegafur administered orally (19). When tegafur is combined with CDHP, which is 180-fold more potent than uracil at inhibiting dihydropyrimidine dehydrogenase *in vitro*, biologically relevant plasma 5-FU concentrations are sustained in both plasma and tumors (19–21). The rationale for oxonic acid as a constituent of S-1 is its potential to reduce gastrointestinal toxicity by inhibiting orotate phosphoribosyl transferase and, in turn, 5-FU phosphorylation or activation in gastrointestinal tissues (21–22). Therefore, oxonic acid may reduce gastrointestinal toxicity without impeding the antitumor activity of 5-FU due to the inhibitory effects of 5-FU on thymidylate synthase and DNA synthesis as well the antimetabolic effects of 5-FU on RNA.

The antitumor activity of S-1 was established in various experimental models including rodent tumors and human xenografts (19, 21–23). In studies in which the antitumor effects of S-1 and UFT were compared, S-1 demonstrated superior activity against human gastric, colorectal, and breast cancer xenografts (24). Furthermore, S-1 demonstrated greater antitumor activity and less toxicity than 5-FU administered as a protracted infusion (25). The initial clinical development of S-1 involved twice daily dosing for 21–28 days followed by a 7-day rest period (26–28). Diarrhea was the principal dose-limiting toxicity, and recommended doses ranged from 30 to 35 mg/m^2. In Phase II studies, S-1 demonstrated notable activity in patients with advanced gastric, colorectal, breast, and head and neck cancers, and the agent has received regulatory approval in Japan for patients with advanced gastric cancer (29–36).

This Phase I and pharmacokinetic study of S-1 was undertaken to evaluate the feasibility, safety, and pharmacokinetics of a once-daily schedule to improve the safety, tolerability, convenience, and possibly compliance of S-1 while maintaining efficacy. It was reasoned that prolonged inhibition of dihydropyrimidine dehydrogenase by CDHP with resultant diminution of 5-FU clearance might render once-daily dosing feasible. The principal objectives of this study were as follows (*a*) to determine the maximum tolerated dose of S-1 administered once daily for 28 days, repeated every 5 weeks and to recommend a dose for Phase II trials; (*b*) to characterize the toxicities associated with this schedule of administration; (*c*) to describe the pharmacokinetic behavior of S-1 on this schedule; and (*d*) to seek preliminary evidence for antitumor activity.

PATIENTS AND MATERIALS

Patient Selection. Patients with histologically or cytologically confirmed advanced solid malignancies who failed to respond to standard therapy or for whom adequate therapy was not available were eligible. Eligibility criteria also included the following: age $\geq$ 18 years; an Eastern Cooperative Oncology Group performance status $\leq$ 2; life-expectancy of $\geq$3 months; no chemotherapy, immunotherapy, or radiation therapy within 4 weeks of treatment (6 weeks for nitrosoureas and mitomycin C and 8 weeks for irreversible dihydropyrimidine dehydrogenase inhibitors); adequate hematopoietic (absolute neutrophil count $\geq$ 1500/μl, hemoglobin level $\geq$ 9.0 g/dl, platelet count $\geq$ 100,000/μl), hepatic (transaminases $\leq$ 2.0$\times$ institutional normal upper limit, total bilirubin $\leq$ 1.5$\times$ institutional normal upper limit), and renal (creatinine $\leq$ 1.5$\times$ upper institutional normal limit) functions; no chronic enteropathy or history of gastric or small intestinal resections; measurable or evaluable disease; and no coexisting medical conditions of sufficient severity to limit compliance with the study. All concurrent medications were recorded in the case report form. Patients gave written informed consent before treatment, according to federal and institutional guidelines.

Dosage and Drug Administration. S-1 was administered once daily for 28 days every 5 weeks, which was defined as a single course. The starting dose of S-1 was 50 mg/m^2 once daily, which was equivalent to approximately two thirds of the maximally tolerated daily dose of S-1 on a twice-daily dosing schedule (35 mg/m^2 twice daily; Ref. 26). The maximum tolerated dose was defined as the highest dose at which fewer than two of the first six patients experienced dose-limiting toxicity during the first or second courses of treatment. The dose of S-1 was to be escalated in successive cohorts of new patients to 60, 70, and 80 mg/m^2/day or reduced to 40 mg/m^2/day if the starting dose exceeded the maximum tolerated dose. At least three patients were to be treated at each dose level that did not result in dose-limiting toxicity during the first two courses. If one of the initial three patients developed dose-limiting toxicity in courses 1 or 2, then three additional patients were to be entered on the same dose level. At least 10 additional patients could be treated at the maximum tolerated dose. Dose-limiting toxicity was defined as follows: (*a*) grade 3 nonhematological toxicity (excluding nausea, vomiting, or diarrhea associated with suboptimal premedication and/or management); (*b*) any grade 4 nonhematological toxicity; (*c*) platelets $<$ 25,000/μl or $\leq$50,000/μl associated with hemorrhage; (*d*) absolute neutrophil count of $<$500/μl lasting more than 3 days; (*e*) absolute neutrophil count of $\leq$1,000/μl associated with fever ($\geq$38.5°C); (*f*) omission of $>$25% of the planned dose of S-1 due to toxicity; (*g*) any unresolved toxicity requiring a delay in the administration of a subsequent course exceeding 14 days; and (*h*) any grade 2 toxicity which, in the judgment of the investigator and sponsor, required dose reduction or discontinuation of therapy. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria Version 2.0.

Treatment was immediately discontinued in the event of the following toxicities: platelets $\leq$ 50,000/μl; absolute neutrophil count $\leq$ 1,000/μl; or $\geq$grade 2 nonhematological toxicity. Following resolution of the toxicity to $\leq$grade 1 within the

28-day course, S-1 was resumed at the same dose level as long as the event was not dose-limiting. In the event of dose-limiting toxicity, treatment was not resumed until the planned date of the next course, at which time the dose of S-1 was reduced by one level. Dose escalation was permitted in individual patients who had completed at least two courses of S-1 with ≤grade 1 toxicity as long as at least one patient had completed two courses of S-1 at the next higher dose level without ≥grade 2 toxicity.

S-1 was supplied by Bristol-Myers Squibb Pharmaceutical Research Institute (Wallingford, CT). Each capsule contained 20 or 25 mg of tegafur, with the tegafur, CDHP, and oxonic acid constituents in a molar ratio of 1:0.4:1. Doses were calculated according to body surface area. For patients with body surface areas exceeding 2.0 m^2, the S-1 dose was calculated based on a body surface area equivalent to 2.0 m^2. The calculated dose of S-1 was rounded to the nearest 5 mg. Patients were instructed to administer S-1 within 1 h after breakfast between 7 and 10 a.m. because of the potential instability of oxonic acid in acid conditions.

Pretreatment and Follow-Up Studies. Histories that included recording of performance status, interval toxicities, and concurrent medications, physical examinations, complete blood counts, electrolytes, and chemistries were performed pretreatment and weekly. Pretreatment studies also included an electrocardiogram and a pregnancy test in women of childbearing potential and relevant radiological studies for evaluation of all measurable or evaluable sites of malignancy, as well as an assessment of relevant tumor markers. Radiological studies for disease status assessments were repeated after every other course or as needed to confirm response. Patients were able to continue treatment if they did not develop progressive disease. A complete response was scored if there was disappearance of all active disease on two measurements separated by a minimum period of 4 weeks, and a partial response required at least a 50% reduction in the sum of the product of the bidimensional measurements of all lesions documented separated by at least 4 weeks. Any concurrent increase in the size of any lesion by ≥25% or the appearance of any new lesion was considered disease progression.

Pharmacokinetic and Pharmacodynamic Analyses. Blood samples in heparinized tubes were collected on days 7, 14, and 21 of the first course before treatment to measure plasma concentrations of 5-FU, CDHP, and oxonic acid. On day 28, samples were also collected pretreatment and at 15, 30, 60, and 90 min and 2, 3, 5, 8, and 24 h after treatment. The samples were centrifuged for 15 min at 1000 × *g* at 0°C to 5°C immediately after collection. Next, a 1-ml aliquot of plasma was transferred to a sample tube, which was frozen at −70°C until assayed. Tegafur was assayed using high-performance liquid chromatography with UV detection with a standard curve range of 10–4000 ng/ml (37). 5-FU, CDHP, and oxonic acid were assayed using gas chromatography with mass spectrometric detection using standard curve ranges of 1–400, 2–800, and 1–200 ng/ml, respectively (37).

The plasma concentration-time data were analyzed using noncompartmental methods (24 of mer). The peak plasma concentrations (C_{max}) and time to peak plasma concentration (T_{max}) were obtained by experimental observations. Using no weighting factor, the terminal log-linear phase of the concentration-time curve was identified by least squares linear regression of at least three data points, which yielded a minimum mean square error. The elimination half-life ($t_{1/2}$) was calculated as 0.693/*K*, where *K* is the absolute value of the slope of the terminal log-linear phase. The AUC from zero to infinity ($AUC_{0-\infty}$) was equivalent to the sum of the areas from time zero to the time of the last measured concentration, calculated by using the linear trapezoidal method (until C_{max}) and the log-trapezpoidal method (until the last measurable concentration), and the extrapolated area. The extrapolated area was determined by dividing the final measured concentration by the slope of the terminal log-linear phase. AUC over the dosing interval, AUC(TAU), AUC from 0 to the last measurable plasma concentration, was determined using linear trapezoidal and log-trapezoidal methods. Trough values on days 7, 14, and 21 were averaged on each day for each dose level. The relationships between pharmacokinetic parameters and toxicity were explored using Spearman rank correlation analysis.

RESULTS

General. Twenty patients, whose pertinent characteristics are listed in Table 1, were treated with 72 courses of S-1 through three planned dose levels ranging from 50 to 70 mg/m^2/day, and a fourth dose level, 40 mg/m^2/day, was used for two patients who required dose reduction due to toxicity at the 50 mg/m^2/day dose level. Eighteen (90%) patients had either locally advanced or metastatic colorectal carcinoma that had been previously treated with a fluoropyrimidine-based chemotherapy

Table 1 Patient characteristics

Characteristic	No. of patients
No. of patients (fully evaluable)	20 (20)
Median no. of courses/patient (range)	3 (1–10)
Median age (range) (yrs)	60 (37–74)
Gender (M:F)	15:5
Median performance status (ECOG)	1
0	5
1	10
2	5
Previous therapy	
Chemotherapy only	17
Chemotherapy and radiation	3
Previous chemotherapy	
5-FU	18
Irinotecan	17
Carboplatin or cisplatin (≥6 courses)	2
Mitomycin C (≥2 courses)	1
Extent of prior myelosuppressive therapy*	
Minimally pretreated*	14
Heavily pretreated*	6
Tumor types	
Colorectal	18
Gastric	1
Lung (small cell)	1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

* Heavily pretreated patients were defined retrospectively as those subjects who received >6 courses of chemotherapy containing an alkylating agent (except low-dose cisplatin), >2 courses of a nitrosourea or mitomycin C, radiation therapy to >25% of bone marrow-bearing bones, or diffuse bone metastases.

Table 2 Dose escalation scheme

S-1 dose (mg/m^2/day)	No. of patients			No. of courses	No. of patients with DLT	
	New	With dose reduction	Total		First two courses	All courses
40	0	2	2	4	0/0	0/4
50	9	3	12	47	0/9	1/47
60	8	1	9	18	4/8	4/18
70	3	0	3	3	3/3	3/3

Abbreviation: DLT, dose-limiting toxicity.

regimen. Six of the 20 (30%) patients were considered heavily pretreated with respect to the extent of prior myelotoxic therapy consisting of treatment with either wide-field radiation or carboplatin or mitomycin C. The total numbers of new patients treated at each dose level, number of courses, and dose escalation scheme are depicted in Table 2. All patients were fully evaluable for toxicity. The median number of courses administered per patient was 3 (range, 1–10). Three patients required dose reduction on one occasion for either severe (grade 3) or chronic grade 2 diarrhea, and one subject required dose reduction on two occasions. S-1 was administered at an unplanned dose level, 40 mg/m^2/day, in two individuals including one patient who experienced grade 3 diarrhea after five courses of S-1 at the 50 mg/m^2/day dose level and a second patient who required two sequential dose reductions for grade 2 diarrhea at the 60 and 50 mg/m^2/day dose levels.

After no or negligible drug-related adverse effects were noted in the first two courses of the three patients treated at the 50 mg/m^2/day dose level, the dose of S-1 was increased to 60 mg/m^2/day. At 60 mg/m^2/day, one of the first three patients experienced dose-limiting toxicity, which consisted of grade 4 diarrhea and grade 3 mucositis in the first course; therefore, three additional patients were treated and did not experience unacceptable toxicity in courses 1 and 2. In contrast, dose-limiting toxicity occurred in the first courses of all three individuals treated with S-1 at the 70 mg/m^2/day dose level, which resulted in further patient accrual at the next lower dose level. Because the next two subjects treated with 60 mg/m^2/day of S-1 also experienced dose-limiting toxicity in course 1, additional patients were treated at the 50 mg/m^2/day dose level. None of nine new patients treated with 50 mg/m^2/day of S-1 experienced dose-limiting toxicity in both courses 1 and 2, and only one dose-limiting toxicity was noted with repetitive treatment. Based on these results, the maximum tolerated dose was determined to be 50 mg/m^2/day.

Nonhematological Toxicity. The distributions of the worst grade of the most common nonhematological toxicities of S-1 experienced by each individual subject as a function of dose level are displayed in Table 3. Diarrhea was the most common adverse effect and principal dose-limiting toxicity of S-1. Fifteen (75%) patients experienced diarrhea at some time during treatment. Both the incidence and severity of diarrhea appeared to be dose-related within the narrow dose range evaluated. The onset of diarrhea was typically during the third and fourth weeks of treatment. In most patients, symptoms were mild to moderate in severity and successfully managed with loperamide alone; however, diarrhea also appeared to improve and/or resolve in the 1-week planned rest period following the 28 days of daily treatment. Severe (grade 3–4) diarrhea was experienced by five patients, including three and two patients each at the 60 and 70 mg/m^2/day dose levels, respectively. At 50 mg/m^2/day, diarrhea rarely precluded retreatment with each successive 4-week course of S-1 following each planned 1-week rest period. The exceptions were two patients who required dose reductions from 50 to 40 mg/m^2/day. In the first individual, the dose was reduced after seven courses due to recurrent grade 2 diarrhea, whereas the dose was reduced twice in the second patient, initially from 60 to 50 mg/m^2/day due to protracted grade 2 diarrhea, and then again from 50 to 40 mg/m^2/day due to severe (grade 3) diarrhea in course 5. Other adverse effects, possibly related to the same pathophysiological processes as diarrhea, included abdominal pain, cramping, flatulence, and ileus. Overall, abdominal pain and/or cramping were experienced by 45% of patients. Severe (grade 4) abdominal discomfort concomitant with grade 2 or 3 diarrhea and ileus occurred in two patients who were treated with 70 mg/m^2/day of S-1. One of the subjects developed grade 2 diarrhea on days 11–13 of course 1 followed by ileus on day 21. Computerized tomographic scanning demonstrated that the ileus was due to progressive intra-abdominal disease. The patient expired on day 24. The second patient developed a short-lived ileus on the ninth day of his first course, which was felt to be possibly related to S-1.

Hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia, and dehydration were infrequently noted in several

Table 3 Nonhematological toxicity

S-1 dose level (mg/m^2/day)	No. of patients (courses)	Worst NCI CTC toxicity grade experienced per patient													
		Fatigue		Anorexia		Diarrhea		Nausea		Abdominal pain/cramping		Vomiting		Mucositis	
		1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
40	2 (4)	0/1	0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
50	12 (47)	3/3	0/0	1/1	0/0	5/2	1/0	4/0	0/0	2/3	0/0	2/1	0/0	1/0	0/0
60	9 (18)	3/2	0/0	3/3	1/0	2/2*	1/1	4/1	1/0	1/0	0/0	2/1	0/0	0/2	1/0
70	3 (3)	0/0	0/0	0/1	1/0	0/1*	2/0	0/1	0/0	0/1	0/2	0/0	1/0	0/2	0/0

Abbreviations: NCI, National Cancer Institute; CTC, Common Toxicity Criteria.

* Although grade 2 in severity, two events and one event at 60 and 70 mg/m^2/day were considered dose-limiting because S-1 treatment required premature discontinuation.

subjects who developed diarrhea. Fifty-five percent of patients experienced anorexia; however, it was mild or moderate in most cases. Furthermore, anorexia was noted across the entire S-1 dosing range, and definitive temporal relationships could not be discerned, suggesting that the underlying malignant process may have contributed. Two patients developed grade 3 anorexia; however, one event occurred concomitant with rapid disease progression, and the other event occurred in association with diarrhea of grade 3 severity.

Nausea and vomiting, which were either mild (grade 1) or moderate (grade 2) in severity, occurred in 50% and 35% of patients, respectively. One patient treated with 70 mg/m^2/day of S-1 experienced severe (grade 3) nausea and vomiting. Nausea and vomiting were prevented and/or managed successfully with prochlorperazine, and routine premedication was not necessary because most events consisted of nausea alone and were mild in severity and sporadic. Thirty percent of patients complained of mucositis at some time during treatment. Except for one subject who experienced grade 3 mucositis associated with grade 4 diarrhea and several other gastrointestinal toxicities during the first course of S-1 at the 60 mg/m^2 dose level, all other events were either mild or moderate in severity. The onset of mucositis was typically following the second week of treatment and usually lasted 5–7 days. All events were uncomplicated. Mild elevations in hepatic transaminases and/or serum bilirubin were observed in 50% of patients; however, most episodes were isolated, mild, asymptomatic, and occurred concurrent with progression of liver metastases.

Dermatological manifestations, consisting principally of a maculopapular rash and dry skin, were experienced by 45% of patients. One patient each developed a typical, albeit mild (grade 1), hand-foot syndrome and onycholysis after three and five courses of S-1 at the 50 mg/m^2/day dose level, respectively. Four patients who received treatment with S-1 at doses of at least 60 mg/m^2 developed excessive lacrimation, which was associated with a blocked lacrimal duct, conjunctival injection, and blurred vision in one patient each.

Signs and symptoms resembling fluoropyrimidine-induced cerebellar toxicity, including dizziness and vertigo, were experienced by three patients. Two subjects complained of mild, noncumulative dizziness throughout nine and six courses at the 50 and 60 mg/m^2/day dose levels, whereas another individual developed grade 2 cerebellar symptoms concurrent with nausea, vomiting, ileus, and dehydration in his first course of S-1 at the 70 mg/m^2/day dose level. Fatigue was a relatively common complaint, but it was not dose related and generally occurred in association with diarrhea and/or disease progression.

Hematological Toxicity. Hematological toxicities were generally mild or moderate in severity. Anemia was the most common hematological effect noted during treatment. Seventeen patients (85%) had at least grade 1 anemia, but the anemia predated the onset of S-1 treatment in eight subjects. One patient developed abrupt worsening of preexisting anemia from grade 2 to 4 after one course of S-1, and three subjects developed grade 3 anemia during therapy. In one of these subjects, anemia was attributed to progressive disease involving the gastrointestinal tract. In another individual, a myelodysplastic syndrome, which was attributed to previous treatment with a nitrosourea and mitomycin C, was documented. Three patients required transfusions of red blood cells.

Effects on neutrophils and platelets were uncommon. Four (20%) and three (15%) patients developed neutropenia and thrombocytopenia, respectively. All neutropenic events were mild to moderate in severity and occurred after treatment at the two highest S-1 dose levels. Thrombocytopenia was always mild (grade 1), except for a grade 3 event experienced during the tenth course in a patient who experienced several episodes of grade 1 thrombocytopenia during earlier courses and was subsequently determined to have a myelodysplastic syndrome, as discussed previously.

Antineoplastic Activity. Ten (50%) patients experienced either objective antitumor activity or stable disease as their best response to S-1. Clear evidence of antineoplastic activity was noted in two patients. The first patient, a 60-year-old male with colorectal carcinoma and hepatic and pulmonary metastases that were previously demonstrated to be refractory to 5-FU, irinotecan, and pemetrexed, experienced a 93% reduction in the size of lesions (partial response) after treatment with two courses of S-1 at the 60 and 70 mg/m^2/day dose levels. He received five additional courses of S-1 at 50 mg/m^2/day but experienced progressive disease at 10 months. The second patient, a 67-year-old male with metastatic colorectal carcinoma that had progressed during prior treatment with 5-FU, irinotecan, and several investigational agents, experienced a 49% reduction in the size of lesions. Tumor regression was documented after two courses of S-1 at the 60 and 50 mg/m^2/day dose levels. He received three additional courses of S-1 at the 50 mg/m^2 dose level, but progressive disease was documented at 6 months after the initiation of treatment. Two other patients with metastatic colorectal carcinoma that had clearly progressed immediately before the onset of therapy with S-1 experienced stable disease of notable duration. The first patient, a 71-year-old male whose disease had been demonstrated to be refractory to regimens consisting of 5-FU/methotrexate/carmustine/mitomcyin C and 5-FU/leucovorin, as well as several investigational agents, experienced substantial improvement in disease-related pulmonary symptoms and his performance status and stable disease that persisted during 10 courses of S-1 at the 50 mg/m^2/day dose level. Another individual, a 63-year-old male whose metastatic colorectal carcinoma had progressed through treatment with 5-FU/leucovorin/irinotecan and several investigational agents, experienced considerable improvement in disease-related symptoms and stable disease during six courses of S-1 treatment at the 50 mg/m^2/day dose level. Six other patients had stable disease as their best response.

Pharmacokinetics. Plasma sampling was performed for pharmacokinetic studies in eight and five patients treated with S-1 at the 50 and 60 mg/m^2/day dose levels, respectively, but sampling was incomplete in the patients treated at the 70 mg/m^2/day dose level due to the interruption of treatment for toxicity in course 1. In most subjects, plasma concentrations were quantifiable until 24 h for tegafur and CDHP and until 8 h for 5-FU and oxonic acid. Mean plasma concentration *versus* time profiles for tegafur, 5-FU, DHDP, and oxonic acid from plasma sampling performed on the last day of the first course are shown in Fig. 1, and mean pharmacokinetic parameters for these S-1 components derived using noncompartmental methods are

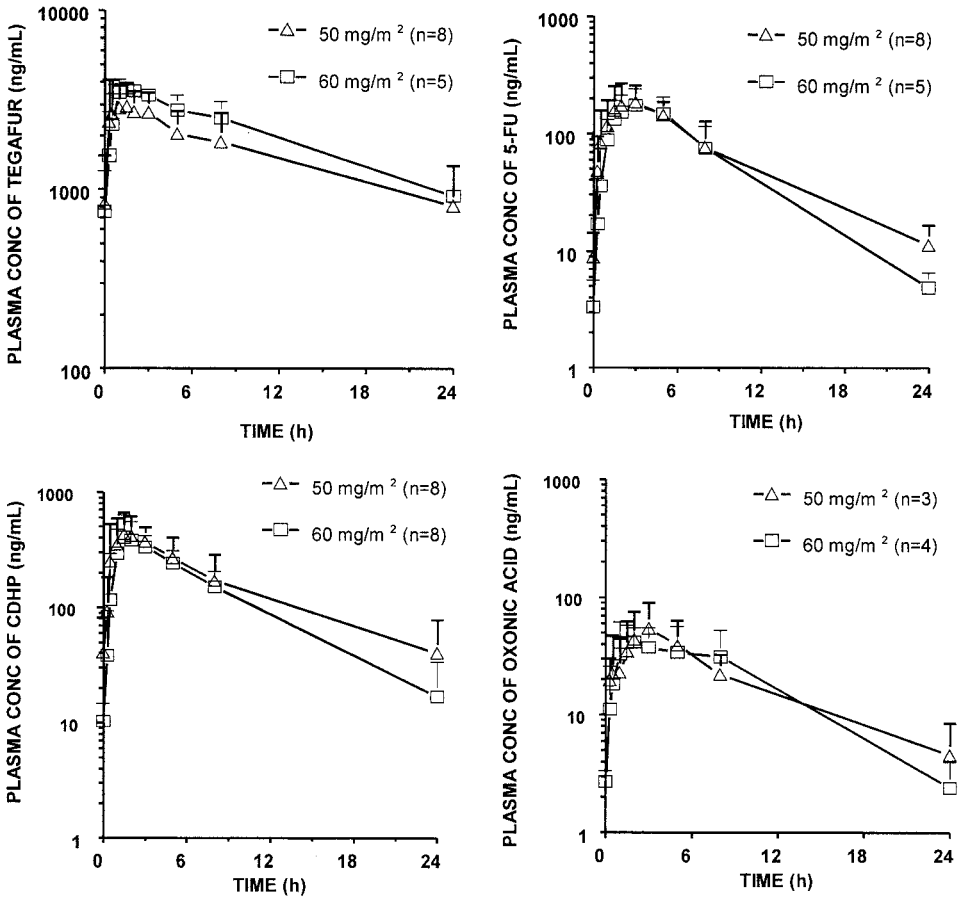

Fig. 1 Mean plasma concentration *versus* time curves of S-1 components and 5-FU. *A*–*D*, mean plasma concentration *versus* time curves of (*A*) tegafur, (*B*) 5-FU, (*C*) CDHP, and (*D*) oxonic acid. *Bars*, SD.

listed in Table 4. For tegafur, dose-related increases in C_{max} and AUC(TAU) were observed between 50 and 60 mg/m^2/day. For 5-FU, CDHP, and oxonic acid, C_{max} and AUC(TAU) values appeared to be reasonably similar between the two dose levels.

Gastrointestinal absorption of S-1 was rapid, with C_{max} values for tegafur and CDHP observed at 1.5 and 1.75 h, respectively, whereas C_{max} values for oxonic acid and 5-FU were noted at 2.5 and 3.0 h, respectively, after treatment with S-1. Elimination $t_{1/2}$ values for tegafur were higher than those of 5-FU (mean ± SD, 12.1 ± 2.5 *versus* 3.4 ± 1.7 h). Mean 5-FU trough concentrations at steady-state measured on days 6, 13, 20, and 27 ranged from 1.06 to 14.56 ng/ml at the 50 and 60 mg/m^2/day dose levels, respectively, but several values were below the level of assay detection. Interestingly, two of three patients treated in the 70 mg/m^2/day cohort had extraordinarily high 5-FU trough concentrations on day 6 (7.63 and 12.36 ng/ml), which may explain the occurrence of dose-limiting toxicity in both patients during course 1.

Relationships between pharmacokinetic parameters reflecting exposure to the principal components of S-1 and both demographic and toxicological elements were sought, but none were strong. Moderate relationships between the severity of diarrhea, as assessed by National Cancer Institute Common Toxicity Criteria grade, and the AUC(TAU) of 5-FU (r = 0.5752; P = 0.0504; Fig. 2) and age and the clearance of tegafur (r = −0.5620; P = 0.0456) were evident. The effects of gender, liver metastases, and hepatic dysfunction on the exposure of the principal metabolites of S-1 could not be adequately assessed because of the small numbers of females, subjects with liver

Table 4 Noncompartmental pharmacokinetic parameters

S-1 dose (mg/m^2/day)	C_{max} (ng/ml)	T_{max} (h)	AUC (TAU) (ng-h/ml)	Half-life (h)
Tegafur				
50 (n = 8)	3353 (1228)	1.5	38763 (17400)	12.4 (3.5)
60 (n = 5)	3918 (57)	1.0	48646 (11232)	11.5 (2.2)
5-FU				
50 (n = 8)	208 (68)	3.0	1541 (426)	3.4 (1.9)
60 (n = 5)	189 (55)	3.0	1350 (438)	3.4 (1.4)
CDHP				
50 (n = 8)	514 (188)	1.75	3600 (1829)	5.8 (2.5)
60 (n = 5)	474 (172)	1.5	2938 (684)	4.6 (1.2)
Oxonic acid				
50 (n = 8)	135 (158)	2.5	976 (1119)	6.1 (4.1)
60 (n = 5)	82 (73)	3.0	880 (969)	7.8 (7.0)

NOTE. Values represent mean (SD) values. Median values are listed for T_{max}.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, peak plasma concentration; T_{max}, time to peak plasma concentration.

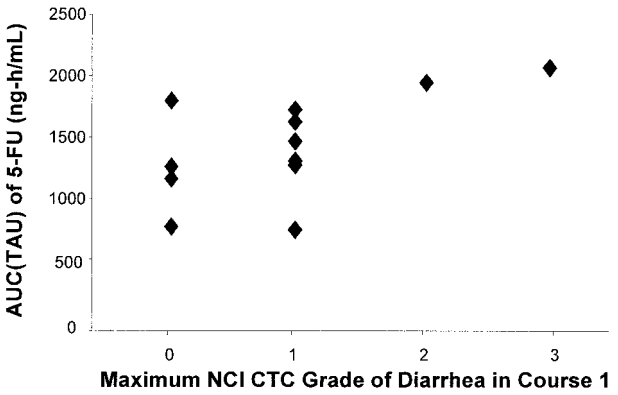

Fig. 2 Scatterplot of AUC(TAU) values for 5-FU as a function of National Cancer Institute Common Toxicity Criteria grade of diarrhea in course 1 ($r = 0.5752$; $P = 0.0504$).

metastasis, and those with hepatic dysfunction who had plasma sampled for pharmacokinetic studies.

DISCUSSION

The inactivation of both dihydropyrimidine dehydrogenase and orotate phosphoribosyl transferase by the CDHP and oxonic acid component of S-1 represents a highly effective means of increasing the therapeutic index of 5-FU, particularly when administering oral 5-FU or 5-FU prodrugs, which, historically, have been associated with unpredictable bioavailability, pharmacokinetics, and erratic toxicity (38–41). Dihydropyrimidine dehydrogenase is principally responsible for the disposition of 5-FU and its erratic oral bioavailability and large intersubject variation in pharmacokinetics and toxicity (4, 5, 12–16). The inactivation of dihydropyrimidine dehydrogenase is attractive for modulating fluoropyrimidine-based therapy because it may (*a*) ensure predictable oral administration of 5-FU because dihydropyrimidine dehydrogenase is principally responsible for the catabolism and erratic bioavailability of oral 5-FU; (*b*) result in more predictable pharmacological and toxicological profiles by decreasing intersubject variability in 5-FU clearance; (*c*) improve the toxicity profile of 5-FU by decreasing the formation of toxic metabolites; (*d*) enhance antitumor activity by suppressing 5-FU catabolism in tumors; and (*e*) provide the benefits of continuous 5-FU administration without requiring central venous access and cumbersome infusion pumps. Although the therapeutic merits of inhibiting orotate phosphoribosyl transferase have been less thoroughly investigated, the principal objective of this maneuver is to decrease the incidence and severity of diarrhea due to protracted fluoropyrimidine exposure.

From a pharmaceutical standpoint, the availability of tegafur and the dihydropyrimidine dehydrogenase inhibitor CDHP in a combined oral dosing form reduces the likelihood of administering inadvertently high or low doses of tegafur. The most serious concern is that the inadvertent administration of even a slightly higher than appropriate dose of 5-FU in a CDHP-induced dihydropyrimidine dehydrogenase-deficient state may result in severe toxicity. Additionally, the availability of separate oral dosing forms increases the likelihood that patients will be treated with inappropriately low doses of CDHP, which can result in low tegafur absorption and therapeutic efficacy. Similar concerns exist for the development of tegafur/5-FU and inhibitors of orotate phosphoribosyl transferase as separate formulations. For these reasons, S-1, a fixed combination of tegafur, CHDP, and oxonic acid, has been developed. Furthermore, the use of a combined formulation ensures the administration of all three components in a fixed ratio, which has resulted in an optimal therapeutic index in experimental animal tumor models (19). The principal objective of the present study was to characterize the safety and pharmacokinetics of S-1 administered once daily for 28 days every 5 weeks and to recommend a dose for disease-directed studies on this schedule.

The results of the present study demonstrated that the maximum tolerated dose of S-1 is 50 mg/m^2/day when administered to patients with advanced cancer once daily for 28 days, followed by a 1-week drug-free period. To recommend a clinically relevant oral dose of S-1 that would be tolerated for protracted period, the derivation of the maximum tolerated dose and recommended Phase II dose was based on the incidence of unacceptable toxicities occurring during the first two 35-day courses. Unacceptably high incidences of dose-limiting toxicities, principally severe and unmanageable diarrhea or moderate diarrhea requiring the interruption of S-1 treatment, were observed at S-1 dose levels above 50 mg/m^2/day. Furthermore, diarrhea was also compounded by other, perhaps more worrisome manifestations of fluoropyrimidine-induced enteritis, particularly ileus, at high doses. In essence, oxonic acid did not drastically modify the toxicological profile of protracted fluoropyrimidine administration. However, although it is clear that the oxonic acid component of S-1 did not completely prevent the development of diarrhea, the incidence and severity of diarrhea appeared to be dose related, predictable, and not erratic. At the 60 and 70 mg/m^2/day dose levels, four of eight (50%) patients and two of three (66%) patients experienced dose-limiting toxicity during the first two courses of S-1. Interestingly, patients who tolerated at least two courses of S-1 at the 60 mg/m^2/day dose level without unacceptable toxicity did not experience dose-limiting events after successive treatment at the same dose level. At 50 mg/m^2, the maximum tolerated dose and recommended dose, none of the nine patients experienced dose-limiting toxicity during their first two courses and only 1 of 47 (2%) courses was associated with dose-limiting toxicity.

The maximum tolerated dose and recommended Phase II doses derived in the present study are similar to those determined in other investigations in North America. For example, the maximum tolerated dose and recommended Phase II doses in this study were identical to those reported by Cohen *et al.* (42), who evaluated S-1 on a once-daily-for-21-day dosing schedule, and slightly lower than those reported by Hoff *et al.* (27), who recommended 30 mg/m^2 twice daily for 28 days every 35 days for subsequent Phase II studies. In a European trial, slightly higher S-1 doses, 40 and 35 mg/m^2 twice daily for 28 days every 35 days, were recommended for Phase II studies in untreated and previously treated patients, respectively (26). In all of these investigations, diarrhea was the principal dose-limiting toxicity. In contrast, myelosuppression was the principal toxicity that has precluded dose escalation in studies conducted in Japan, whereas gastrointestinal effects were generally

mild and infrequent (28). Furthermore, maximum tolerated doses were slightly higher in the Japanese study, as calculated by Hoff *et al.* (27), than those derived in North American and European studies (26, 42). The precise explanation for these differences is not clear at this juncture, however, pharmacogenetic differences between Western and Japanese patients have been proposed (27). Although the pharmacokinetic behavior of S-1 and its components, particularly parameters that reflect drug exposure, in the present study are strikingly similar to those previously reported in North American and European investigations, Hoff *et al.* (27) have noted that 5-FU AUC values were similar among the various trials, but tegafur AUC values were much higher in Japanese patients. This observation, which is further supported by the present study, has raised the question as to whether pharmacogenetic variability could account for the quantitative and qualitative differences in the toxicity profile between Japanese and Western studies. In support of such speculation is the demonstration that Japanese individuals express cytochrome P-450 isoenzyme CYP2A6, which is the principal enzyme responsible for the biotransformation of tegafur to 5-FU, to a much greater degree than Caucasians (43).

S-1 was rapidly absorbed from the gastrointestinal tract, with tegafur and 5-FU plasma concentrations peaking at 1.5 and 3 h posttreatment, respectively. As discussed previously, the pharmacokinetic behavior of S-1 and its components was similar to that reported in previous trials of S-1 on a wide range of schedules. Furthermore, the pharmacokinetic parameters reflecting systemic exposure of the principal constituents were nearly identical to those reported in studies evaluating twice-daily administration of S-1, which has been the principal mode of S-1 administration in Japan and elsewhere (26–28). For tegafur, dose-related increases in C_{max} and AUC values were observed between the 50 and 60 mg/m^2/day dose levels. For 5-FU, CDHP, and oxonic acid, however, these values appeared to be reasonably similar. Although this observation may be due to the small absolute differences between these dose levels, a saturable biotransformation process from tegafur to 5-FU may also be raised as an alternate explanation. Most importantly, the clearance of 5-FU resulting from S-1 was remarkably higher than that reported with 5-FU as an intravenous infusion due to its potent dihydropyrimidine dehydrogenase inhibitor constituent CDHP, with $t_{1/2}$ values averaging 3.4 h compared with 10–20 min (2, 15). From a pharmacological standpoint, this observation is similar to those reported with other attempts to biomodulate 5-FU using dihydropyrimidine dehydrogenase inhibitors in oral formulations such as eniluracil (eniluracil/5-FU) and uracil (UFT), in that the pharmacokinetic parameters that reflect 5-FU exposure, such as AUC and mean trough concentration, achieved with all formulations administered for 28 days simulate those achieved with 5-FU administered as a continuous intravenous infusion for 28 days (18, 41, 44–46). In the present study, 5-FU trough concentrations were nearly identical to steady-state 5-FU concentrations reported with 5-FU administered as a continuous infusion at 300 mg/m^2/day for 28 days (45, 46). With regard to the relative potency of dihydropyrimidine dehydrogenase inhibition conferred by uracil and CDHP in UFT and S-1, respectively, a proposed theoretical dose of 300 mg/m^2 of UFT results in a steady-state 5-FU AUC value of 226 ng-h/ml; however, a 50 mg/m^2 dose of S-1 results in a steady-state 5-FU AUC value of 1541 ng-h/ml, which means that a 6-fold reduction in the tegafur dose (300 to 50 mg/m^2; doses based on tegafur content) results in an approximately 7-fold higher exposure of 5-FU from S-1 compared with UFT (18). This is presumably due to CDHP being a much more potent inhibitor of dihydropyrimidine dehydrogenase than uracil.

The results of this study support those of previous Phase I studies of S-1 administered on other schedules, as well as disease-directed studies, suggesting that the further development of the agent is warranted, particularly in the treatment of gastrointestinal malignancies. However, it is clear that additional efforts in terms of schedule optimization may be warranted. For example, administration schedules with built-in drug-free rest periods or developing criteria for drug discontinuation after the development of toxicity may hypothetically permit the sustained delivery of biologically relevant doses and a higher therapeutic index. Regardless, the results of Phase II studies of S-1 on dose schedules similar to that evaluated in the present study in patients with metastatic gastric and colorectal cancers have been especially intriguing. In one Phase II study of patients with metastatic gastric cancer, a 44% response rate was reported, and only 12% of patients experienced grade 3–4 toxicity after treatment with 40–60 mg/m^2 of S-1 twice daily (29). In addition, a 35% response rate with grade 3–4 toxicities, principally neutropenia, in 13% of patients has been noted in patients with metastatic colorectal cancer treated with S-1 as a single agent (30). With the availability of a wide variety of oral fluoropyrimidines, further evaluations to discern their relative merits and to determine whether the therapeutic index of fluoropyrimidine therapy may be higher for any particular subpopulation of patients in treating specific malignancies based on biochemical determinants may be warranted.

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