Cancer Chemother Pharmacol (2011) 67:249–254
DOI 10.1007/s00280-010-1311-3

ORIGINAL ARTICLE

Phase II study of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer

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Received: 3 December 2009 / Accepted: 10 March 2010 / Published online: 30 March 2010

Abstract
Purpose The primary objective of this study was to assess the efficacy and safety of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer.
Methods Patients with histologically or cytologically proven, advanced pancreatic cancer who had received first-line chemotherapy with gemcitabine were eligible for this study. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for 28 days, followed by 14 days' rest. Treatment was repeated every 6 weeks until disease progression.
Results Twenty-one patients were enrolled in this study. Grade 3 and 4 toxicities included anorexia in 14% of the patients, abdominal pain in 4.8% and infection without neutropenia in 4.8%. S-1 was discontinued in two patients because of toxicity. Of the 21 eligible patients, 2 (9.5%) achieved a partial response and 9 (43%) had stable disease. A marked decrease (≥50%) in tumor marker (CA19-9) was observed in 5 (28%) of the 18 evaluable patients. The median progression-free survival and the median survival time from the first day of S-1 therapy were 4.1 months (95% CI, 1.3–6.9 months) and 6.3 months (95% CI, 3.6–8.9 months), respectively.
Conclusions Second-line chemotherapy with S-1 was tolerated with acceptable toxicity and resulted in a relatively high disease control rate in patients with gemcitabine-resistant advanced pancreatic cancer. As an oral agent, S-1 may be a feasible treatment option for this patient population.

Keywords Pancreatic cancer · S-1 · Second-line therapy · Phase II study

Introduction

Pancreatic cancer is one of the most prevalent gastrointestinal tumors and its prognosis is extremely poor. A previous randomized trial of gemcitabine in patients with advanced pancreatic cancer has shown this drug is superior to 5-fluorouracil (5-FU) in terms of overall survival and clinical benefit [1], and treatment with gemcitabine alone has been accepted as the only approved therapy for unresectable pancreatic cancer. In an effort to improve therapeutic efficacy, various studies have investigated gemcitabine-based combination regimens. However, most of those studies have found a low impact on survival, and gemcitabine monotherapy is still considered as the standard treatment for this disease.

There is no accepted second-line treatment for advanced pancreatic cancer after gemcitabine failure. Although several studies have shown the efficacy and safety of second-line chemotherapy in a selected patient population [2], second-line strategies are often hard to implement due to the poor condition and prognosis of the patients. Thus,

This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. All study participants provided written informed consent. This manuscript has not been published and is not under consideration for publication elsewhere.

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there is an urgent need to develop effective therapies for tumors refractory to treatment with gemcitabine.

S-1 is an oral fluorinated pyrimidine, which was designed to improve the antitumor activity of 5-FU while reducing gastrointestinal toxicity, based on a hypothetical biochemical modulation of 5-FU. S-1 contains tegafur, 5-chloro-2, 4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a molar ratio of 1:0.4:1 [3]. Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU by hepatic microsomal enzymes. Gimeracil inhibits the degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD) and it is 180 times more potent than uracil, a DPD inhibitor included in UFT; thus, an efficacious concentration of 5-FU is maintained both in plasma and tumor tissues [4]. Oteracil is a competitive inhibitor of orotate phosphoribosyltransferase that inhibits phosphorylation of 5-FU in the gastrointestinal tract. Because oteracil preferentially acts in the gastrointestinal tract after oral administration, it reduces the gastrointestinal toxicity associated with 5-FU [5].

S-1 has shown favorable antitumor activity in several phase II studies in patients with various solid tumors [6–9], and a recent phase II study of S-1 in patients with metastatic pancreatic cancer yielded a good response rate of 37.5% and median survival of 9.2 months [10]. Furthermore, recent studies of combination chemotherapy with S-1 and gemcitabine for metastatic pancreatic cancer yielded a promising response rate of 44–48% and a median survival time of 10.1–12.5 months [11, 12]. Based on currently available data, S-1 seems to have significant activity against advanced pancreatic cancer; thus, we selected S-1 to treat patients with gemcitabine-resistant pancreatic cancer.

Patients and methods

Eligibility

Patients with histologically or cytologically proven, advanced adenocarcinoma of the pancreas who had received first-line chemotherapy with gemcitabine were eligible for this study. Participants were required to be at least 20 years old and to have an Eastern Cooperative Oncology Group performance status of 2 or less and adequate organ function defined by the following parameters: leukocytes $\geq$3,500/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dL, normal serum creatinine, a serum glutamic oxaloacetic transaminase (GOT) <150 IU/L, a serum glutamic pyruvic transaminase (GPT) <150 IU/L and serum bilirubin $\leq$2.0 mg/dL.

Patients were excluded if they had interstitial pneumonitis, active inflammatory bowel disease, active infection, mental disorder, or other severe concurrent disease. Patients with other malignancies and pregnant or lactating women were also excluded.

This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. Written informed consent was obtained from all patients before their inclusion into the study.

Treatment

S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily after a meal for 28 consecutive days, and the course was repeated after 14 days' rest, until disease progression or unacceptable toxicities. Three initial doses were established according to the body surface area (BAS) as follows: BSA $<$ 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA $<$ 1.50 m^2, 100 mg/day; 1.50 m^2 $\leq$ BSA, 120 mg/day.

Dose modification

S-1 was temporally discontinued when any of the following conditions were encountered: leukocytes <2,000/mm^3, neutrophils <1,000/mm^3, hemoglobin <8.0 g/dL, platelets <75,000/mm^3, serum GOT/GPT $\geq$ 150 IU/L, serum total bilirubin $\geq$3.0 mg/dL, serum creatinine $\geq$1.5 mg/dL, or when grade 3 non-hematological toxicity was observed. Administration was resumed when the toxicity resolved. When grade 4 hematological toxicity or grade 3 or greater non-hematological toxicity occurred, the dose of S-1 was reduced by 20 mg/day. If it was difficult to administer S-1 for 28 consecutive days because of tumor-related symptoms or non-severe toxicity, which did not meet the dose reduction criteria (e.g. grade 2 anorexia or nausea), a regimen consisting of S-1 administration for 14 consecutive days followed by 7 days' rest (2-week administration regimen) was permitted, since this regimen was recently reported to be more feasible and did not require a change in dose intensity, when compared to the standard 4-week administration regimen (28 consecutive days followed by 14 days' rest) [13].

Follow-up evaluation

Pretreatment evaluation included a medical history and physical examination, complete blood count and biochemistry test, a chest radiogram, and CT of the abdomen and pelvis. Complete blood counts and serum biochemistry tests were performed weekly during the first course of S-1 and every other week after the second course. Biochemistry

tests included standard serum tests such as total protein, albumin, bilirubin, GOT, GPT, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, creatinine, and C-reactive protein. Treatment-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Follow-up CT was performed every 2 months to assess objective tumor response according to the Response Evaluation Criteria in Solid Tumors. Serum CA 19-9 levels were measured monthly using a commercially available chemiluminescent enzyme immunoassay kit based on the two-step sandwich method (CL-EIA). A value of 39.5 U/mL was defined as the upper normal limit.

Statistics

The primary end-point was the objective response rate (complete response or partial response), with secondary end-points including overall and progression-free survival, disease control rate (complete response, partial response or stable disease), and safety of S-1. The number of patients required for this study was calculated according to the optimal two-stage design. The threshold response rate and expected response rate were 5% and 20%, respectively. The number of patients was 19 (α- and β-error probabilities 0.05 and 0.2). Both survival and tumor response were determined according to the intention-to-treat principle in all enrolled patients. Overall survival and progression-free survival were calculated with the Kaplan–Meier method.

Results

Patient characteristics

From March 2005 to July 2006, 21 patients entered this study. The patients' characteristics are listed in Table 1. All patients had been treated with gemcitabine alone. The median progression-free survival with first-line gemcitabine was 3.2 months. At the time of enrollment, most patients (95%) had evidence of metastatic disease and one patient had locally advanced unresectable disease. Seventy-one percent of the patients had an ECOG performance status of 0 or 1.

A total of 66 cycles were delivered (median, 3; range, 0–13). Based on the dose modification guidelines, the 2-week administration regimen was adopted in ten patients (48%).

Toxicity

All treated patients ($n = 21$) were assessed for toxicities. The toxicities observed during treatment are listed in Table 2. Generally, hematological toxicity was mild, and no grade 3 or higher toxicity was observed. As for non-hematological toxicity, grade 3 anorexia (14%), grade 3 abdominal pain (4.8%), and grade 3 infection (4.8%) was experienced. One patient developed duodenal bleeding 54 days after the beginning of S-1 treatment requiring embolization under angiography. This was considered to be tumor bleeding unrelated to the medication. Second-line chemotherapy with S-1 was feasible with acceptable toxicity and no treatment-related deaths occurred.

Table 1 Patient characteristics

Number of patients	21
Gender	
Men	13
Women	8
Age, years	
Median (range)	64 (32–75)
ECOG performance status	
0	4
1	11
2	6
Disease status	
Locally advanced	1
Metastatic	20

ECOG Eastern cooperative oncology group

Table 2 Toxicity ($n = 21$)

Toxicity	No. of patients (%)		
	Grade 1/2	Grade 3	Grade 4
Hematological toxicity			
Leukocytopenia	6 (29)	0	0
Neutropenia	4 (19)	0	0
Anemia	4 (19)	0	0
Thrombocytopenia	7 (33)	0	0
Non-hematological toxicity			
Anorexia	4 (19)	3 (14)	0
Nausea	5 (24)	0	–
Vomiting	2 (9.5)	0	0
Diarrhea	3 (14)	0	0
Stomatitis	2 (9.5)	0	0
Elevation of GOT/GPT	5 (24)	0	0
Elevation of creatinine	1 (4.8)	0	0
Hyperbilirubinemia	1 (4.8)		
Abdominal pain	2 (9.5)	1 (4.8)	0
Infection without neutropenia	2 (9.5)	1 (4.8)	0

GOT glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase

Response and survival

Partial response was achieved in 2 patients, and the disease remained stable in 9, with a response rate of 9.5% (95% CI, 0–22%) and a disease control rate of 52%. Eighteen patients had elevated serum levels of CA 19-9 (median/range, 1998/42-49420 U/mL) without jaundice before treatment. The CA 19-9 level after treatment decreased more than 50% in 5 (28%) of those 18 patients and showed a normal value in 2 (11%).

The median progression-free survival and the median survival time from the first day of S-1 therapy were 4.1 months (95% CI, 1.3–6.9 months) and 6.3 months (95% CI, 3.6–8.9 months), respectively (Fig. 1).

Discussion

There is no accepted second-line treatment for patients with advanced pancreatic cancer who do not respond to treatment with gemcitabine. This study evaluated the use of S-1, a novel oral fluoropyrimidine preparation. As first-line treatment for metastatic pancreatic cancer, S-1 has shown favorable efficacy in clinical trials, but the efficacy and safety of S-1 as a second-line therapy has not been fully evaluated as yet.

In the current study, S-1 showed a modest activity against gemcitabine-resistant pancreatic cancer, yielding a response rate of 9.5%. Although it is difficult to compare our results with those of other studies (Table 3) because of differences in patients' backgrounds, the response rate compares with that (15%) obtained in a previous phase II study of S-1 for gemcitabine-refractory metastatic pancreatic cancer reported by Morizane et al. [14]; and it was equivalent to that of other second-line regimens such as rubitecan (7%) [15], irinotecan (9%) [16], 5FU + celecoxib (12%) [17] or 5FU + paclitaxel (10%) [18]. On the other hand, the disease control rate (52%) of S-1 in the current study was relatively high and comparable to that observed in other active combination regimens for gemcitabine-resistant pancreatic cancer, such as gemcitabine + oxaliplatin (PR 22.6%, SD 38.7%) [19], 5FU + leucovorin + oxaliplatin (PR 23.3%, SD 30%) [20] or irinotecan + raltitrexed (PR 16%, SD 37%) [21]. The median survival time (6.3 months) in this study was also comparable to that (6–6.5 months) reported with other active combination regimens [19–21].

Most patients in the current study had some symptoms related to disease progression or prior chemotherapy at the study entry. It was often difficult to administer S-1 for 28 consecutive days because of tumor-related symptoms or toxicity. To improve therapeutic compliance, the 2-week administration regimen was adopted in ten patients (48%) based on the guidelines for dose modification, since this regimen was recently reported to be more feasible without changing dose intensity compared to the standard treatment schedule [13]. Hematological toxicity of S-1 was mild, and the occurrence of grade 3 or higher hematological toxicity seemed to be lower when compared to other combination regimens. The most common grade 3 non-hematological toxicity of second-line S-1 was anorexia (14%). In the current study, second-line chemotherapy with S-1 was feasible with acceptable toxicity in patients with gemcitabine-resistant advanced pancreatic cancer.

Although the response rate (9.5%) to S-1 in the current study was modest, we consider that the relatively high disease control rate, favorable survival data and toxicity profile may support the use of S-1 as second-line treatment. Furthermore, S-1 has the clinical advantage of being orally administered when compared with infusion regimens. Oral administration of S-1 reduces hospital visits for outpatients and has advantages in terms of quality of life. Considering the extremely poor prognosis of patients with gemcitabine-resistant pancreatic cancer, treatment should be more concerned with their quality of life.

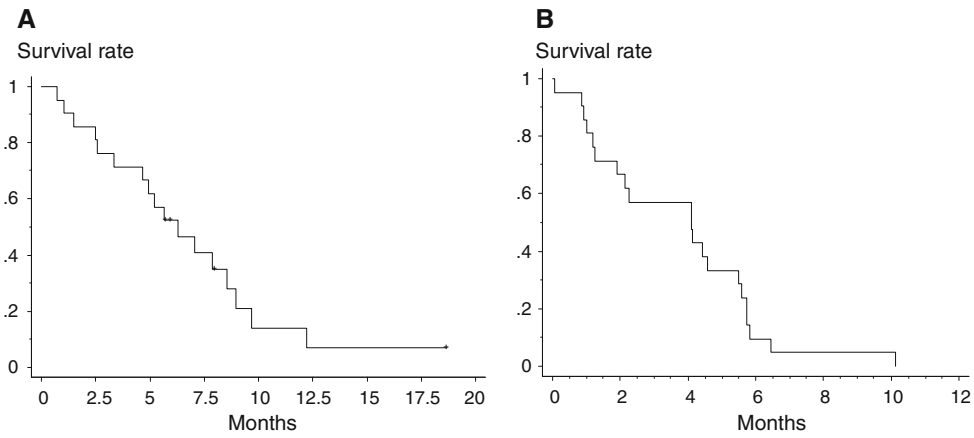

Fig. 1 Overall survival time curve (**a**) and progression-free survival (**b**) from the first day of S-1 therapy

Table 3 Clinical trials in patients with gemcitabine-pretreated advanced pancreatic cancer

Treatment	Number of patients	Response rate (%)	Disease control rate (%)	Progression-free survival	Median overall survival
Oxaliplatin	18	0	16.7	2 months	N/A
Capecitabine	39	0	39	2.3 months	7.6 months
Rubitecan	58	7	23	59 days	92 days
Irinotecan	33	9	48	2 months	6.6 months
S-1	40	15	58	2 months	4.5 months
Oxaliplatin + 5FU + leucovorin	30	23.3	53.3	22 weeks	25 weeks
Xelox (oxaliplatin + capecitabine)	41	2.6	28	9.9 weeks	23 weeks
FDR-GEM + oxaliplatin	33	22.6	61	4.2 months	6 months
5FU + celecoxib	17	12	24	8 weeks	15 weeks
5FU + paclitaxel	28	10	30	2.5 months	7.6 months
Docetaxel + gefitinib	41	2.4	49	1.8 months	4.5 months
Irinotecan + raltitrexed	19	16	53	4 months	6.5 months

FDR fixed dose rate, *N/A* not available

In conclusion, this study has shown that second-line chemotherapy with S-1 is tolerated with acceptable toxicity, and yields a relatively high disease control rate in patients with gemcitabine-resistant pancreatic cancer. As an oral agent, S-1 is a feasible treatment option considering QOL. Our data warrant further studies regarding second-line treatment using S-1 after gemcitabine failure.

Conflicts of interest statement No financial support for this study was provided. The authors report no conflicts of interest.

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