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ORIGINAL ARTICLE

A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer

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Abstract
Purpose Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. After disease progression, there is no standard regimen available. In a previous phase II trial, S-1 has been reported to show considerable efficacy, achieving a response rate of 37.5% in chemo-naïve patients with pancreatic cancer. This study evaluated the efficacy and toxicity of S-1 in patients with gemcitabine-refractory metastatic pancreatic cancer.
Methods Eligibility criteria were histologically proven pancreatic adenocarcinoma with confirmation of progressive disease while receiving gemcitabine-based first-line chemotherapy, 20–74 years of age, Karnofsky performance status of 80–100 points, with measurable metastatic lesions, adequate hematological, renal and liver functions, and written informed consent. S-1 was administered orally at 40 mg/m^2 twice daily for 28 days with a rest period of 14 days as one course. Administration was repeated until the appearance of disease progression or unacceptable toxicity. The primary endpoint of this study was an objective response, and secondary endpoints included toxicity, progression-free survival (PFS) and overall survival, as well as clinical benefit response in symptomatic patients.
Results Forty patients from two institutions were enrolled between September 2004 and November 2005. The most common adverse reactions were fatigue and anorexia, although most of those adverse reactions were tolerable and reversible. One patient developed grade 3 pneumonitis without neutropenia and recovered with appropriate antibiotic treatment. Although no complete response was seen, partial response was obtained in six patients (15, 95% confidence interval, 3.9–26%). Stable disease was noted in 17 patients (43%), and progressive disease in 15 patients (38%). Out of 19 evaluable patients, a clinical benefit response was observed in four patients (21%). The median PFS was 2.0 months, and the median survival time was 4.5 months with a 1-year survival rate of 14.1%.
Conclusion S-1 as monotherapy had marginal anti-tumor activity with tolerable toxicity in patients with gemcitabine refractory metastatic pancreatic cancer.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Salvage

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Background

The prognosis of patients with pancreatic carcinoma is extremely poor because of difficulty in the early detection of this disease, the high incidence of postoperative recurrence, and ineffectiveness of nonsurgical treatments. Gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU [3]. However, the benefit provided was inadequate, with an objective response rate of less than 15% and a median survival of 5–7 months. To improve the prognosis of patients with pancreatic cancer, one of the strategies is to develop the effective first-line chemotherapy including

gemcitabine combinations. Among various combinations with gemcitabine plus other agents as a first-line chemotherapy, only a few regimens have shown any survival benefit over single-agent gemcitabine [6, 20, 25], although the worldwide consensus regarding the results of these studies has not been established. Another strategy is to develop an effective second-line chemotherapy regimen after disease progression during first-line chemotherapy. However, despite the fact that several studies have investigated second-line chemotherapy in pancreatic cancer, the therapeutic results have been disappointing with poor response rate and survival [1, 2, 4, 5, 7, 14, 16, 18, 19, 21, 26, 27, 33, 34, 36, 38] Effective treatment in patients failing gemcitabine-based chemotherapy is eagerly awaited.

S-1 is a novel orally administered drug that is a combination of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and oteracil potassium (Oxo) in a 1:0.4:1 molar concentration ratio [31]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and acts to maintain efficacious concentrations of 5-FU in plasma and tumor tissues [35]. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, reducing the serious gastrointestinal toxicity associated with 5-FU [32]. The antitumour effect of S-1 has already been demonstrated in a variety of solid tumors such as advanced gastric cancer [15, 30], colorectal cancer [23], non-small-cell lung cancer [13], head and neck cancer [11], and breast cancer [29].

Concerning pancreatic cancer, a recent late phase II study of S-1 for chemo-naïve advanced pancreatic cancer patients demonstrated promising results with a response rate of 37.5% and a favorable toxicity profile [24]. Furthermore, clinical studies have reported activity of gemcitabine in pancreatic cancer patients with refractoriness to 5-FU [28], suggesting the lack of crossresistance between the gemcitabine and fluorinated pyrimidine, including S-1. Therefore, we conducted the present phase II study to investigate the feasibility and efficacy of S-1 in patients with advanced pancreatic adenocarcinoma in a progressive state under gemcitabine-based first-line chemotherapy.

Patients and methods

Patients

All patients were required to show histologically proven pancreatic adenocarcinoma with measurable metastatic lesions. Additional criteria included the following: progressive disease under gemcitabine-based first-line chemotherapy, post operative recurrence or metastatic disease before the start of first-line chemotherapy, 20–74 years of age, Karnofsky performance status (KPS) of 80–100 points, more than 3 weeks intervals between the last administration of the prior chemotherapy regimen and study entry, adequate bone marrow function (white blood cell count $\geq$ 3,000/mm^3, neutrophil count $\geq$ 1500/mm^3, platelet count $\geq$ 100,000/mm^3, haemoglobin level $\geq$ 9.0 g/dl), adequate renal function (serum creatinine level $\leq$ 1.5 mg/dL), and adequate liver function (serum total bilirubin level $\leq$ 2.0 mg/dL, transaminases level $\leq$ 2.5 times the upper limits of normal). Patients who had obstructive jaundice or liver metastasis were considered eligible if their transaminases levels could be reduced to within 5 times the upper normal limit of normal after biliary drainage. The exclusion criteria were as follows: regular use of phenytoin, warfarin or frucitocin, history of fluorinated pyrimidine use, severe mental disorder, active infection, ileus, interstitial pneumonia or pulmonary fibrosis, refractory diabetes mellitus, heart failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, brain metastasis, active concomitant malignancy. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center in Japan.

Treatments

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily after breakfast and dinner. Three initial doses were established according to the body surface area (BSA) as follows: BSA $<$ 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA $<$ 1.50 m^2, 100 mg/day; and 1.50 m^2 $\leq$ BSA, 120 mg/day. S-1 was administered at the respective dose for 28 days, followed by a 14-day rest period; this treatment course was repeated until the occurrence of disease progression, unacceptable toxicities, or the patient's refusal to continue. When a grade 3 or greater haematologic or grade 2 or greater nonhaeamatologic toxicity occurred, either the temporary interruption of the S-1 administrations until the toxicity decreased to grade 1 or less, or dose reduction by 20 mg/day (minimum dose, 80 mg/day) was recommended. If no toxicity occurred, the rest period was shortened to 7 days or the dose was gradually escalated in the next course (maximum dose, 150 mg/day), or both were permitted according to the judgment of the individual physicians. If a rest period of more than 28 days was required because of toxicity, the patient was withdrawn from the study. Patients were not allowed to receive concomitant radiation therapy, chemotherapy, or hormonal therapy during the study. Patients maintained a daily journal to record their intake of S-1 and any signs or symptoms that they experienced.

Response and toxicity evaluation

The response after each course was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Primary pancreatic lesions were not considered to be measurable lesions because the dimensions of such lesions are difficult to measure accurately. Physical examinations, complete blood cell counts, biochemistry tests, and urinalyses were performed at least weekly. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Clinical benefit response

The clinical benefit response (CBR) was evaluated using the KPS and pain score, as described below [3]. The KPS was recorded weekly by the attending physician. Pain was evaluated by measuring the change from the baseline pain intensity and the daily dose of morphine or morphine-equivalent (doses of analgesic agents were converted to morphine-equivalent doses, i.e., 10 mg oxycodone = 15 mg morphine). The pain intensity was graded from 0 (no pain) to 100 (worst pain) using a visual analog scale and was recorded on a pain assessment card every day. Patients who fulfilled at least one of the following criteria were defined as eligible CBR analysis: (1) baseline pain intensity $\geq$20, or (2) baseline morphine consumption $\geq$10 mg/day. Moreover, all the patients underwent a 'pain stabilization period' for 2 days to ensure that the baseline values were stable before treatment: when the variation in the morphine consumption between 2 days was within 10 mg and the variation of the pain intensity was within 20, the patient was considered eligible for inclusion in the CBR analysis. For pain intensity, a positive response occurred when the score was improved by $\geq$50% from baseline, sustained for $\geq$4 weeks. For analgesic consumption, a positive response occurred when the weekly consumption was reduced by $\geq$50% from baseline, maintained for $\geq$4 weeks. A positive response for KPS was defined as an improvement of $\geq$20 points from baseline, sustained for at least 4 weeks. Any worsening from baseline, sustained for 4 weeks, was considered a negative response for each of the three domains. All the other results were considered stable. Pain intensity and analgesic consumption were compared to give a composite pain score. Each patient was classified positive, stable or negative for each of the primary measures (pain and KPS). In order to achieve a positive clinical benefit response, patients had to be positive for at least one parameter without being negative for any of the others for a minimum of 4 weeks. Patients who were stable in the two primary measures were classified as stable.

Statistical design

The primary endpoint of this study was objective response rate. The secondary endpoint of this study was clinical benefit response; toxicity; progression-free survival; and survival. The number of patients to be enrolled was planned using a SWOG's standard design (attained design) [8, 9]. The null hypothesis was that the overall response rate would be $\leq$5% and the alternative hypothesis was that the overall response rate would be $\geq$20%, the α error was 5% (one-tailed) and the β error was 10% (one-tailed). The alternative hypothesis was established based on the preferable data from previous reports [7, 16, 27, 36, 38]. Interim analysis was planned when 20 patients were enrolled. If none of the first 20 patients had a partial response or complete response, the study was to be ended. If a response was detected in any of the first 20 patients studied, an additional 20 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. If the lower limit of the 90% confidence interval exceeded the 5% threshold (objective response in seven or more of the 40 patients), S-1 was judged to be effective and we would proceed to the next large-scale study.

The progression-free survival was calculated from the date of study entry to the date of documented disease progression or death due to any cause (whichever occurred first); and overall survival time was calculated from the date of study entry to the date of death or the last follow-up. The median probability of the survival period and progression-free survival were estimated using the Kaplan–Meier method. The relative dose intensity of S-1 was calculated according to the Hryniuk method [10].

Results

Patients

Forty consecutive patients with metastatic pancreatic cancer which was progressing under gemcitabine-based first-line chemotherapy were enrolled in this study between September 2004 and November 2005. The patient characteristics are shown in Table 1. Thirty-six of the forty patients showed a KPS of $\geq$90. Prior treatment was gemcitabine monotherapy in all patients. Thirty-six of the forty patients (90%) received gemcitabine as a standard 30 min infusion, and the remaining four patients (10%) received gemcitabine administered by fixed dose rate infusion. Of 40 patients, 4 patients (10%) showed a partial response, 21 patients (53%) showed stable disease, and 12 (30%) patients showed progressive disease in first-line gemcitabine therapy. Three patients had received first-line chemotherapy at another hospital and accurate data about

Table 1 Patient characteristics ($n = 40$)

Age	
Median (range)	62 (36–74)
Gender	
Male	21
Female	19
KPS	
100	17
90	19
80	4
Biliary drainage	
(+)	6
Prior pancreatectomy	
(+)	7
Location of primary tumor	
Head	17
Body	14
Tail	9
Sites of metastasis	
Liver	33
Lymph node	16
Lung	3
Peritoneum	4
Prior chemotherapy	
Gemcitabine[a]	36
FDR-GEM[b]	4
TTP of prior treatment (months)	
Median (range)	2.8 (0.7–13.5)
CEA (ng/ml)	
Median (range)	14.9 (1.1–1,187)
CA19-9 (U/ml)	
Median (range)	4,673 (0.1–2,960,000)

KPS Karnofsky performance status, *TTP* time to progression, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9

[a] Gemcitabine as a standard 30-min infusion

[b] FDR-GEM: gemcitabine as a fixed dose rate infusion

treatment response could not be obtained. The median time to progression in the prior treatment was 2.8 months (range 0.7–13.5 months).

Treatments

A total of 94 courses were administered to the 40 patients with a median of two courses per patient (range 1–12). The initial administered dose of S-1 was 80 mg/day in 1 patient, 100 mg/day in 18 patients, and 120 mg/day in 21 patients. Treatment interruption was necessary in 18 patients, due to fatigue (grade 3: one patients, grade 2: one patient, grade 1: two patients), nausea (grade 2: three patients, grade 1: one patient), diarrhea (grade 3: two patients, grade 1: two patients), drainage tube related problem (two patients), grade 3 appetite loss (1), grade 1 leukocytopenia (1), grade 2 hand-foot skin reaction (1), and grade 1 pneumonitis (1). Dose reduction was required in three patients because of grade 3 diarrhea (1), grade 2 fatigue (1), and grade 1 nausea (1). The relative dose intensity was 94.7%. The reasons for discontinuation of treatment were radiologically confirmed progressive disease (PD) in 31 patients, clinical PD without radiological PD in 6 patients, at the patients request due to unacceptable toxicities in 2 patients (grade 2 fatigue and grade 3 anorexia), and loss to follow up in one patient.

Toxicity

All 40 eligible patients were assessable for adverse events. The treatment-related adverse reactions are listed in Table 2. One patient developed grade 3 pneumonitis without neutropenia and required hospitalization, but she recovered from the pneumonitis with antibiotic treatment. As to other grade 3 non-hematological toxicities, aspartate aminotransferase elevation (two patients), alanine aminotransferase elevation (2), fatigue (2), anorexia (2), diarrhea (2) were noted. Regarding hematological toxicities, grade 3 anemia was noted in one patient. No other severe or unexpected adverse reactions were noted. The most common adverse reactions were fatigue (78%) and anorexia (73%), although most of those adverse reactions were tolerable and reversible. Although five patients died within 4 weeks after discontinuation of treatment due to rapid disease progression, no treatment-related deaths were observed.

Efficacy

Out of the total of 40 eligible patients, 38 patients were assessable for response. Two patients discontinued chemotherapy at their request due to unacceptable toxicities (grade 2 fatigue and grade 3 anorexia) and moved to another hospital before tumor assessment. Although no complete response was seen, partial response was obtained in six patients (15, 95%, confidence interval 3.9–26%). Stable disease was noted in 17 patients (43%), and progressive disease in 15 patients (38%). Tumor responses to second-line S-1 therapy are classified according to tumor responses to first-line gemcitabine in Table 3. The serum CA 19-9 level was reduced to less than half in 8 (23%) of 35 patients with a pretreatment serum CA19-9 level of the upper limit of normal or greater. At the time of enrollment, nineteen of forty (47.5%) patients were eligible for the evaluation of clinical benefit response. Out of nineteen evaluable patients, a clinical benefit response was observed in four patients (21%). The median progression free survival time was 2.0 months, and the median survival time was 4.5 months (range 1.2–14.3+) with a 1-year survival rate of 14.1% (Fig. 1).

Table 2 Treatment-related adverse events ($n = 40$): worst grade reported during treatment period

	Grade				Grade 1–4	Grade 3–4
	1	2	3	4	*n* (%)	*n* (%)
Hematological toxicity						
Leukocytes	8	2	0	0	10 (25)	0 (0)
Neutrophils	3	2	0	0	5 (13)	0 (0)
Hemoglobin	5	13	1	0	19 (48)	1 (3)
Platelets	9	0	0	0	9 (23)	0 (0)
Non-hematological toxicity						
Aspartate aminotransferase elevation	13	1	2	0	16 (40)	2 (5)
Alanine aminotransferase elevation	8	1	2	0	11 (28)	2 (5)
Total bilirubin elevation	4	3	0	0	7 (18)	0 (0)
Fatigue	21	8	2	0	31 (78)	2 (5)
Nausea	18	6	0	0	24 (60)	0 (0)
Vomiting	5	1	0	0	6 (15)	0 (0)
Anorexia	22	5	2	0	29 (73)	2 (5)
Stomatitis	11	3	0	0	14 (35)	0 (0)
Diarrhea	8	4	2	0	14 (35)	2 (5)
Rash	3	0	0	0	3 (8)	0 (0)
Pigmentation	6	1	–	–	7 (18)	–
Hand-foot skin reaction	1	1	0	–	2 (5)	0 (0)
Pneumonitis without neutropenia	0	0	1	0	0 (0)	1 (3)

Table 3 Objective tumor response (RECIST criteria) ($n = 40$)

Response (2nd line)	*n* (%)	Response (1st line)			
		PR	SD	PD	NE
CR	0 (0%)	0	0	0	0
PR	6 (15%)	1	4	0	1[a]
SD	17 (43%)	2	9	5	1[a]
PD	15 (38%)	1	6	7	1[a]
NE	2 (5%)	0	2	0	0
Total	40 (100%)	4	21	12	3

Treatment response to second-line S-1 therapy is tabulated according to treatment response to first-line gemcitabine

[a] Three patients received first-line chemotherapy at another hospital and accurate data about treatment ressponse was unobtainable

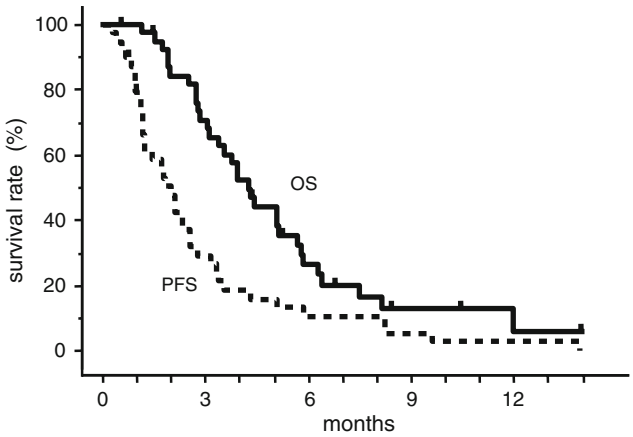

Fig. 1 Survival ($n = 40$). Progression free survival (*dashed line*), and overall survival time (*solid line*) curves of patients with gemcitabine refractory pancreatic cancer receiving systemic chemotherapy with S-1

Discussion

Over the last several years, many studies have been designed to establish effective treatment for gemcitabine-refractory pancreatic cancer patients. So far, the results of two randomized phase III studies had been reported. Jacobs et al. reported on a phase III study comparing Rubitecan, a new topoisomerase I inhibitor, versus "physicians' choice" in 409 pretreated patients. The study was unable to indicate any statistically significant survival benefit in the Rubitecan arm (3.7 months vs. 3.1 months, $P = 0.626$), although progression-free survival was significantly improved in Rubitecan arm (1.9 months vs. 1.6 months, $P = 0.001$) [12]. On the other hand, Oettle et al. [22] reported on phase III study comparing a combination of oxaliplatin, 5-FU and folinic acid with best supportive care (BSC). The BSC arm closed to accrual after 46 out of 165 planned patients were enrolled because physicians deemed it unethical. The median survival of second-line therapy was 21 weeks compared to 10 weeks for the BSC group ($P = 0.0077$). However, a worldwide consensus regarding this result has not been established because of the small number of patients in

this study. Other studies have investigated the feasibility and activity of second-line treatments in phase II studies [1, 4, 7, 17, 19, 26, 27, 33, 36, 38]. Compared with monotherapy, combination regimens exhibited superior activity in these studies. Fluoropyrimidine-, Irinotecan- or oxaliplatin-based combinations indicated relatively preferable activity with objective responses rate of about 20% and a median survival of 5–6 months in this setting [7, 17, 27, 36, 38]. The safety profiles of such combination regimens require further careful evaluation, and well-designed, larger randomized controlled studies are needed.

In the current study, S-1 produced a response rate of 15%, which was superior to the rates obtained for other reported single agents, including paclitaxel (5.5%) [21], raltitrexed (0%) [38], rubitecan (7%) [4]. However, this response rate failed to reach the pre-established boundary of 17.5% required for the agent to be considered effective. Furthermore, the progression-free survival (median 2 months) and the overall survival (median 4.5 months) were still extremely poor in this study. Although S-1 seems to have some degree of anti-tumor activity in patients with gemcitabine refractory metastatic pancreatic cancer, monotherapy may be insufficient to prolong survival. This limitation may be due to the strong chemo-resistance and heterogeneity of the tumors caused by the nature of the disease and acquired from previous chemotherapy regimens.

The toxicity of S-1 was acceptable and no life-threatening toxicities were observed. Although a population with an extremely poor prognosis was targeted in this study and the general condition of the participating patients was expected to be unstable, the toxicities were similar to the results of previous clinical studies for S-1 in chemo-naïve patients with pancreatic cancers [24, 37]. The safety profile of this study suggests that S-1 can be safely administered to pancreatic cancer patients even in a second-line setting, at least in selected populations.

We conclude that S-1 as monotherapy had marginal anti-tumor activity with tolerable toxicity in patients with gemcitabine refractory metastatic pancreatic cancer. In view of the favorable toxicity profile, its combination with other agents might have potential to improve therapeutic results.

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