Cancer Chemother Pharmacol (2009) 63:535–541
DOI 10.1007/s00280-008-0836-1

ORIGINAL ARTICLE

Phase II trial of S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer

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Received: 24 June 2008 / Accepted: 9 September 2008 / Published online: 1 October 2008

Abstract
Purpose S-1 has a favorable effect in unresectable pancreatic cancer and a potential radiosensitizer. In addition, daily oral administration of S-1 is more convenient than continuous infusion of 5-fluorouracil. This study was designed to evaluate the efficacy and safety of S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer.
Methods Eligibility criteria were histologically proven pancreatic adenocarcinoma, locally advanced disease, and no previous treatment. S-1 was administered orally at a dose of 40 mg/m^2 twice daily from day 1 to 14 and from day 22 to 35, and concurrent radiotherapy (a total dose of 50.4 Gy) was delivered in 28 fractions. One month after treatment completion, tumor response was evaluated by computed tomography (CT).
Results A total of 25 patients were evaluable for efficacy and toxicity on the basis of the intention-to-treat analysis. The response rate and disease control rate were 24.0 and 68.0%, respectively. There was no treatment-related death or grade 4 toxicity. The most common grade 3 hematologic and non-hematologic toxicities were thrombocytopenia (4.0%) and anorexia (20%), respectively. All toxicities were tolerable and transient. The median time-to-progression and median overall survival were 6.5 months (95% confidence interval, 4.1–9.0 months) and 12.9 months (95% confidence interval, 6.7–19.0 months), respectively, and the 1-year survival rate was estimated to be 43%.
Conclusions S-1 and concurrent radiotherapy shows favorable efficacy for disease control against locally advanced pancreatic cancer and was well tolerated with no severe toxicities.

Keywords S-1 · Pancreatic cancer · Locally advanced · Concurrent chemoradiotherapy

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Introduction

Pancreatic cancer was the fifth leading cause of cancer death in Korea in 2005, with an annual incidence of approximately 1,600 men and 1,100 women in Korea from 1998 to 2002 was. Pancreatic cancer has a poor prognosis with a 5-year survival of less than 5%, because approximately 90% of patients have unresectable pancreatic cancer at the time of diagnosis. At diagnosis, 40–50% of unresectable pancreatic cancer is locally advanced disease without distant metastasis [5, 6], which is generally incurable and has a median survival of 8–12 months [5, 25].

Concurrent chemoradiotherapy has been shown to improve survival in locally advanced pancreatic cancer. From several phase III studies, 5-fluorouracil (5-FU)-based chemoradiotherapy has been proven beneficial toward survival [6, 18, 19]. To further increase the survival of locally advanced disease, various chemotherapeutic agents other

than 5-FU have been tested, but the optimal combination for chemoradiotherapy remains elusive [5].

S-1, a new oral fluoropyrimidine derivative drug, consists of tegafur (a prodrug for 5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate [28]. CHDP and potassium oxonate prolong a higher concentration of 5-FU in the bloodstream and diminish the toxicity of 5-FU. The effectiveness of S-1 has been demonstrated against some gastrointestinal tumors, including gastric cancer and colorectal cancer [22, 26], and S-1 has been reported to be effective against metastatic pancreatic cancer [23, 32]. Like 5-FU, S-1 may also act as a radiosensitizer, and preclinical and clinical studies have demonstrated radiosensitizing potency of S-1 [4, 7–9, 21, 31]. The daily oral administration of S-1 during concomitant radiotherapy would produce a beneficial outcome as a protracted infusion of 5-FU, because the pharmacokinetics of orally administered S-1 is proved to be similar to that of continuous intravenous infusion of 5-FU [10]. S-1 is also more convenient than intravenous agents. Collectively, these properties make S-1 a good candidate agent for chemoradiotherapy to control the primary tumor and to prevent distant metastasis in locally advanced pancreatic cancer.

The aim of this study was to evaluate tumor response to S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer and to evaluate toxicities, time-to-progression and overall survival.

Patients and methods

Eligibility

Patients who were diagnosed with locally advanced pancreatic cancer at Severance Hospital in Seoul, Korea, were enrolled. Tumors were staged using the American Joint of Committee on Cancer Staging System; Stage III was considered as locally advanced disease. Inclusion criteria included histologically or cytologically confirmed pancreatic adenocarcinoma, no history of prior chemotherapy or radiotherapy, an Eastern Cooperative Oncology Group (ECOG) performance scale ranging from 0 to 2, adequate hematologic profile (neutrophil count $\geq$2,000 mm^{-3}, platelet count $\geq$100,000 mm^{-3}), adequate renal function (serum creatinine $\leq$1.5 mg/100 mL), and adequate hepatic function (total bilirubin level $\leq$5 mg/100 mL, transaminase level $\leq$2.5 times the upper limit of normal level). Exclusion criteria included metastasis from pancreatic adenocarcinoma, coincident other cancer, active infection, and uncontrolled comorbidity.

Pretreatment evaluation included physical examination, laboratory tests including tumor markers, abdomen, and chest radiography, multidetector computed tomography (CT), and biopsy. Positron emission tomography (PET) was performed to detect distant metastasis before treatment. Any patients with obstructive jaundice underwent percutaneous or endoscopic biliary drainage before or during treatment. This study design was approved by the Institutional Review Board of Severance Hospital and written informed consent was obtained from all patients.

Treatment plan

Treatment was given on an outpatient basis. S-1 was given orally at a dose of 40 mg/m^2 twice a day from day 1 to 14 and from day 22 to 35, with a break from day 15 to 21. The initial doses were determined according to the body surface area (BSA) and divided into three categories as follows: BSA <1.25 m^2, 80 mg/day; BSA $\geq$1.25 m^2 and <1.5 m^2, 100 mg/day; and BSA $\geq$1.5 m^2, 120 mg/day. All patients underwent concurrent chemoradiotherapy with 3-D conformal radiotherapy. A total dose of 50.4 Gy was applied in daily fractions of 1.8 Gy, 5 days per week using a 10 MV linear accelerator. The gross tumor volume (GTV) was confined to the primary tumor and regional lymphadenopathy. The clinical target volume (CTV) included the GTV and the draining lymph node area of the pancreas. The planning target volume was defined as the CTV plus a 5 mm margin to account for respiratory motion and daily set-up error. This treatment plan was continued until completion, or until uncontrolled toxicities occurred and/or the patient refused to receive further treatment. The S-1 dose was adjusted according to toxicity and if S-1 was withheld due to toxicity on days of concurrent chemoradiotherapy, radiotherapy was also withheld. After evaluating the tumor response followed by completion of chemoradiotherapy, gemcitabine-based maintenance chemotherapy was administered to available patients until disease progression.

Response and toxicity evaluation

We regarded objective tumor response as the primary endpoint to evaluate the effect of chemoradiotherapy rather than the gemcitabine-based chemotherapy after chemoradiotherapy. Tumor response was assessed using multidetector CT with 16 or 64 channels, according to the guidelines of the response evaluation criteria in solid tumors (RECIST) 4 weeks after completing the treatment [30].

The secondary endpoints were toxicity, 1-year survival rate, time-to-progression, and overall survival. Time-to-progression was estimated from the treatment start date until documented disease progression or death, and overall survival was estimated from the treatment start date to the date of death or the last follow-up. To monitor toxicities, physical examinations and blood biochemistry measurements were conducted weekly from the start of treatment to

the day of evaluation. Toxicities were evaluated using the National Cancer Institute Common Toxicity Criteria version 2.0.

Statistical analysis

Recently, many studies of chemoradiotherapy for locally advanced pancreatic cancer have reported good response rates of up to 50% [24], and a phase I study of S-1 chemoradiotherapy by Sudo et al. [29] reported a response rate of 43.8%. Accordingly, we assumed that if the response rate was 30% or higher, the treatment would be beneficial. To test the alternative hypothesis that the minimum response rate was 30% with a null hypothesis that the response rate was 10% or lower, the required number of patients for a one-sided test was 25 with a type I error of 5%, and a power of 80%, according to single-stage phase II design [1]. If six or more patients were responsive, the treatment would be considered acceptable [1]. Tumor response and toxicity were evaluated with an intention-to-treat analysis, and patients who received at least a single dose of S-1 or a single fraction of radiotherapy were evaluated for tumor response and toxicity. The Kaplan–Meier method was used to estimate overall survival, time-to-progression and the 1-year survival rate. Statistical analysis was performed using SPSS version 11.0 for Windows.

Results

Patients' characteristics

A total of 27 patients were enrolled between August 2006 and November 2007, but two patients were excluded because of suspicious histologic diagnosis. Ultimately, 25 patients were evaluated for efficacy and toxicity. Patients' characteristics are summarized in Table 1. The median age was 67.5 years and the median follow-up time was 7.5 months. Before treatment, 12 patients underwent endoscopic retrograde biliary drainage, and two patients underwent percutaneous transhepatic biliary drainage. No patients developed obstructive jaundice during treatment.

Treatment outcomes

A total of 25 patients underwent at least one dose of S-1 and fractionated radiotherapy and 22 patients completed the full course of chemoradiotherapy as planned. The planned dose intensities of S-1 and radiotherapy were 740.6 mg/m^2 per week and 1,260 cGy per seven fractions, respectively. The mean relative dose intensities of S-1 and radiotherapy were 96.1 and 92.9%, respectively. Two (8%) patients did not complete the planned treatment. One expired due to biliary sepsis in the early days of treatment, but his death was not associated with chemoradiotherapy. The other stopped S-1 treatment at day 22–35 and 14-day consecutive concurrent radiation at her own request, but did not experience any toxicity. After evaluating tumor response and toxicity, 18 (75%) of 24 patients received gemcitabine-based chemotherapy, three patients received conservative care on their own request, and one patient underwent curative resection.

Table 1 Baseline characteristics of the patients

Characteristics	*n*	%
Total patients	25	
Men:women	17 (68%):8 (32%)	
Median age (range)	67.5 years (44–88)	
Median body surface area (range)	1.6 m^2 (1.3–1.9)	
Performance status		
ECOG 0-1	21	84.0
ECOG 2	4	16.0
Histology		
Ductal adenocarcinoma	25	100
Tumor location		
Head	18	72
body	7	28
Median tumor size[a] (range)	3.4 cm (2.0–7.0)	
Tumor marker		
Median CEA (range)	3.0 ng/mL (0.6–272.2)	
Median CA 19-9 (range)	546 U/L (0.7–13500.0)	

ECOG Easter Cooperative Oncology Group

[a] Longest diameter

Response and survival

A total of 25 patients were evaluated for efficacy with the intention-to-treat analysis (Table 2). Complete response was not observed in any patient. Partial remission (PR) and stable disease (SD) were achieved in six and 11 patients, respectively. The overall response rate and disease control rate were 24.0 and 68.0%, respectively. The median overall

Table 2 Tumor response

Tumor response	ITT (*n* = 25)		PPA (*n* = 23)	
	n	%	*n*	%
Complete remission	0	0	0	0
Partial remission	6	24.0	6	26.1
Stable disease	11	44.0	10	43.5
Progressive disease	7	28.0	7	30.4
Early death for other cause	1	4.0	–	–
Overall response	6	24.0	6	26.1

ITT intention-to-treat analysis, *PPA* per-protocol analysis

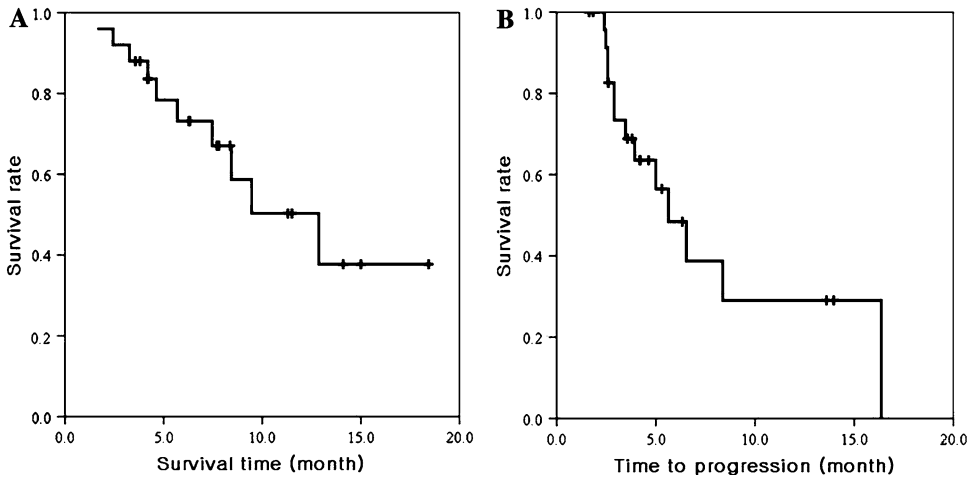

Fig. 1 Overall survival time curve (**a**) and time-to-progression curve (**b**) of patients with locally advanced pancreatic cancer receiving S-1 and concurrent radiotherapy

survival time was 12.9 months (95% confidence interval, 6.7–18.0) (Fig. 1a). Median time-to-progression was 6.5 months (95% confidence interval, 4.1–9.0) (Fig. 1b). The 1-year survival rate was estimated to be 43%.

Toxicity

A total of 25 patients were evaluated for toxicity (Table 3). There were no treatment-related deaths and no grade 4 toxicity. The most severe hematologic toxicity was grade 3 thrombocytopenia in only one patient (4.0%). The most common grade 3–4 toxicity was anorexia, seen in five patients (20.0%). All toxicities were tolerable and reversible after temporarily withholding therapy. A reduction in the S-1 dose was needed in only one patient because of grade 3 anorexia. Treatment was suspended for 10 days and a 30% reduction in the S-1 dose was used without recurrence of anorexia.

Table 3 Treatment-related toxicity ($n = 25$)

Toxicity	Grade					Toxicity of grade 1–4 (%)	Toxicity of grade 3–4 (%)
	0	1	2	3	4		
Hematologic							
Leukopenia	17	4	4	0	0	32.0	0
Neutropenia	20	2	3	0	0	20.0	0
Anemia	11	8	6	0	0	56.0	0
Thrombocytopenia	14	10	0	1	0	44.0	4.0
Non-hematologic							
Nausea	20	2	2	1	0	21.2	4.0
Vomiting	24	1	0	1	0	8.0	4.0
Anorexia	16	2	2	5	0	36.0	20.0
Diarrhea	23	2	0	0	0	8.0	0
Fatigue	21	1	2	1	0	16.0	4.0
Weight loss	24	1	0	0	0	4.0	0
Gastric ulcer	23	0	1	1	0	8.0	4.0
Duodenal ulcer	24	0	0	1	0	4.0	4.0
Dyspepsia	24	1	1	0	0	8.0	0
Abdominal pain	22	1	1	1	0	12.0	4.0
Dizziness	24	1	0	0	0	4.0	0
Pruritus	24	0	1	0	0	4.0	0
Fever	23	2	0	0	0	8.0	0

Discussion

Chemoradiotherapy is generally considered as the standard treatment for locally advanced pancreatic cancer, as compared to radiotherapy alone [14], although controversy remains over whether chemoradiotherapy or chemotherapy alone represents the superior treatment. The Gastrointestinal Tumor Study Group (GITSG) reported that the median survival time in patients with locally advanced pancreatic cancer treated with 5-FU and concurrent radiotherapy of 60 Gy was 11.4 months, compared to 5.3 months after radiotherapy alone [19]. Another study by GITSG showed significant survival benefits of 5-FU-based chemoradiotherapy with a median survival of 9.7 months over 5-FU-based chemotherapy alone with a median survival of 7.4 months [6]. Nonetheless, the results for chemoradiotherapy and chemotherapy alone are conflicting. In a phase III trial conducted by the Eastern Cooperative Oncology Group, the median overall survival times of 5-FU-based chemoradiotherapy and 5-FU chemotherapy alone were 8.3 and 8.2 months, respectively, with no significant difference [16]. In addition, metastasis during or after chemoradiotherapy and the toxicities of chemoradiotherapy could offset the survival benefit of the treatment. Recently, in the Groupe Coordinateur Multidisciplinaire en Oncologie (GERCOR) phase II/III study of locally advanced pancreatic cancer, the sequential treatment of induction chemotherapy followed by chemoradiotherapy was reported to

improve survival compared to chemotherapy alone, and the median overall survival from each treatment was 15.0 and 11.7 months, respectively [11]. This sequential treatment could prevent unnecessary chemoradiotherapy in patients experiencing metastatic disease during or after induction chemotherapy (29.3%), as compared to the standard chemoradiotherapy composed of chemoradiotherapy followed by chemotherapy. However, the favorable results of the GERCOR phase II/III study may be partly attributed to the exclusion of metastatic disease, based on the results of a recent GERCOR phase II study in which the incomplete exclusion of patients with metastasis progression resulted in a failure to demonstrate substantial benefits [20]. In the present study, 28% of 25 patients had progressive disease after chemoradiotherapy. If these patients had been excluded from the analysis, the positive effect would have been greater. The GERCOR phase II/III study suggested that induction chemotherapy followed by chemoradiotherapy is superior to chemotherapy alone, but it should not be directly compared to standard chemoradiotherapy.

The ideal chemotherapeutic agent for chemoradiotherapy should have systemic cytotoxicity to reduce distant metastasis during radiotherapy, and have radiosensitizing properties to gain local control of the primary tumor [5]. 5-FU has been used for a long time as a radiosensitizer in pancreatic cancer. Gemcitabine is considered a good substitute for 5-FU because gemcitabine chemotherapy has survival benefits over 5-FU chemotherapy in advanced pancreatic cancer [3], and gemcitabine has radiosensitizing potential [17]. Although there has been no phase III study comparing gemcitabine-based chemoradiotherapy to 5-FU-based chemoradiotherapy, several phase II trials of gemcitabine-based chemoradiotherapy have reported a favorable response rate and longer overall survival. The use of other various chemotherapeutic agents as radiosensitizers, such as paclitaxel, capecitabine, and molecular target drugs, has been demonstrated no significant improvement in survival [5].

S-1 was developed to improve the tumor-selective cytotoxicity of 5-FU, while reducing gastrointestinal toxicity through the addition of two modulator, CDHP and potassium oxonate [7]. CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU degradation, and is expected to prolong 5-FU concentrations in serum [28]. Potassium oxonate ameliorates the gastrointestinal toxicity of tegafur by decreasing 5-fluorodeoxyuridine monophosphate production in the gastrointestinal mucosa [23]. S-1 has shown a significant clinical effect against advanced pancreatic cancer (Table 4). Two phase II studies of S-1 chemotherapy found response rates of 21.1 and 37.5%, respectively, in metastatic pancreatic cancer [23, 32]. S-1 also has a radiosensitizing effect, which has been demonstrated in preclinical trials of a human oral cancer cell line, human oral cancer xenografts and human colon cancer xenografts [8, 9, 21], and in clinical trials of S-1 and concurrent radiotherapy for pancreatic cancer, rectal cancer, oral squamous cell carcinoma, and glottic cancer [4, 7, 12, 27, 29].

To the best of our knowledge, three phase I studies of S-1 and concurrent radiotherapy in locally advanced pancreatic cancer have been published. Sudo et al. [29] recommended a daily S-1 dose of 80 mg/m^2 per day from day 1 to 14 and 22 to 35 with concurrent radiotherapy at a total dose of 50.4 Gy in 28 fractions, with an observed response rate of 43.8% in 16 patients with locally advanced pancreatic cancer. Ikeda et al. [12] recommended a daily S-1 dose of 80 mg/m^2 daily with concurrent radiotherapy at a total dose of 50.4 Gy in 28 fractions, with an observed response rate of 19% in 21 patients with locally advanced pancreatic cancer. Shinchi et al. [27] also recommended a daily dose S-1 dose of 80 mg/m^2 with concurrent radiotherapy at a total dose of 50 Gy in 40 fractions, with an observed response rate of 35% in 17 patients with unresectable pancreatic cancer, including seven cases of metastatic diseases. We selected a dose and schedule that were similar to those recommended by Sudo et al. [29], and the 2-week S-1 dosing regimen with a 1-week break of S-1 is reported to alleviate adverse reactions without diminishing the response [15].

We found that S-1 based chemoradiotherapy in patients with locally advanced pancreatic cancer had a relatively

Table 4 Studies of S-1 chemotherapy alone and S-1 chemoradiotherapy in advanced pancreatic cancer

	Author	Phase	No. of patients	S-1 [mg/(m^2 day)]		Radiation dose (fractions)	Response rate (%)	Overall survival (months)	One-year survival rate (%)
				Dose	Schedule				
Chemotherapy	Ueno et al. [32]	II	19	80	D1–D28	–	21.1	5.6	15.8
	Okusaka et al. [23]	II	40	80	D1–D28	–	37.5	9.2	32.5
Chemoradiotherapy	Sudo et al. [29]	I	16	80 (RD)	D1–D14, D22–D35	50.4 Gy (28)	43.8	13.7	71.3
	Ikeda et al. [12]	I	21	80 (RD)	During radiotherapy	50.4 Gy (28)	19	11.0	42.9
	Shinichi H et al. [27]	I	17	80 (RD)	D1–D21	50 Gy (40)	36	12.3	–
	Present trial	II	25	80	D1–D14, D22–D35	50.4 Gy (28)	24.0	12.9	43.0

RD recommended dose, *D* day

modest response rate (24.0%) and a high disease control rate (68%). The median survival time was 12.9 months but the gemcitabine chemotherapy after chemoradiotherapy might be partly responsible for the favorable survival in the present study. The accurate measurement of tumor response in pancreatic cancer is not easy due to invasive growth and desmoplastic reaction [13]. Of the 11 patients assessed at SD, some might have actually been PR or progressive disease instead. Therefore, the number of PR patients might have been underestimated by CT. PET can help to assess tumor response in pancreatic cancer after chemoradiotherapy [2], but PET was not performed in all patients after treatment. However, a number of clinical trials have accepted objective response by CT as their end point [13], and the observed number of PR cases satisfied the cutoff value of 6 of 25 in the present study. In addition, S-1 based chemoradiotherapy was well tolerated, and there were no serious adverse events or treatment-related deaths. The toxicity profiles we observed were similar to a different study using S-1 as a single agent in metastatic pancreatic cancer [32]. The most common grade 3–4 toxicity we observed was anorexia (20%), which was consistent with other studies [23, 32].

In conclusion, S-1-based concurrent chemoradiotherapy had favorable efficacy in patients with locally advanced pancreatic cancer and has a low toxicity profile with good tolerance. Further studies to compare S-1-based chemoradiotherapy to other agent-based chemoradiotherapies are needed.

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