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ORIGINAL ARTICLE

Phase II trial of S-1 in combination with gemcitabine for chemo-naïve patients with locally advanced or metastatic pancreatic cancer

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Abstract
Background We performed a phase II study of combination chemotherapy with S-1 plus gemcitabine for treating chemo-naïve patients with unresectable pancreatic cancer to evaluate the efficacy and toxicity.
Patients and methods Patients with histologically confirmed unresectable pancreatic cancer were eligible. The treatment consisted of S-1 (40 mg/m^2 p.o. b.i.d. from D1 to 14) and gemcitabine (1,250 mg/m^2 on D1 and 8), repeated every 3 weeks.
Results Thirty-two patients were enrolled between March 2005 and December 2007. No complete response was observed and a partial response was observed in 14 patients (44.0%), stable disease in eight patients (25.0%), and progressive disease in eight patients (25.0%). The median time to progression was 4.92 months (95% CI: 4.16–5.67 months), and the median overall survival was 7.89 months (95% CI: 5.96–9.82 months). The survival duration was significantly longer for the patients with a good performance status compared with that of the patients with a poor performance status. The major toxicities were grade 3–4 neutropenia (9, 28.1%), grade 3/4 thrombocytopenia (5, 15.6%), and grade 3 diarrhea (5, 15.6%).
Conclusion The combination chemotherapy of S-1 and gemcitabine showed promising antitumor activity and manageable toxicities, and especially for the good performance status patients with unresectable pancreatic cancer.

Keywords Gemcitabine · S-1 · Pancreatic cancer · Combination chemotherapy

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Introduction

Pancreatic cancer is a major leading cause of cancer-related death worldwide. The prognosis for patients with pancreatic cancer still remains dismal despite the improvements in the diagnostic and therapeutic modalities.

A variety of chemotherapy regimens for the treatment of inoperable pancreatic cancer have been evaluated. Of all the available chemotherapeutic agents, 5-flourouracil (5-FU) was the most widely used drug for inoperable pancreatic cancer, although the objective response rate was less than 10% [1–6]. After that, gemcitabine monotherapy was accepted as a standard first-line treatment for inoperable pancreatic cancer on the basis of the results of a randomized trial comparing gemcitabine with bolus 5-FU [1, 7].

S-1 (TS-1, Taiho Pharmaceutical) is a novel oral fluoropyrimidine derivative in which tegafur, as a prodrug of 5-FU, has been combined with two 5-FU-modulating

substances, 5-chloro-2,4-dihydroxypyridine (gimeracil), and potassium oxonate (oteracil), at a molar ratio of tegafur:gimeracil:oteracil = 1:0.4:1 [8–11]. Gimeracil is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and so it maintains efficacious 5-FU concentrations in the plasma and tumor tissues [8–11]. Oteracil is a competitive inhibitor of orotate phosphoribosyltransferase, and it inhibits phosphorylation of 5-FU in the gastrointestinal tract and so it reduces the serious gastrointestinal toxicity associated with 5-FU [8–12]. The combinations of gemcitabine and 5-FU was shown to have a marked synergistic cytotoxic effect against pancreatic cancer cells in vitro [13–16]. However, there are few clinical trials that have been concerned with locally advanced or metastatic pancreatic cancer. Therefore, we conducted a phase II trial of S-1 in combination with gemcitabine in chemo-naïve patients with locally advanced or metastatic pancreatic cancer to prospectively evaluate the efficacy and toxicity profile.

Patients and methods

Patient selection

The patients with histologically confirmed unresectable locally advanced or metastatic pancreatic cancer were eligible for this study. No prior chemotherapy and no prior radiotherapy were allowed. The patients' ages were between 18 and 75 years, they had an ECOG performance status (PS) of 0–2 and measurable disease according to the response evaluation criteria in solid tumors (RECIST) [17], adequate renal and liver function (normal serum creatinine and creatinine clearance >60 ml/min, total bilirubin <2 mg/dl, serum AST and ALT <3 times the upper limit of normal) and adequate bone marrow function (neutrophils $\geq$1,500/μl, platelet count $\geq$100,000/μl, hemoglobin $\geq$10 g/dl). Those patients with symptomatic brain metastases, active infection, active coronary artery disease, unstable diabetes mellitus or an active concomitant malignancy were excluded from the study. Informed consent was obtained from all the patients and this study's protocol was approved by the institutional review board of Gyeongsang National University Hospital, Jinju, Korea.

Treatment schedule and dose modification

The selected eligible patients were treated as follows: S-1 (Taiho Pharmaceutical Co. Ltd, Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily for 14 consecutive days and this was followed by a 7-day break period; Gemcitabine 1,250 mg/m^2 was administered intravenously over 30 min on day 1 and day 8 of each cycle. This treatment was repeated every 3 weeks until the maximum six cycles.

Blood cell counts, assessing the serum creatinine and liver function tests were performed before each course of chemotherapy. Those patients whose absolute neutrophil count and platelet count were greater than or equal to 1,500 and 100,000/μl, respectively, and who had lower than or equal to grade 1 non-hematologic toxicity (excluding alopecia) received chemotherapy on day 1 of each cycle.

On day 8 of each cycle, the minimum requirements to administer gemcitabine were an absolute neutrophil count between 1,000 and 1,500/mm^3, a platelet count $\geq$75,000/mm^3 and no grade $\geq$2 non-hematologic toxicity (excluding alopecia).

If these conditions were not met on day 1 or 8, then the chemotherapy was postponed 1 week. A delay of more than 3 weeks resulted in withdrawal from this study.

In the case of grade 3 or 4 hematologic toxicities or greater than or equal to grade 3 non-hematologic toxicities with excluding diarrhea or mucositis, the dosages of both gemcitabine and S-1 were reduced by 25% for the all subsequent courses. In the case of greater than or equal to grade 3 diarrhea or mucositis, the dose of only S-1 was reduced by 25% for all the subsequent courses.

Assessment

The diagnostic staging was re-evaluated by performing CT scanning after every two consecutive cycles of chemotherapy unless indicated otherwise. Treatment was stopped at any time for documented disease progression, unacceptable toxicity or withdrawal of patient consent. The tumor response was assessed with using the RECIST criteria.

Statistical analysis

The sample size was calculated according to Simon's two stage optimal design. Assuming a response rate of 30%, a probability of error of 5% and a power of 80%, a total of 29 assessable patients were recruited. Treatment was considered inactive if the response rate was below 10%.

For the initial stage of the study, ten evaluable patients were to be entered into the study and they were evaluated for their response. If $\geq$1 response was observed in the first stage, then 19 additional patients were to be entered in the second stage to achieve a target sample size of 29 evaluable patients. The duration of response, the overall survival and the time to progression were assessed by the Kaplan–Meier method. The SPSS version 11.0 statistical software program (SPSS, Chicago, IL, USA) was used for all the statistical analyses.

Results

Patient characteristics

A total of 32 patients with unresectable locally advanced or metastatic pancreatic cancer were enrolled in this study between March 2005 and December 2007. The patients' characteristics are shown in Table 1. The median age was 63.5 years (range: 35–75). There were 24 men (75.0%) and 8 women (25%). 15 patients (47.0%) had an ECOG PS of 2. Twenty-nine patients (90.6%) had metastatic disease. Ten patients (31.2%) had extra-abdominal metastases (lung and bone) (Table 2).

Efficacy

A total of 114 cycles were given, with a median of 3 cycles (range: 1–6 cycles). There were no complete responses observed. Fourteen patients had a partial response (PR) [44.0, 95% confidence interval (95% CI): 26.6–60.9%], eight patients had stable disease (SD) (25.0%) and eight patients' disease progressed during the treatment (25.0%). Of the two non-assessable patients, one patient refused further chemotherapy due to toxicity after the first cycles and this patient was lost to follow up. The median overall survival was 7.89 (95% CI: 5.96–9.82 months) after the median follow-up duration of 20.9 months (range: 8–35 months) (Fig. 1), and the median time to progression (TTP) was 4.92 months (95% CI: 4.16–5.67) (Fig. 2). The patients with an ECOG 0-1 performance status (11.42 months, range: 7.18–15.66 months) showed significantly better survival compared with the patients with an ECOG 2 performance status (3.40 months, range: 1.36–5.44 months) (Fig. 3).

Table 1 Baseline patient characteristics ($N = 32$)

Characteristics	No. of patients	%
Age	63.5 (35–75)	
Gender		
Male	24	75.0
Female	8	25.0
ECOG PS		
0–1	17	53.0
2	15	47.0
Disease		
Locally advanced	3	9.4
Metastatic	29	90.6
Primary lesion		
Head of pancreas	14	43.8
Body of pancreas	8	25
Tail of pancreas	5	15.6
Combined	5	15.6
Metastatic site		
Intra-abdominal disease only (liver, bowel, peritoneum)	22	68.8
Extra-abdominal metastases (lung, bone)	10	31.2

PS performance status, *ECOG* Eastern Cooperative Oncology Group

Table 2 Treatment outcome ($N = 32$)

Response	Number of patients (%)
Partial response	14 (44)
Stable disease	8 (25)
Progressive disease	8 (25)
Not evaluable	2 (6)

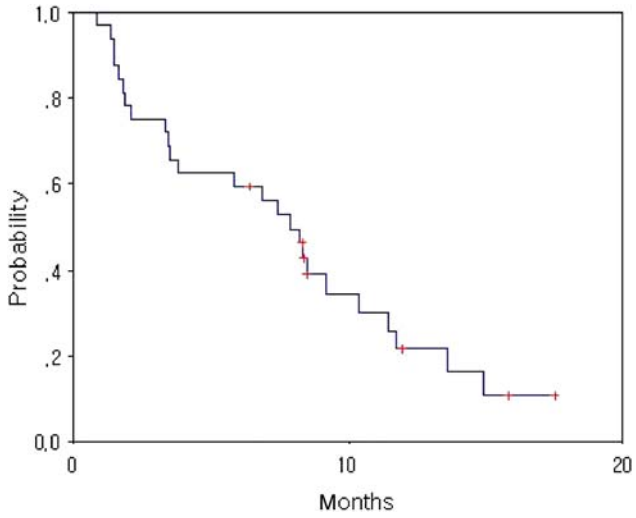

Fig. 1 Kaplan–Meier survival curve for the overall survival

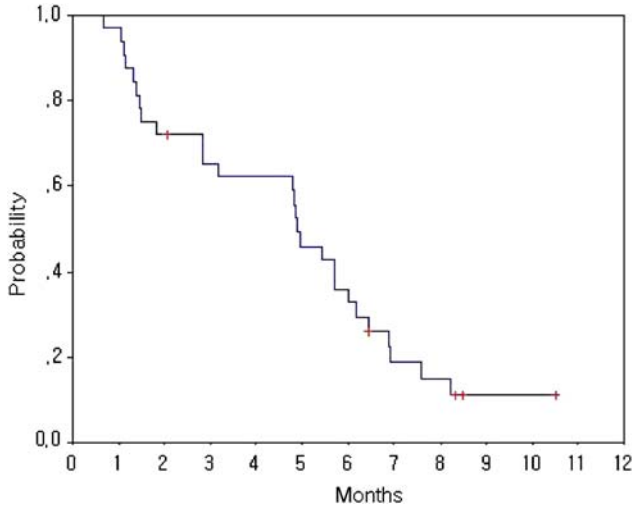

Fig. 2 Kaplan–Meier survival curve for the time to progression

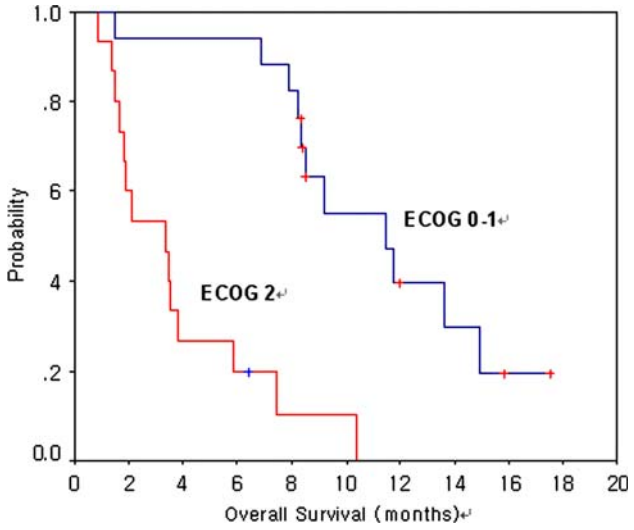

Fig. 3 Kaplan–Meier survival curve of survival difference according to an ECOG performance status 0–1 versus 2 (log-rank test $P < 0.001$)

Dose intensity and toxicity

The toxicities that were encountered during treatment are summarized in Table 3. The most common adverse effect was neutropenia ($n = 9$, 28.1%). The other grade 3–4 hematologic toxicities included thrombocytopenia ($n = 5$, 15.6%), febrile neutropenia ($n = 3$, 9.4%) and anemia ($n = 2$, 6.3%), and the grade 3 non-hematologic toxicities included diarrhea ($n = 5$, 15.6%), mucositis ($n = 4$, 12.5%) and asthenia ($n = 3$, 9.4%). There were two treatment-related deaths; one death was caused by biliary sepsis and one death was caused by severe pneumonia concomitant with febrile neutropenia. The first treatment-related death due to biliary sepsis on day 7 of the first cycle was not clearly related to this trial, but it was included in the treatment-related deaths.

The actual administered mean dose-intensities are shown in Table 4. The actual administered median dose-intensities were 789 mg/m^2/week for gemcitabine (range: 357–833 mg/m^2/week, relative dose intensity (RDI): 94.7%) and 353 mg/m^2/week for S-1 (range: 160–373 mg/m^2/week, RDI: 94.6%).

Discussion

The combination of gemcitabine and S-1 was a feasible and relatively tolerable regimen for patients suffering with pancreatic cancer [18–20], and non-small cell lung cancer [21].

Although gemcitabine is currently considered as the standard first-line treatment that demonstrates a survival benefit and improvement of the disease-related symptoms in patients with unresectable pancreatic cancer, as compared with 5-fluorouracil in a randomized phase III trial, the median survival duration is still poor. Therefore, the recent trials have focused on evaluating gemcitabine combined with other cytotoxic agents to improve the efficacy and survival.

The rationale of combining S-1 and gemcitabine in this study are as follows [21]. First, each single agent, gemcitabine and fluoropyrimidine, has activity in patients with pancreatic cancer. Second, the two drugs have different mechanisms of action and they lack cross resistance. Third, the major toxicity profiles of S-1 and gemcitabine do not overlap. Hematologic toxicities such as neutropenia and thrombocytopenia are the major toxicities of gemcitabine, whereas gastrointestinal toxicity is the main adverse effect of S-1. Fourth, the preclinical and clinical studies have shown the synergistic efficacy of fluoropyrimidine combined with gemcitabine [15, 16, 22, 23].

The results of previous published phase II trials that are concerned with using the combination of gemcitabine and oral fluoropyrimidine for treating unresectable pancreatic cancer are shown in Table 5.

In a phase II clinical trial of capecitabine combined with gemcitabine in Korean patients with advanced pancreatic cancer, the authors indicated that the adopted doses for

Table 3 Grade 3 and 4 adverse effects

Adverse event	No. of patients (%) Grade 3/4 toxicity	ECOG 0/1 (%)	ECOG 2 (%)	*P* value
Hematologic				
Neutropenia	7 (21.9)/2 (6.2)	1 (3.1)/1 (3.1)	6 (18.8)/1 (3.1)	0.049
Anemia	2 (6.2)/0 (0)	1 (3.1)	1 (3.1)	0.473
Thrombocytopenia	5 (15.6)/0 (0)	1 (3.1)	4 (12.5)	0.161
Febrile neutropenia	2 (6.2)/1 (3.1)	0 (0)	2 (6.2)/1 (3.1)	0.589
Nonhematologic				
Diarrhea	5 (15.6)/0 (0)	1 (3.1)	4 (12.5)	0.161
Mucositis	4 (12.5)/0 (0)	0 (0)	4 (12.5)	0.038
Asthenia	3 (9.4)/0 (0)	1 (3.1)	2 (6.2)	0.508

Table 4 Relative dose intensity

Gemcitabine	789 mg/m^2/week (357–833)	94.7%
S-1	353 mg/m^2/week (160–373)	94.6%

phase II studies were oral capecitabine 1,000 mg/m^2 twice a day for 14 consecutive days and gemcitiabine 1,000 mg/m^2 on days 1 and 8 of a 21-day cycle. For 45 patients with measurable disease, they observed one CR and 17 PRs for an overall RR of 40% (95% CI: 25.1–54.9%).The median TTP was 5.4 months (95% CI: 1.8–9.0 months) and the OS was 10.4 months (95% CI: 6.2–14.5 months) [24].

Another phase II clinical trial that used capecitabine combined with gemcitabine for patients with inoperable or metastatic pancreatic cancer adopted the doses of oral capecitabine 650 mg/m^2 twice a day for 14 consecutive days and gemcitiabine 1,000 mg/m^2 on days 8 and 15 of a 21-day cycle. For 53 patients with measurable disease, they observed 10 PRs for an overall RR of 18.9% (95% CI: 8.33–29.4%). The median TTP was 6.5 months (95% CI: 3.5–15.5 months) and the OS was 8 months (95% CI: 1.0–15.5 months) [25].

A Japanese phase II clinical trial of S-1 combined with gemcitabine for treating patients with metastatic pancreatic cancer indicated that the recommended doses were S-1 30 mg/m^2 twice a day for 14 consecutive days and gemcitabine 1,000 mg/m^2 on days 8 and 15 of a 21-day cycle. For 33 patients with measurable disease, they observed one CR and 15 PRs for an overall RR of 48% (95% CI: 33–65%). The median TTP was 5.4 months (95% CI: 2.5–8.4 months) and the overall survival was 12.5 months (95% CI: 5.9–19.1 months) [18].

Our study showed comparable efficacy, as compared with the previous studies on metastatic pancreatic cancer that used oral fluoropyrimidine combined with gemcitabine. However, the overall survival of this study was relatively inferior to the previous combination trials with gemcitabine and capecitabine or the Japanese trial using S-1 and gemcitabine, and this could be explained by the higher proportion of patients with a poor performance in our study. There were 15 (49%) patients who had an ECOG PS of 2 in this study as compared with 2 (6%) such patients in the Japanese study (Table 5). The performance status has been proven to be an important prognostic factor, in terms of the overall survival, for patients with unresectable pancreatic cancer and who received palliative chemotherapy. A good performance status is closely related with good compliance to chemotherapy, a low incidence of treatment-related morbidities and a better outcome for patients with unresectable pancreatic cancer [26–30].

Our study also demonstrated that the median survival of patients with a good performance status was significantly superior to that of the patients with a poor performance status for unresectable locally advanced or metastatic pancreatic cancer.

As a result, the high proportion of patients with a poor performance status in our study may have caused the inferior survival compared with the previous capecitabine-based studies and the Japanese study that used S-1 combined with gemcitabine for patients with unresectable pancreatic cancer.

The toxicities of this study were tolerable and manageable, although the dosages of gemcitabine and S-1 in this trial were higher than the recommended doses (gemcitabine: 800–1,000 mg/m^2/week, S-1: 30–40 mg/m^2 days 1–14) based on the previous Japanese phase I/II study.

The main grade 3/4 toxicity was neutropenia, and grade 3/4 thrombocytopenia occurred in five patients (15.6%) in this study, but it was easily managed.

According to the previous Korean or Japanese S-1 based studies [18–21, 31]. Hand-foot syndrome was usually less common as compared with the capecitabine based studies. No grade 3/4 hand-foot syndrome was observed in this study.

Table 5 Phase II studies on oral fluoropyrimidine combined with gemcitabine for unresectable pancreatic cancer

Study	Park (21)	Stathopoulos (22)	Nakamura (23)	Our study
Regimen	Gemcitabine, Capecitabine	Gemcitabine, Capecitabine	Gemcitabine, S-1	Gemcitabine, S-1
Number of patients	45	53	33	32
ECOG PS				
0–1	45 (100%)	52 (98%)	31 (94%)	17 (53%)
2	0	1 (2%)	2 (6%)	15 (47%)
Disease extent				
Locally advanced	10 (22.2%)	8 (15%)	0	3 (9.4%)
Metastatic	35 (77.8%)	45 (85%)	33 (100%)	29 (90.6%)
Response rate (%)	44%	18.9%	48%	44%
Median TTP (months)	5.4	6.5	5.4	4.92
Median OS (months)	10.4	8	12.5	7.89

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *TTP* time to progression, *OS* overall survival

The administration of S-1 demonstrated enough good compliance and convenience to replace a continuous infusion of 5-FU, which requires infusion pumps or protracted catheter with their potential risks of catheter-related infection and thrombosis, and S-1 also contributed to shortening the hospitalization during chemotherapy, and most patients were treated at an outpatient setting.[31–33].

In conclusion, the combination chemotherapy with S-1 and gemcitabine is a feasible, convenient and tolerated treatment for patients with unresectable locally advanced or metastatic pancreatic cancer, and especially for those patients with a good performance status. Nevertheless, the survival outcome for patients with poor performance status was still unsatisfactory.

Further evaluation will be needed to compare a combination strategy of S-1 and gemcitabine with gemcitabine monotherapy in terms of the survival benefit and improvement of the quality of life for patients with unresectable locally advanced or metastatic pancreatic cancer. Additional investigation needs to be done for determining the reasonable dosage and modified schedules with using with gemcitabine and S-1 for poor performance status patients with unresectable locally advanced or metastatic pancreatic cancer.

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Conflict of interest statement None.

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