Cancer Chemother Pharmacol (2011) 68:677–683
DOI 10.1007/s00280-010-1531-6

ORIGINAL ARTICLE

Prospective multicenter study to investigate the introduction rate of second-line S-1 in gemcitabine-refractory unresectable pancreatic cancer

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Received: 24 September 2010 / Accepted: 14 November 2010 / Published online: 5 December 2010

Abstract
Purpose S-1 is one of the second-line candidate agents for gemcitabine-refractory unresectable pancreatic cancer. Two phase II studies have been reported for second-line chemotherapy with S-1, but these studies did not investigate introduction rate and suitable dose of second-line S-1. Therefore, we conducted a prospective multicenter study in which chemo-naïve patients were enrolled and had two levels of S-1 dose.
Methods Chemo-naïve patients with unresectable pancreatic cancer were enrolled. This study started with 80 mg/m^2/day dose of S-1 as second-line chemotherapy and tolerability was checked. When tolerability was not confirmed in initial patients, the dose of S-1 was shifted to 60 mg/m^2/day. When tolerability was confirmed at 80 or 60 mg/m^2/day, the study continued, and up to 20 patients were accumulated with the dose. In addition, the introduction rate of second-line S-1 was examined.
Results Six of the initial 7 patients with 80 mg/m^2/day dose of S-1 completed one course of second-line chemotherapy. Twenty patients were accumulated with an 80 mg/m^2/day dose of S-1. With the exception of one patient continued gemcitabine chemotherapy, two of the remaining 19 patients withdrew from this study because of toxicity during the period of gemcitabine chemotherapy. Fifteen of the remaining 17 gemcitabine-refractory patients could complete one course of S-1 as second-line chemotherapy with acceptable toxicity.
Conclusions This prospective multicenter study showed that 15 (78.9%) out of 19 chemo-naïve unresectable pancreatic cancer patients could complete one course of

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80 mg/m^2/day dose of S-1 as second-line chemotherapy after first-line gemcitabine chemotherapy failure with tolerable toxicity.

Keywords Pancreatic cancer · Second-line therapy · Prospective study · S-1 · Gemcitabine

Background

Even though imaging modalities such as endoscopic ultrasonography [1] have made progress, pancreatic cancer is a common tumor with a poor prognosis. Gemcitabine has been established as a first-line therapy for unresectable pancreatic cancer [2]. However, the benefit of gemcitabine is not satisfactory. Although various studies have investigated gemcitabine-based combination regimens, none of the combinations has been proved to be superior to gemcitabine monotherapy, except for a few regimens [3–5]. To improve the prognosis of unresectable pancreatic cancer, the development of a new effective therapy different from chemotherapy [6], more effective than first-line chemotherapy including gemcitabine combinations or second-line chemotherapy after disease progression during gemcitabine monotherapy or gemcitabine-based chemotherapy, is required. Many studies of second-line chemotherapy have demonstrated some potential clinical benefit [7–9]. S-1, which is an oral agent consisting of a mixture of tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate at a molar ratio of 1:0.4:1 [10], is one of them.

In two phase II studies of S-1 monotherapy as second-line chemotherapy for advanced pancreatic cancer [11, 12] after gemcitabine failure, it was reported that partial response was obtained in 9.5–15% of cases, stable disease was noted in 43%, the median progression-free survival (PFS) was 2.0–4.1 months, the median survival time (MST) was 4.5–6.3 months and toxicity was acceptable. Although these studies showed that S-1 might be a feasible treatment option for patients with gemcitabine-refractory advanced pancreatic cancer, there might be a limitation in that all patients were enrolled in these studies after gemcitabine-based or gemcitabine chemotherapy failure. Therefore, it is not yet clear for how many patients S-1 as second-line chemotherapy is acceptable or what amount of S-1 administered is suitable for second-line chemotherapy. To investigate introduction and completion rates of one course of S-1 as second-line chemotherapy in gemcitabine-refractory unresectable pancreatic cancer in relation to the dose of S-1, we conducted a prospective multicenter study in which patients were enrolled before gemcitabine chemotherapy and had two levels of S-1 dose (80 and 60 mg/m^2/day).

Patients and methods

This study was a prospective multicenter study. All patients provided written informed consent. A total of seven centers participated in this study (Nagoya University Hospital, Ogaki Municipal Hospital, Japanese Red Cross Nagoya Daiichi Hospital, Komaki City Hospital, Yamashita Hospital, Nagoya Kyoritsu Hospital and Fujita Health University Hospital). This study was approved by the Institutional Review Board at each center and was conducted in accordance with the Declaration of Helsinki. This study was also registered as UMIN000000834 (UMIN Clinical Trials Registry (UMIN-CTR)).

Patients

The following inclusion criteria were used for the selection of patients: histologically or cytologically proven pancreatic adenocarcinoma, unresectable locally advanced or metastatic disease, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, no previous chemotherapy or radiotherapy, no previous radical operation, without another malignant disease, 20–74 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, estimated life expectancy more than 3 months, adequate bone marrow function (white blood cell count $\geqq$4,000/mm^3, neutrophil count $\geqq$2,000/mm^3, platelet count $\geqq$100,000/mm^3, hemoglobin level $\geqq$9.5 g/dl), adequate renal function (serum creatinine level $\leqq$1.5 mg/dl), adequate liver function (serum total bilirubin level $\leqq$2 times the upper limits of normal (ULN), transaminases levels $\leqq$3 times ULN), adequate respiratory function (SpO_2 $\geqq$93%) and adequate oral intake.

The exclusion criteria were as follows: cardiac angina or cardiac infarction within 3 months, uncontrollable diabetes mellitus, uncontrollable liver function disorder, interstitial pneumonia or pulmonary fibrosis, active infection (C-reactive protein $\geqq$3), pregnant or lactating women, severe neurologic impairment or mental disorder and severe drug-induced allergy.

Treatment

Gemcitabine at 1,000 mg/m^2 was intravenously administered as a 30-min infusion on days 1, 8 and 15 of a 28-day cycle until disease progression. When progressive disease (PD) was confirmed, S-1 was administered as second-line chemotherapy. In this study, a dose of S-1 was set at two levels (level 1: 80 mg/m^2/day, level 2: 60 mg/m^2/day). S-1 was administered orally at a dose of 40 mg/m^2 in level 1 or 30 mg/m^2 in level 2 twice daily after breakfast and dinner.

One course of S-1 consisted of consecutive administration of S-1 for 28 days followed by a 14-day rest period.

This study started with level 1 dose of S-1, and the completion rate of one course of S-1 was checked in the initial 7 patients for confirmation of tolerability. When tolerability was not confirmed, the dose of S-1 was shifted to level 2. When tolerability was not confirmed for the level 2 dose of S-1, the study was canceled. When the tolerability was confirmed in level 1 or 2, the study continued with the given dose of S-1.

Dose modification

Subsequent treatment cycles with gemcitabine were started only under the following conditions: white blood cell count $\geqq$3,000/mm^3, neutrophil count $\geqq$1,500/mm^3, platelet count $\geqq$100,000/mm^3, hemoglobin level $\geqq$9.0 g/dl, without active infection, without $\geqq$grade 2 toxicities of liver, renal, heart and respiratory function and without $\geqq$grade 3 of other adverse events.

The protocol was temporarily discontinued when any of the following conditions were encountered: leukocytes <2,000/mm^3, neutrophils <1,000/mm^3, platelets <75,000/mm^3, hemoglobin <8.0 g/dl, active infection, $\geqq$grade 2 liver, renal, heart, respiratory or neurological toxicity, $\geqq$grade 3 non-hematological toxicity other than anorexia, fatigue or alopecia. If patients who experienced the above adverse effects received 800 mg/m^2 gemcitabine in the subsequent course, no dose adjustment was allowed during the same course.

If a rest period of more than 21 days was required because of toxicity, $\geqq$grade 4 non-hematological toxicity was experienced, ECOG performance status was 4, dose reduction was necessary twice, or patient's consent was withdrawn, the patient was excluded from this study.

Follow-up evaluation

Pretreatment evaluation included medical history and physical examination, complete blood count and biochemistry test, a chest radiogram and computed tomography (CT) of the abdomen. Complete blood counts and serum biochemistry tests were performed weekly during the first course of each of gemcitabine and S-1, more than once per course after the second course. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0. Follow-up CT was performed at least once in every course to assess objective tumor response according to the RECIST. The definition of PD was the sum longest diameter of target lesions increased $\geqq$20% compared to minimal diameter, appearance of new lesions or non-target lesions obviously increased.

Statistics

The primary endpoint was completion rate of one course of chemotherapy with S-1 as the second-line treatment in gemcitabine-refractory patients. The secondary endpoint was safety (frequency and degree of toxicity) of this protocol.

The number of patients required for this study was calculated according to the optimal two-stage design by Simon [13]. The threshold completion rate and expected completion rate were 50% and 80%, respectively. Twenty patients were required in each level (α- and β-error probabilities 0.05 and 0.2, respectively). The tolerability was checked by a two-step method. The first step was as follows: when less than 5 patients of the initial 7 patients completed one course of the level 1 dose of S-1, the dose of S-1 was shifted to level 2. When less than 5 patients of the following 7 patients completed one course of the level 2 dose of S-1, this study was terminated. When 5 or more of the 7 patients completed one course of the level 1 or the level 2 dose of S-1, this study continued until up to 20 patients were accumulated with the dose of S-1. The second step was as follows: when more than 13 patients of the 20 patients completed one course of S-1, expected completion rate was achieved, and this treatment protocol was determined to be tolerable for pancreatic cancer patients. Therefore, this study needed 14–27 patients (Fig. 1). Following treatment of one course of S-1 was not defined in this study protocol. The overall survival was calculated from the date of study entry to the date of death or the last follow-up date. The PFS was calculated from the date of study entry to the date of PD confirmed. The median probability of the survival period and PFS were estimated using the Kaplan–Meier method.

Results

Patients

The initial 7 patients were enrolled between October 2007 and January 2008. Six of the 7 patients completed one course of the level 1 dose of S-1. Only one patient withdrew from this study owing to continuous splenic abscess without neutropenia. Therefore, this study was continued for up to 20 patients accumulated with the level 1 dose (80 mg/m^2/day) of S-1. Another 13 patients were enrolled between August 2008 and August 2009. Characteristics of all 20 patients are shown in Table 1. Nineteen of the 20 patients had an ECOG performance status of 0.

With the exception of one patient who continued gemcitabine chemotherapy, two of the remaining 19 patients withdrew from this study because of toxicity in the period of gemcitabine chemotherapy. One patient exhibited splenic abscess as mentioned above and the

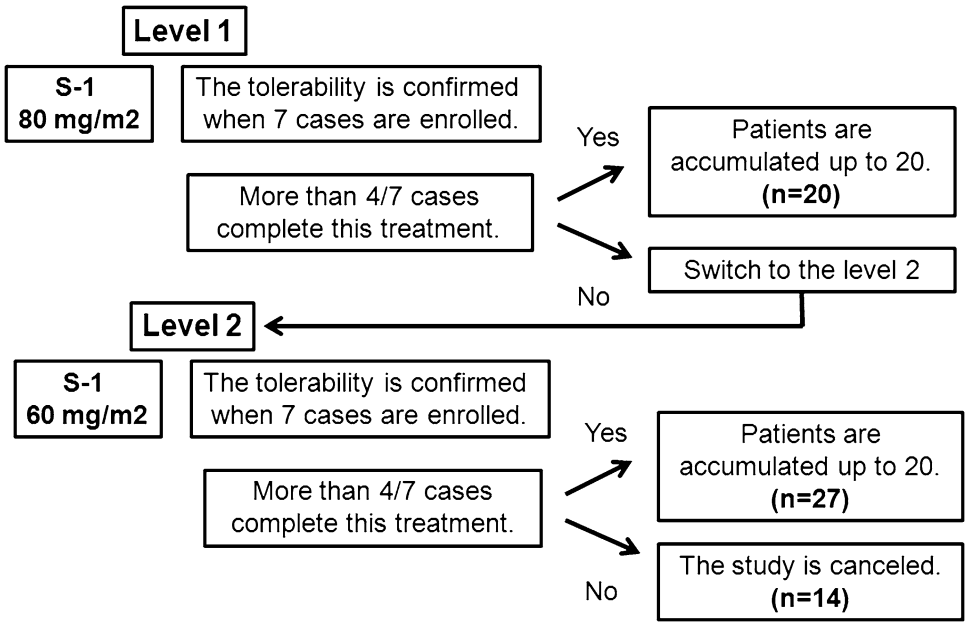

Fig. 1 S-1 dose of each level and required number of patients. This study started with level 1 (80 mg/m^2/day) dose of S-1 and the completion rate of one course of S-1 was checked in the initial 7 patients for confirmation of tolerability. When tolerability was not confirmed, the dose of S-1 was shifted to level 2 (60 mg/m^2/day) dose. When tolerability was not confirmed for the level 2 dose, the study was canceled. When the tolerability was confirmed in level 1 or 2, the study continued with the given dose of S-1

Table 1 Patient characteristics

Number of patients	20
Age	
Median (range)	67 (44–73)
Gender	
Male	11
Female	9
ECOG PS	
0	19
1	0
2	1
Biliary drainage	9
Location of primary tumor	
Head	11
Body	6
Tail	3
Site of metastasis	
Liver	8
Lymph node	12
Lung	3
Peritoneum	2
Ascites	0
Ca19.9 (U/ml)	
Median (range)	635 (0.1–11,222)

ECOG Eastern cooperative oncology group

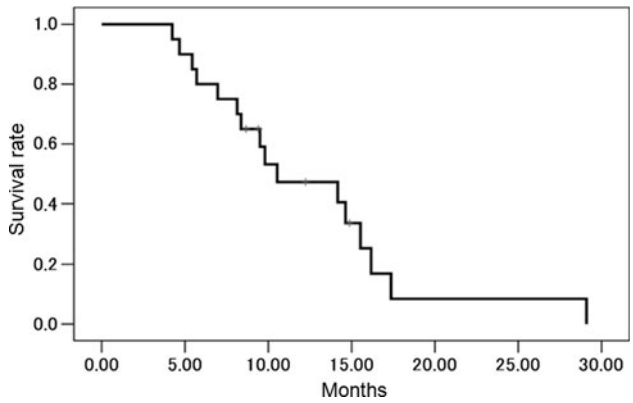

Fig. 2 Overall survival time curve from the date of study entry

other had gemcitabine-related grade 3 renal failure. Fifteen of the remaining 17 patients with PD against gemcitabine chemotherapy could complete one course of level 1 dose (80 mg/m^2/day) of S-1 as second-line chemotherapy in accordance with the protocol. Among these 15 patients, 10 patients had PS of 0 and 5 patients had PS of 1 when PD was confirmed with gemcitabine. One of the 2 patients who could not complete one course of S-1 had ileus because of disease progression; the other patient had PS of 2 at the entry point, so oral intake of S-1 could only be carried out for 6 days because the patient's general condition was poor when gemcitabine failed.

Tumor responses to first-line gemcitabine ($n = 20$) were as follows: no complete response was seen, partial response was obtained in 2 patients (10%), while stable disease was noted in 10 patients (50%). The median PFS of first-line gemcitabine was 3.4 months (95% confidence interval (CI), 0.73–6.1 months). In the period of one course of second-line S-1 ($n = 15$), partial response was obtained in 1 patient (6.7%). The MST from the date of study entry was 10.5 months (95% CI, 4.8–16 months) (Fig. 2).

Table 2 Toxicity of gemcitabine ($n = 20$)

	Grade				Grade 3–4 *n* (%)
	1	2	3	4	
Hematological toxicity					
Leukocytes	3	8	4	0	4 (20)
Neutrophils	1	5	8	0	8 (40)
Hemoglobin	11	6	1	0	1 (5)
Platelets	10	1	3	0	3 (15)
Non-hematological toxicity					
Anorexia	6	4	0	0	0
Nausea/Vomiting	5	0	0	0	0
Diarrhea	2	1	0	0	0
Constipation	0	1	0	0	0
Fatigue	6	2	1	0	1 (5)
Rush	1	0	0	0	0
Elevation of GOT/GPT	7	2	0	0	0
Hyperbilirubinemia	3	1	0	0	0
Splenic abscess without neutropenia	0	0	1	0	1 (5)
Renal failure	0	0	1	0	1 (5)

GOT glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase

Table 3 Toxicity of one course S-1 as second line ($n = 15$)

	Grade				Grade 3–4 *n* (%)
	1	2	3	4	
Hematological toxicity					
Leukocytes	3	1	1	0	1 (6.7)
Neutrophils	1	3	0	0	0
Hemoglobin	6	2	1	1	1 (6.7)
Platelets	2	0	0	0	0
Non-hematological toxicity					
Anorexia	3	1	1	0	1 (6.7)
Nausea/Vomiting	4	2	0	0	0
Diarrhea	1	1	0	0	0
Fatigue	4	0	1	0	1 (6.7)
Elevation of GOT/GPT	1	0	0	0	0
Hyperbilirubinemia	2	0	0	0	0

GOT glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase

Toxicity

All 20 patients were assessed for toxicities. The toxicities observed during gemcitabine and one course of S-1 are listed in Tables 2 and 3, respectively. In the period of first-line gemcitabine, grade 3 neutropenia occurred in 40% of cases. All hematological toxicities were improved by the rest period of gemcitabine. No patient withdrew from this study because of hematological toxicity. Dose reduction of gemcitabine in accordance with the protocol was required in 40% of patients. In the period of one course of S-1, grade 3 leukocytopenia, anemia, anorexia and fatigue were observed in one patient each. There were no treatment-related deaths.

Discussion

Many studies have reported effective second-line treatment for gemcitabine-refractory pancreatic cancer patients [7–9, 11, 12]. However, even though the rate of introduction of second-line chemotherapy may greatly affect a patient's survival, it has received little attention. Reports of phase II studies of S-1 as second-line chemotherapy for gemcitabine-refractory pancreatic cancer did not mention the introduction rate. The only retrospective studies of S-1 as second-line chemotherapy reported that the introduction rates were 45.9–61.9% [14, 15].

In this multicenter prospective study, it was confirmed that 80 mg/m^2/day dose of S-1 as second-line chemotherapy

was tolerable in 7 initial patients. Fifteen of 19 patients (78.9%) completed one course of the 80 mg/m^2/day dose of S-1 chemotherapy with tolerable toxicities. Therefore, this treatment protocol was determined to be associated with a higher than expected completion rate. The reason for the high completion rate of one course of S-1 was that general conditions were maintained well at the point of gemcitabine failure. This result would be of reference to another study of second-line chemotherapy for gemcitabine-refractory pancreatic cancer.

Although the incidence of grade 3 hematological toxicity was high, all hematological toxicities were reversible, so no patients withdrew from this study because of hematological toxicity. On the other hand, the patients with grade 3 non-hematological toxicity except fatigue could not resume gemcitabine chemotherapy or start another treatment. The cause of failure to complete one course of S-1 in this study was that oral intake was impossible because of disease progression. The oral agent S-1 was difficult to administer to patients with digestive symptoms.

Even though selection bias should be considered, the MST (10.5 months) of this study was superior to those of gemcitabine monotherapy in one arm of recent phase III studies [16, 17], despite the median PFS (3.4 months) in this study being comparable to those in the previous studies. This result suggested that second-line S-1 prolonged MST of gemcitabine-refractory unresectable pancreatic cancer. The coefficient of correlation between the median PFS of gemcitabine chemotherapy and the MST of this study was significant (Pearson's product moment correlation coefficient, $P < 0.01$, $r = 0.655$), which might suggest that the duration of gemcitabine chemotherapy was the critical factor determining prognosis. In addition, the MST of this study was similar to those of phase II studies of gemcitabine and S-1 combination chemotherapy [18–20]. The conclusion of how to use gemcitabine and S-1 will be determined from the results of ongoing phase III study of gemcitabine, S-1 and combination chemotherapy.

In conclusion, this prospective multicenter study determined that 78.9% chemo-naïve unresectable pancreatic cancer could complete one course of conventional dose of S-1 (80 mg/m^2/day) as second line with tolerable toxicity after gemcitabine failure.

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