A Phase II Study of S-1 in Elderly Patients with Unresectable Pancreatic Cancer

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ABSTRACT

Background/Aims: The aim of this study was to investigate the efficacy and safety of the oral fluoropyrimidine derivative S-1 in elderly patients with unresectable pancreatic cancer.

Methods: Patients were eligible if they were at least 70 years old and had unresectable pancreatic carcinoma. S-1 was administered orally twice daily after meals at doses of 80, 100, and 120 mg/day for body surface areas for 28 consecutive days, followed by a 14-day rest period. Administration was repeated until the appearance of disease progression or unacceptable toxicity.

Results: Twenty-one patients were enrolled in this study. Five patients (23.8%) achieved a partial response (95% CI, 8.2-47.2%), stable disease was observed in 9 patients (42.9%), and progressive disease was observed in 5 patients (23.8%). The disease control rate was 66.7%. The median time to progression and overall survival time were 3.7 months (95% CI, 2.3-6.5 months) and 7.3 months (95% confidence interval, 4.9-12.1 months), respectively. Toxicity was generally mild, and the most common grade 3/4 toxicities were neutropenia (14.3%), anemia (14.3%), leucopenia (9.5%), thrombocytopenia (9.5%), anorexia (9.5%), and diarrhea (9.5%). There were no treatment-related deaths.

Conclusions: Monotherapy with S-1 is an effective and well-tolerated regimen for elderly patients with unresectable pancreatic cancer.

Key words: pancreatic cancer, chemotherapy, elderly patients, S-1

INTRODUCTION

Pancreatic cancer is one of the most common types of gastrointestinal cancer, and its prognosis remains extremely poor. Indeed, pancreatic cancer is the fifth leading cause of cancer death in Japan, the US and European countries (1). Of all the treatments available for pancreatic cancer, only resection offers the chance of a cure. However, owing to the high frequency of local extension and/or metastatic disease at the time of diagnosis, only a small minority of patients are candidates

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for curative resection. Moreover, surgery alone is limited, showing an unsatisfactory prognosis and a high incidence of postoperative recurrence. To improve the survival rate of patients with pancreatic cancer, effective non-surgical treatments are urgently needed.

Gemcitabine (GEM) has become the standard treatment for advanced pancreatic cancer because it improves overall survival (OS) compared with fluorouracil (2). Although various GEM-based combination regimens have been evaluated, only erlotinib combined with GEM showed a survival benefit over GEM alone, and that benefit was marginal (3).

The GEM-free combination regimen fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX) was recently demonstrated to have clear survival benefits relative to GEM for patients with metastatic pancreatic cancer with a performance status of 0 to 1 (4). However, because FOLFIRINOX has significant toxicity, this regimen requires close monitoring and must be limited to patients with a good performance status (5).

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 (6,7). Tegafur is hydroxylated and converted to 5-fluorouracil (5-FU) by hepatic microsomal enzymes. 5-Chloro-2,4-dihydroxypyridine is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and it acts to maintain efficacious concentrations of 5-FU in the plasma and tumor tissues. Oteracil potassium, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, thereby reducing the serious gastrointestinal toxicity associated with 5-FU. S-1 shows broad activity against a variety of tumors and is currently approved in Japan for use in patients with non-small cell lung cancer, gastric cancer, colorectal cancer, breast cancer, head and neck cancer, biliary tract cancer and pancreatic cancer (8-14).

Two phase II studies (15) of S-1 in untreated patients with metastatic pancreatic cancer demonstrated that this compound is an active and well-tolerated drug. Consequently, S-1 was approved for the treatment of pancreatic cancer in Japan in 2006. A randomized, open-label, three-arm, phase III study (GEST) (16) was subsequently reported, in which 834 chemotherapy naïve unresectable advanced pancreatic cancer patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 were randomly assigned to receive GEM (1,000 mg/m² on days 1, 8, and 15, q4w), S-1 (60/80/100 mg/d based on body surface

area (BSA) on days 1-28, q6w), or GS (GEM 1,000 mg/m² on days 1 and 8, plus S-1 60/80/100 mg/d based on BSA on days 1-14, q3w). S-1 was confirmed to be non-inferior to GEM with respect to OS (9.7 months vs. 8.8 months, $P < 0.001$). Grade 3/4 hematologic toxicities were more common in the GEM arm than the S-1 arm (neutropenia, 41.0% vs. 8.8%; thrombocytopenia, 11.0% vs. 1.5%, respectively), whereas digestive toxicities were more common in the S-1 arm than in the GEM arm (anorexia, 11.4% vs. 7.3%; diarrhea, 5.5% vs. 1.1%, respectively). This trial was the first to demonstrate that oral S-1 has an efficacy similar to that of GEM with tolerable toxicity.

As the Japanese population grows older, more patients over the age of 70 are being diagnosed with unresectable pancreatic cancer. Indeed, increases in the incidence rate have been observed among both males and females 75 years or older. Thus, the application of chemotherapy for elderly patients with unresectable pancreatic cancer is an important issue. S-1 appears advantageous because it has few side effects and can be administered on an outpatient basis. Additionally, S-1 offers the possibility of treating patients with conditions such as pancreatic cancer with poor prognosis without affecting their quality of life (QOL), making it particularly promising for the treatment of elderly patients with advanced pancreatic cancer (17,18). However, very few reports have evaluated the effects of S-1 on unresectable pancreatic cancer in a cohort of elderly patients (19).

Therefore, we conducted a phase II study of monotherapy with S-1 in elderly patients with advanced unresectable pancreatic cancer and assessed the efficacy and toxicity of this regimen.

METHODS

End point

The primary end point of this study was to determine the efficacy of monotherapy with S-1 in elderly patients with unresectable pancreatic cancer. The secondary end points were to assess toxicity, time to progression (TTP), and survival.

Patients

The eligibility criteria were as follows: (1) pancreatic adenocarcinoma diagnosed by pathological examination or typical radiographic findings; (2) unresectable locally advanced or metastatic disease; (3) at least one measurable lesion; (4) 70-90 years of age; (5) no history of prior antitumor treatment, except resection; (6) a Karnofsky performance status (KPS) of 50-100 points; (7) an estimated life expectancy of at least 8 weeks; and

(8) adequate renal function (normal serum creatinine and creatinine clearance ≥ 50 ml/min), liver function (total bilirubin < 3.0 mg/dl and transaminase level ≤ 150 IU/l) and bone marrow reserves (white blood cell (WBC) count $\geq 3,500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, and hemoglobin ≥ 9.0 g/dl). The exclusion criteria were as follows: (1) under regular treatment with phenytoin, warfarin, or flucytosine; (2) severe complications such as a mental disorder, active infection, ileus, heart failure, liver failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, or watery diarrhea; (3) active concomitant malignancy; or (4) pregnancy or lactation.

Study treatment

S-1 was administered orally at a dose of 40 mg/m² twice daily after breakfast and dinner. Three initial doses were established based on BSA as follows: BSA < 1.25 m², 80 mg/day; $1.25 \text{ m}^2 \leq \text{BSA} < 1.50 \text{ m}^2$, 100 mg/day; and $1.50 \text{ m}^2 \leq \text{BSA}$, 120 mg/day. S-1 was administered for 28 days, followed by a 14-day rest period. This treatment course was repeated until the occurrence of disease progression, unacceptable toxicities were reached, or the patient refused to continue.

The occurrence of any grade 3 or higher severe hematologic toxicity or grade 2 or higher severe non-hematologic toxicity resulted in the temporary discontinuation of S-1 until the toxicity recovered to grade 1 or less; then, the S-1 dose was reduced by 20 mg/day in the next treatment cycle (minimum dose, 80 mg/day). If no toxicity occurred, shortening of the rest period to 7 days was allowed. If a rest period of more than 28 days was required due to toxicity, the patient was withdrawn from the study. Patients were not allowed to receive concomitant radiation therapy, chemotherapy, or hormonal therapy during the study.

Response and toxicity evaluation

The response after each course was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (20). Physical examination, complete blood cell counts, biochemistry tests, and urinalyses were performed at least biweekly. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (21).

The response duration was calculated from the day of the first sign of a response until disease progression. TTP was calculated from the date of study entry until documented disease progression. The OS time was calculated from the date of study entry to the date of death or the last follow-up.

Statistical analysis

The number of patients required for the study was determined according to the optimal two-stage design. The threshold response rate and expected response rate were 10% and 30%, respectively. The sample size of this trial was 21 patients (α - and β -error probabilities of 0.05 and 0.2, respectively). Time-related parameters were analyzed using the Kaplan-Meier method in an intention-to-treat analysis.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients treated with S-1. This study was conducted with the approval of the hospital institutional review board. The study is registered with the UMIN Clinical Trials Registry under UMIN000006369.

RESULTS

Patient characteristics

A total of 21 patients with unresectable pancreatic cancer were enrolled in the study between August 2008 and June 2013. All patients were eligible and assessable for responses and adverse events. The patient characteristics are summarized in *table 1*. Fourteen males and 7 females with a median age of 76 years (range 70–84 years) were treated with S-1. Of the 21 patients, 18 had metastatic disease at the time of enrollment in the study, whereas three patients were diagnosed with locally advanced disease. The liver was the most common site of metastasis (10 patients), followed by the distant lymph nodes (5 patients) and the lungs (two patients).

A total of 110 cycles of therapy were delivered, with a median of 2 cycles (range, 1–38). The initial administered dose of S-1 was 80 mg/day in one patient, 100 mg/day in 12 patients and 120 mg/day in 8 patients. Dose reduction was required in 7 patients for the following reasons: grade 4 anemia (one patient); grade 3 thrombocytopenia (two patients); grade 2 gastrointestinal toxicity, including anorexia, nausea and stomatitis (one patient each); and grade 2 rash (one patient). All patients were treated as outpatients.

Efficacy

Twenty-one patients were assessed for their response to treatment. These responses are shown in *table 2*. There was no case of complete remission (CR); however, 5 patients showed partial remission (PR). Nine

Table 1 - Patient characteristics (n = 21)

Characteristics	Patients	%
Gender		
Male	14	67
Female	7	33
Median age, years (range)	76 (70-84)	
Karnofsky performance status (%)		
100	5	24
90	9	43
80	3	14
70	4	19
First dose (mg)		
40	1	5
50	12	57
60	8	38
Stage		
Locally advanced	3	14
Metastatic	18	86
History of pancreatectomy	0	0
Sites of metastasis		
Liver	10	48
Distant lymph node	5	24
Lung	2	10
Peritoneum	1	5

Table 2 - Tumor responses

Tumor response	Total (n = 21)
Complete response (CR)	0
Partial response (PR)	5
Stable disease (SD)	9
Progressive disease (PD)	5
Not evaluated# (NE)	2
Response rate (%)	23.8
Disease control rate (%) (CR+PR+SD)	66.7

Radiographic assessment was not determined

patients showed stable disease (SD), and 5 patients showed progressive disease (PD). The overall response rate was 23.8% (95% CI, 8.2–47.2%), and the disease control rate was 66.7% (95% CI, 43.0–85.4%). At the time of analysis, 19 of the 21 patients had died due to disease progression. The median TTP was 3.7 months, the OS was 7.3 months, and the one-year survival rate was 28.6% (fig. 1).

Toxicity

All 21 patients were evaluated for toxicity using the National Cancer Institute Common Toxicity Criteria version 3.0. Hematologic and non-hematologic toxicities

Figure 1 - Kaplan-Meier curves for overall survival (OS; solid line) and time to progression (TTP; dotted line)

are summarized in *table 3*. Treatment was generally well tolerated throughout the study. Although hematologic and gastrointestinal toxicities were common, most of these toxicities were mild and transient. Grade 3/4 anemia and neutropenia each occurred in three patients (14.3%), and grade 3 leucopenia, thrombo-cytopenia, anorexia, and diarrhea each occurred in two patients (9.5%). Although one patient died within 8 weeks of study enrollment due to rapid disease progression, no treatment-related deaths were observed.

Table 3 - Treatment-related adverse events (n = 21): Worst grade reported during treatment period. AST = aspartate aminotransferase; ALT = alanine aminotransferase

Toxicity	Grade				Grade 1-4	Grade 3-4
	1	2	3	4	%	%
Hematological toxicity						
Leukopenia	5	3	2	0	47.6	9.5
Neutropenia	2	2	3	0	33.3	14.3
Hemoglobin reduction	3	8	2	1	66.7	14.3
Thrombocytopenia	7	1	2	0	47.6	9.5
Non-hematological toxicity						
Anorexia	5	5	2	0	57.1	9.5
Nausea	4	2	0	0	28.6	0
Vomiting	1	0	1	0	9.5	4.8
Diarrhea	2	0	2	0	19.0	9.5
Stomatitis	1	3	0	0	19.0	0
Rash	2	3	0	0	23.8	0
Pigmentation	4	0	0	0	19.0	0
Colitis	0	0	1	0	4.8	4.8
Biliary tract infection	0	4	0	0	19.0	0
Fatigue	1	0	0	0	4.8	0
Thrombophlebitis	1	0	0	0	4.8	0
AST elevation	3	1	0	0	19.0	0
ALT elevation	1	1	0	0	9.5	0
Total bilirubin elevation	2	1	1	0	19.0	4.8
Creatinine elevation	4	0	0	0	19.0	0

DISCUSSION

Based on the latest cancer statistics put forth by the National Cancer Research Center, pancreatic cancer is the fifth leading cause of cancer death in Japan (22). Additionally, the prevalence of pancreatic cancer has increased in both men and women aged 75 years or older. Therefore, studies performed in elderly populations are necessary, particularly as the incidence of pancreatic cancer in this group is expected to increase in the future.

For pancreatic cancer patients with a poor prognosis, the effect of treatments on QOL is very important. We decided to test S-1 therapy in elderly pancreatic cancer patients for several reasons. First, S-1 therapy is simple and presents few side effects; thus, we could treat these patients as outpatients. Second, the GEST trial (16) revealed that GEM therapy and S-1 therapy were similarly effective, which allowed us to choose S-1 therapy as a first-line treatment. In our trial, all patients could receive S-1 therapy in the outpatient department and were able to maintain their QOL.

A retrospective study of GEM therapy involving 39 elderly pancreatic cancer patients (23) showed that 59% of the patients could be treated with full-dose GEM therapy. The grade 3/4 side effects included neutropenia (38%), thrombopenia (28%) and anemia

(18%). The TTP was 7 months, and the OS was 10 months. In summary, the selected elderly patients could obtain benefits from GEM therapy similar to those achieved in younger patients.

Two prospective studies of S-1 therapy for younger pancreatic cancer patients have been reported. First, Ueno et al. (24) showed in an early phase II trial that the response rate was 21.1%, disease control rate was 73.7%, OS was 5.6 months, and 1-year survival rate was 15.8%. The grade 3/4 side effects included anorexia (15.8%), nausea (15.8%), ileus (15.8%), neutropenia (5.3%) and anemia (5%). Second, Okusaka et al. (25) showed in a late phase II trial that the response rate was 37.5%, disease control rate was 67.5%, OS was 9.2 months, 1-year survival rate was 32.5%, and TTP was 3.7 months. The grade 3/4 side effects included anorexia (12.5%), nausea (7.5%), neutropenia (12.5%) and anemia (5.0%).

In contrast, our study showed that the response rate was 23.8%, disease control rate was 66.7%, OS was 7.3 months, 1-year survival rate was 28.6%, and TTP was 3.7 months. The grade 3/4 side effects included anorexia (9.5%), nausea (0%), diarrhea (9.5%), leukopenia (9.5%), neutropenia (14.3%), thrombopenia (9.5%) and anemia (14.3%).

Variables contributing to our favorable results were the selective registration criteria, a good KPS (≥ 70) in all

patients and ≥ 80 in 17/21 patients) and the fact that most of the patients were treated with second-line therapy (12/19 patients).

Myelosuppression was observed as a side effect in many patients, which was not observed in previous studies. We speculate that the bone marrow of the elderly patients could not with stand long-term chemotherapy. After S-1 therapy was repeated for more than 10 courses, one patient presented with neutropenia, two with anemia and one with thrombopenia. One patient treated with 42 courses of S-1 therapy presented with the side effects of grade 4 anemia and grade 3 neutropenia; however, this patient's tumor showed only aPR.

In a previous S-1 trial in Japan, there were few reports of diarrhea. In contrast, diarrhea is commonly reported in Western patients on S-1 therapy. In this study, we found that grade 3/4 diarrhea occurred in 9.5% of patients. One patient with digestive organ toxicity (anorexia, diarrhea and vomiting with a grade of 3 or 4) was withdrawn from treatment after 1 or 2 courses of S-1 therapy.

CONCLUSION

In conclusion, monotherapy with S-1 may be an effective and well-tolerated regimen for elderly patients with unresectable pancreatic cancer. Because this study had a small sample size and may have been subject to bias, it was not possible to make simple comparisons between our results and those of previous studies. Thus, a large-scale prospective study is needed to conclusively demonstrate the safety and efficacy of S-1 in elderly patients, which we hope to conduct in the future.

Conflicts of Interest and Source of Funding

All author has no conflict of interest. No financial support was obtained for this study.

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