cancer and pancreatic cancer in Japan. Based on the results obtained in early phase studies in other locales and the established safety profile of the agent [3, 7, 8, 12, 24, 34, 35, 40], our group has conducted a multicenter, phase II trial of single-agent gemcitabine to investigate the response rate, toxicity, and time-to-event variables (progression-free survival, duration of tumor response, and survival time) in patients with advanced or metastatic biliary tract cancer.

Patients and methods

Eligibility criteria

Enrolled patients had histologically or cytologically confirmed adenocarcinoma of biliary tract, extrahepatic bile duct, gallbladder, or ampulla of Vater. Each patient was required to meet the following eligibility criteria: unresectable biliary tract cancer with at least one bidimensionally measurable tumor; no history of prior chemotherapy; no history of prior antitumor treatment for biliary tract cancer except resection and intraoperative or postoperative adjuvant radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; 20–74 years of age; estimated life expectancy ≥2 months; adequate renal function (creatinine ≤ upper limit of normal [ULN]); adequate liver function (bilirubin ≤ 2 times ULN and aspartate/alanine transaminases [AST/ALT] ≤ 2.5 times ULN); adequate bone marrow reserve (white blood cells ≤ 4,000/mm^3, neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥10 g/dl); and written informed consent. Patients with pre-existing obstructive jaundice were also eligible after their bilirubin levels met the criteria by biliary stent insertion or percutaneous biliary drainage.

Patients were excluded from the study if they had pulmonary fibrosis, interstitial pneumonia, New York Heart Association class III or IV congestive heart failure, myocardial infarction within the preceding 6 months, diabetes mellitus with severe complications, marked pleural or pericardial effusion, marked peripheral edema, or active infection. Additional exclusion criteria included pregnant or lactating females, patients of reproductive potential who did not use effective contraception, severe drug hypersensitivity, central nervous system metastases, active concomitant malignancy, other serious medical conditions, or patients receiving any investigational drug within 30 days before enrollment.

The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual. In addition, the study design was approved by the appropriate ethical review boards.

Study treatment

Gemcitabine (supplied by Eli Lilly, Japan) 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. The treatment was continued until evidence of disease progression or unacceptable toxicity.

For white blood cells <2,000/mm^3, neutrophils <1,000/mm^3, platelets <70,000/mm^3, bilirubin >3 times ULN, or AST/ALT >5 times ULN, gemcitabine was omitted on that day and postponed to the next scheduled treatment day.

In subsequent cycles, gemcitabine was reduced to 800 mg/m^2 if neutrophils <500/mm^3 for 4 days, white blood cells <1,000/mm^3 for 4 days, platelets <25,000/mm^3, bilirubin >3 times ULN, or AST/ALT >5 times ULN. Gemcitabine was also reduced to 800 mg/m^2 if a platelet transfusion was performed due to thrombocytopenia or if gemcitabine was omitted twice in succession due to toxicity. No dose adjustment was allowed during the same cycle. The treatment was discontinued if a second dose reduction was needed, if bilirubin >5.0 times ULN, AST/ALT >20 times ULN, or tumor progression was observed. The use of granulocyte colony-stimulating factor (G-CSF) was permitted for any grade 4 leukopenia or neutropenia or grade 3 neutropenia with high fever (38.0°C). Prophylactic administration of antiemetics was allowed.

Baseline and treatment assessments

Pretreatment evaluation included complete history and physical examination. In addition, complete blood count, biochemistry tests, urinalysis, and chest X-ray were performed. Performance status and laboratory tests, except for urinalysis, were assessed weekly. Urinalysis was performed during days 15–28 in each cycle. Tumor size was measured by CT scan or MRI during days 22–28 in each cycle. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19–9) were quantified every 4 weeks. All 40 patients who received at least one dose of gemcitabine were involved in the efficacy analyses.Objective tumor response was assessed every 4 weeks using WHO criteria [41]. The duration of response was calculated from the first day of treatment until documentation of disease progression. Survival was measured from the first day of treatment.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0 [27]. A monitoring committee independently evaluated the efficacy and safety of the study.

Statistical analysis

Considering the results of previous trials using gemcitabine for advanced or metastatic biliary tract cancer, we expected an overall response rate of 15–20% in this

study. With this population, response rates typically have not exceeded 10% in patients treated with 5-fluorouracil (5-FU); therefore, a response rate of at least 15% in our study would suggest a potential benefit.

Our goal was to enroll 40 eligible patients. If no response occurred in the first 18 patients, accrual was terminated because the chance of a 15% response rate was only 5.3%. If the response rate was 15%, the statistical power (the probability of a 5% response rate) would be 73% with type I error of 5% (one-sided). For a response rate of 17.5%, the statistical power would be 85%, and the statistical power would be 92% for a response rate of 20%.

All time-to-event measures were calculated using the Kaplan–Meier method.

Results

Patient characteristics and disposition

From October 2001 to September 2003, 21 males and 19 females, with a median age of 61 years (range 33–73 years), were enrolled. Table 1 shows the baseline patient characteristics. Twenty-three patients (57.5%) had no prior therapy, and 17 (42.5%) relapsed after resection for primary lesion. The major metastatic lesions were the abdominal lymph nodes (67.5%) and liver (55.0%). Prior to the initiation of study treatment, obstructive jaundice was palliated with percutaneous transhepatic catheter placement (11 patients) or endobiliary stent placement (3 patients).

The reasons for the treatment discontinuation included progressive disease (34 patients), elevated blood pressure associated with worsening of renal function (one patient), hemolytic uremic syndrome (one patient), blood bilirubin increased with progressive disease (one patient), relapse of pre-existing schizophrenia (one patient), patient's refusal due to nausea/vomiting (one patient), and general fatigue (one patient).

Table 1 Baseline patient characteristics ($n=40$)

Characteristic	
Gender, *n* (%)	
Male	21 (52.5)
Female	19 (47.5)
Age, years	
Median (range)	61 (33–73)
ECOG performance status	
0	24 (60.0)
1	16 (40.0)
Primary lesion	
Extrahepatic bile duct	12 (30.0)
Gallbladder	22 (55.0)
Ampulla of Vater	6 (15.0)
CA19–9, *n* (U/ml)	
Median (range)	448.6 (1–77,820)
CEA, *n* (ng/ml)	
Median (range)	10.9 (0.5–1,790)
Metastatic sites, *n* (%)	
Abdominal lymph nodes	27 (67.5)
Liver	22 (55.0)
Peritoneum	4 (10.0)
Lung	2 (5.0)
Bone	1 (2.5)

ECOG Eastern Cooperative Oncology Group; *CA19–9* carbohydrate antigen 19–9; *CEA* carcinoembryonic antigen

Efficacy

All 40 patients were evaluated for efficacy and according to WHO criteria, seven patients achieved a partial response for an overall response rate of 17.5% (95% CI, 7.3–32.8%). The median duration of the response was 9.4 months (range, 2.6–9.4 months). Fifteen patients (37.5%) had stable disease, and 17 patients (42.5%) had progressive disease. Tumor response was not determined in one patient because she was transferred to another hospital before response evaluation. The serum CA 19–9 level was reduced by less than half in 11 (33%) of 33 patients who had a pretreatment level of above upper normal limit, and the CEA level was reduced by less than half in 6 (24%) of 25 patients. Of the 11 patients whose CA 19–9 level was reduced, 4 (36%) showed a partial response. Five (83%) of the six patients with the CEA response achieved a partial response.

At the time of analysis, 35 of 40 patients had died of cancer and two of five patients lived longer than 24 months after the initial administration of gemcitabine. The median progression-free interval was 2.6 months (95% CI, 1.7–3.8 months), and the median survival time was 7.6 months (95% CI, 5.4–9.3 months) (Fig. 1). The 1-year survival rate was 25.0%.

Toxicity

All 40 patients were evaluable for toxicity (Table 2). No toxic deaths occurred. Hematologic toxicity was reversible and manageable. Patients reported grade 3/4 neutropenia (30.0%), leukopenia (12.5%), and anemia (10.0%). Three patients had red blood cell transfusions due to hemolytic uremic syndrome, hemorrhagic shock, and anemia. No grade 3/4 thrombocytopenia was reported. Although two patients were treated with G-CSFs, there was no febrile neutropenia.

The most common nonhematologic toxicities, grades 1–4 were nausea (52.5%) and anorexia (52.5%), but only four patients (10%) required intravenous infusion due to these toxicities. The most common grade 3/4 nonhematologic toxicities were elevated ALT (15.0%) and elevated γ-glutamyltransferase (γ-GTP) (12.5%). Grade 4 elevated γ-GTP was observed in one patient, which was considered to be gemcitabine-related because the level returned to normal after treatment discontinuation. The patient, who had grade 3 uremia, grade 2 serum creatinine elevation, and grade 2 thrombocytopenia, was diagnosed with grade 4 hemolytic uremic syndrome and also recovered from these toxicities by

transfusion without dialysis after discontinuing gemcitabine. In another patient on day 25 of cycle 1, hemorrhagic shock occurred following unexpected hematemesis, which was unlikely to be gemcitabine related. Endoscopic examination showed acute gastric mucosal lesions, and prescribed nonsteroidal anti-inflammatory drugs to control abdominal pain were suspected to be the cause of hemorrhagic shock.

Dose intensity

A median of three cycles was administered (range, 1–14). Eleven patients (27.5%) completed one cycle; eight patients (20.0%) completed two cycles; and five patients (12.5%) completed three cycles. The planned mean dose intensity of gemcitabine was 750 mg/m^2; however, the actual mean dose intensity of gemcitabine was 688.7 mg/m^2. Thus, the dose intensity was 91.8% for gemcitabine. Of the 476 planned infusions, 37 dose omissions (7.8%) occurred, mainly due to neutropenia. There were no dose reductions.

Discussion

The vast majority of patients with biliary tract cancer are candidates for chemotherapy; however, chemotherapy for biliary tract cancer currently has only limited value in clinical practice. 5-FU is the mainstay of palliative chemotherapy, although response rates range from 0 to 13% in phase II trials [6, 11, 39]. It is generally accepted that combinations with 5-FU have little superiority over single-agent 5-FU, and the considerable toxicity often outweighs the benefit for the patients [11, 39]. Except for gemcitabine, no individual agent has shown a reproducible response rate over 15% [1, 12, 19, 29, 31, 33, 37]. Therefore, new agents need to be developed for truly effective chemotherapeutic regimens against this disease.

In a prospective randomized trial [4], gemcitabine is the only agent showing significant efficacy in respect to survival prolongation and symptom relief for patients with advanced pancreatic cancer; these results prompted trials for biliary tract cancer, which, to some extent, shares embryological and clinical features with pancreatic cancer. Several early-phase studies of single-agent gemcitabine at doses of 1,000–2,200 mg/m^2 have reported response rates of 8–60%, and median survival durations ranging from 6.5 to 11.5 months. [3, 7, 8, 14, 21, 24, 34, 35].

In our trial, gemcitabine 1,000 mg/m^2 was administered for 3 weeks with 1 week of rest; this schedule is currently approved in Japan for non-small-cell lung cancer and pancreatic cancer and is considered to be a standard regimen worldwide. Our overall response rate of 17.5% appeared to be comparable to previous trials with gemcitabine or other combination regimens and appeared near the highest results in single-agent therapy. In recent phase II trials of various single agents, responses were 8% in a study with cisplatin [29], 0% in paclitaxel [19], 0–25% in docetaxel [2, 31, 33], 11% in irinotecan [12], and 19% in capecitabine [23]. Our median overall survival of 7.6 months was also comparable to other trials of single-agent therapy, which ranged from 4.5 to 8.0 months [2, 12, 19, 23, 29, 31, 33, 37], and for combination therapies, which ranged from 5.0 to 14.0 months [5, 9, 10, 15, 18, 20, 26, 28, 32, 35, 36, 38]. However, it seemed to be longer when compared with other phase II trials for Japanese patients with advanced or metastatic biliary tract cancer, which was 5.3 months in uracil/tegafur, 5.9 months in cisplatin/

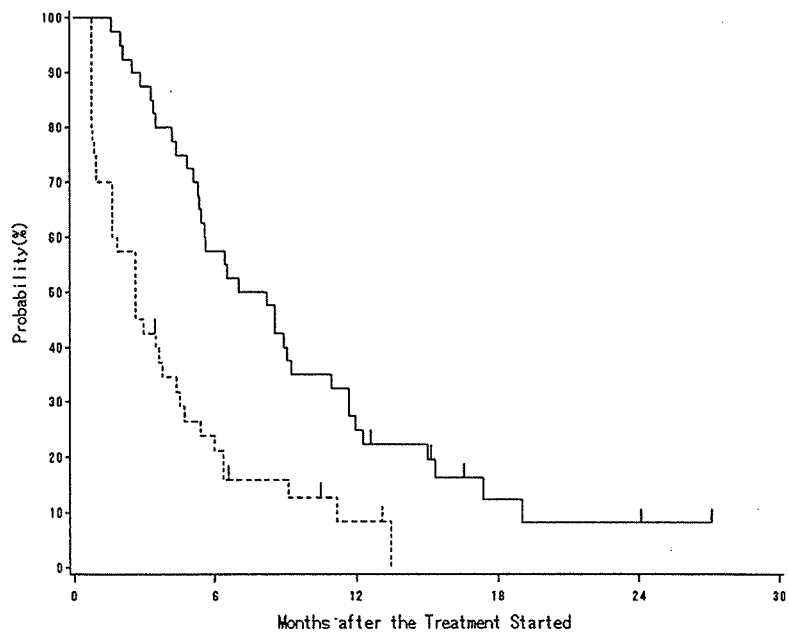

Fig. 1 Progression-free survival (*dashed line*) and overall survival (*solid line*) curves of patients with advanced biliary tract cancer receiving systemic chemotherapy with gemcitabine

Table 2 Adverse drug reaction

Adverse drug reaction	Grade 3		Grade 4	
	n	(%)	*n*	(%)
Hematologic toxicities				
Neutropenia	10	25.0	2	5.0
Leukopenia	5	12.5	0	0.0
Anemia	3	7.5	1	2.5
Thrombocytopenia	0	0.0	0	0.0
Nonhematologic toxicities				
Elevated ALT	6	15.0	0	0.0
Elevated γ-GTP	4	10.0	1	2.5
Elevated AST	2	5.0	0	0.0
Decreased serum sodium	2	5.0	0	0.0
Increased serum ALP	2	5.0	0	0.0
Urinary occult blood positive	1	2.5	0	0.0
Increased serum bilirubin increased	0	0.0	0	0.0
Increased serum creatinine	0	0.0	0	0.0
Proteinuria	0	0.0	0	0.0
Hematuria	0	0.0	0	0.0
Hemolytic uremic syndrome	0	0.0	1	2.5
Constipation	3	7.5	0	0.0
Vomiting	3	7.5	0	0.0
Nausea	2	5.0	0	0.0
Hematemesis	0	0.0	1	2.5
Diarrhoea	0	0.0	0	0.0
Stomatitis	0	0.0	0	0.0
Fatigue	0	0.0	0	0.0
Edema	0	0.0	0	0.0
Pyrexia	0	0.0	0	0.0
Biliary tract infection	1	2.5	0	0.0
Anorexia/Appetite impared	3	7.5	1	2.5
Rash	1	2.5	0	0.0
Alopecia	0	0.0	0	0.0
Hypertension	1	2.5	0	0.0
Hemorrhagic shock	0	0.0	1	2.5

ALT Alanine aminotransferase, *γ-GTP* γ-glutamyltransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase

epirubicin/5-FU, and 5.5 months in a study with cisplatin [18, 26, 29].

The toxicity profile in our study was generally acceptable. The major toxicities were myelosuppression; the incidences of grade 3/4 toxicities were 30.0% in neutropenia, 12.5% in leukopenia, and 10.0% in anemia. However, grade 4 toxicities were infrequent, and neither febrile neutropenia nor treatment-related deaths were observed. The toxicity profile in our study was consistent with past studies using gemcitabine in other tumors. For patients treated with cisplatin, epirubicin, and 5-FU [26], high incidences of grade 3/4 neutropenia (76.0%), leukopenia (59.0%), and death due to treatment-related sepsis 5.0% occurred despite a response rate (19%) similar to that in our study. There was only one episode of cholangitis in this study, although patients with biliary tract cancer are at high-risk for cholangitis, and sometimes severe sepsis occurs, which is derived from cholangitis during chemotherapy [26]. Transient elevations of hepatic enzymes have been reported in gemcitabine therapy for both pancreatic and biliary tract cancer; liver function may be easily affected by cholestasis due to existence of primary and/or metastatic tumors.

One patient developed hemolytic uremic syndrome, which was considered to be a manifestation of thrombotic microangiopathy, although gemcitabine-associated thrombotic microangiopathy is believed to be very rare, with estimated incidences of 0.008–0.31% [13, 17]. The event in this patient seemed to be a treatment-related adverse reaction; however, the patient recovered from hemolytic uremic syndrome without hemodialysis after discontinuation of gemcitabine. Grade 4 anemia was observed in one patient, who suffered grade 4 hematemesis and hemorrhagic shock. This was unlikely to be related to gemcitabine because no thrombocytopenia was observed in this patient. Also, upper gastrointestinal endoscopy revealed acute gastric mucosal lesions as the origin of the bleeding, which seemed to be related to prescribed non-steroidal anti-inflammatory drugs.

Our study was conducted among the largest group of patients with biliary tract cancer to date. In our study, gemcitabine was administered to patients who had biliary stent insertion or percutaneous biliary drainage, and no particular drug-related toxicity was observed in these patients. The result of our study is promising for patients with biliary tract cancer.

In conclusion, chemotherapy with single-agent gemcitabine was feasible and appeared to show efficacy in advanced or metastatic biliary tract cancer. Gemcitabine may provide a more favorable prognosis in patients with this disease compared to other chemotherapeutic regimes or best supportive care.

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Appendix

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An Early Phase II Study of S-1 in Patients with Metastatic Pancreatic Cancer

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Key Words
Chemotherapy · Pancreatic cancer · Phase II study · S-1 · Pharmacokinetics

Abstract
Objective: The aim of this study was to evaluate the efficacy and toxicity of S-1 in patients with metastatic pancreatic cancer. ***Methods:*** Patients were required to have a histological diagnosis of pancreatic adenocarcinoma with measurable metastatic lesions, and no prior chemotherapy. 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. A pharmacokinetic study was done on day 1 in the initial 8 patients. ***Results:*** Nineteen patients were entered into this study. Four patients (21.1%) achieved a partial response with a 95% confidence interval of 6.1–45.6%. No change was noted in 10 patients (52.6%), and progressive disease in 5 patients (26.3%). The median survival time was 5.6 months with a one-year survival rate of 15.8%. The major adverse events were gastrointestinal toxicities such as nausea and anorexia, though most of them were tolerable and reversible. There were no large differences in the pharmacokinetic parameters of S-1 in patients with pancreatic cancer and those in patients with other cancers. ***Conclusion:*** S-1 is active and tolerated in patients with metastatic pancreatic cancer, which will be confirmed in the following large-scale phase II study.

Introduction

Pancreatic cancer is among the most lethal of all solid tumors. More than 80% of patients have unresectable disease at diagnosis, and even if resection is performed, the recurrence rate is extremely high. Consequently, only ≤5% of all patients with pancreatic cancer survive 5 years after diagnosis [1]. Although pancreatic cancer has been considered as a chemotherapy-resistant tumor, recent studies have demonstrated that gemcitabine is an effective tool for the palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer. However, single-agent gemcitabine has provided limited benefit, with objective response rates of less than 15% and a median survival of less than 6 months [2–8]. Therefore, to improve the prognosis of patients with pancreatic cancer, there is a clear need to identify a new effective chemotherapeutic regimen.

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S-1 is an oral anticancer drug, which consists of tegafur (FT) as a prodrug of 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) [9]. The drug has been developed to improve the tumor-selective toxicity of 5-FU by two biochemical modulators, CDHP and Oxo. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase involved in the degradation of 5-FU, and maintains efficacious 5-FU concentrations in plasma and tumor tissues [10]. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits its phosphorylation of 5-FU in the gastrointestinal tract, and reduces the serious gastrointestinal toxicity associated with 5-FU [11]. S-1 has already demonstrated a potent antitumor effect in clinical studies on various solid tumors [12–18]. The response rates in the late phase II studies for advanced colorectal cancer, non-small cell lung cancer, and head and neck cancer were 35, 22, and 29%, respectively [12–14]. In particular, an excellent antitumor effect was demonstrated in the two late phase II studies for advanced gastric cancer, which resulted in response rates of 49 and 44%, respectively [15, 16]. In these late phase II studies, S-1 was administered at a dose of 80 mg/m^2/day for 28 consecutive days followed by a rest period of 14 days, based on the experience of the early phase II studies [17, 18]. The major adverse events recognized in these studies were myelosuppression and gastrointestinal toxicities, though most of them were tolerable and reversible. According to these findings, the commercial availability of S-1 for the treatment of patients with gastric cancer, colorectal cancer and head and neck cancer has been approved in Japan.

As for pancreatic cancer, although the preclinical antitumor efficacy of S-1 on human pancreatic cancer xenografts implanted into nude rats has been reported [19], its clinical activity against pancreatic cancer has not been evaluated. As it is available in an oral form, S-1 has a potential advantage as far as the convenience of the patients is concerned, especially in terms of quality of life. This is very important in pancreatic cancer patients, because the remaining life span of these patients is generally short. Thus, we conducted an early phase II study to evaluate the antitumor effect and safety of S-1 in patients with metastatic pancreatic cancer.

Patients and Methods

Study Patients

All patients were required to show histologically proven pancreatic adenocarcinoma with measurable metastatic lesions. Additional criteria included the following: no history of prior antitumor treatment except pancreatic resection; 20–74 years of age; Karnofsky performance status of 80–100 points; estimated life expectancy ≥2 months; adequate marrow function (white blood cell count 4,000–12,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin level ≥10.0 g/dl), adequate renal function (normal serum creatinine level), adequate liver function (total bilirubin level ≤3 times upper normal limit, transaminases levels ≤2.5 times upper normal limit), and written informed consent from the patients. Patients were excluded if there was a history of drug hypersensitivity, serious complications, symptoms attributable to brain metastasis, active secondary cancer, active infection, marked pleural or peritoneal effusion, and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board at the National Cancer Center Hospital, and conducted in accordance with the Good Clinical Practice guidelines in Japan.

Treatment Schedule

S-1 was administered orally at 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 ≤ BSA <1.50 m^2, 100 mg/day; and 1.50 m^2 ≤ BSA, 120 mg/day. S-1 was administered at the respective dose for 28 days, followed by a 14-day rest period. This schedule was repeated every 6 weeks until the occurrence of disease progression, unacceptable toxicities, or the patient's refusal to continue. If grade 3 or higher hematological toxicity or grade 2 or higher nonhematological toxicity was observed, the temporary interruption of S-1 and/or the dose reduction by 20 mg/day was allowed (minimum dose, 80 mg/day). Unless adverse events appeared, to enhance the pharmacological effect, 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 individual physicians. If a rest period of more than 28 days was required, the patient was withdrawn from the study. During the treatment, patients maintained a daily journal to record their S-1 intake and any adverse events experienced. S-1 was provided by Taiho Pharmaceutical Co. Ltd. (Tokyo, Japan).

Evaluation of Response and Safety

The response was assessed using computed tomography scan or magnetic resonance imaging in each course according to the Japan Society for Cancer Therapy Criteria [20], which is basically similar to the World Health Organization Criteria. Briefly, complete response was defined as the complete disappearance of all measurable and assessable lesions for at least 4 weeks. Partial response was defined as a ≥50% reduction in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks. No change was defined as a <50% reduction or a <25% increase in the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. Progressive disease (PD) was defined as a ≥25% increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [21].

Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during the treatment. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria version 2.0. An external review committee confirmed the objective responses and adverse events.

Table 1. Patient characteristics (n = 19)

Characteristics		Patients	%
Gender			
Male		13	68
Female		6	32
Median age, years (range)	61 (45–73)		
Karnofsky performance status			
100 points		2	11
90 points		16	84
80 points		1	5
Median first dose, mg/m^2 (range)	36.7 (33.7–39.9)		
History of pancreatectomy		1	5
Sites of metastasis			
Liver		15	79
Distant lymph node		3	16
Lung		3	16
Peritoneum		1	5
Median CEA, ng/ml (range)	8.6 (0.4–121)		
Median CA 19-9, U/ml (range)	4,033 (1–155,400)		

Pharmacokinetics

A pharmacokinetic study was performed in the first 8 patients enrolled in the study. Blood (5 ml) was collected with a heparinized syringe on day 1 of the first course before and 1, 2, 4, 6, 8, 10, and 12 h after the administration of S-1. Plasma was separated by centrifugation, and stored at –20 °C until analysis. Plasma concentrations of FT, 5-FU, CDHP, and Oxo were quantified as reported previously [22]. FT was quantified by high-performance liquid chromatography with UV detection, and 5-FU, CDHP, and Oxo were quantified by gas chromatography-negative ion chemical ionization mass spectrometry.

Pharmacokinetic parameters, maximum plasma concentration (C_{max}, ng/ml), time to reach C_{max} (T_{max}, h), area under the concentration versus time curve zero to infinity ($AUC_{0-\infty}$, ng·h/ml), and elimination half-life ($T_{1/2}$, h) were calculated by a noncompartment model in Win-Nonlin Version 3.1 (Pharsight, Apex, NC, USA).

Statistical Analysis

The response duration was calculated from the day of the first demonstration of response until PD; time to progression was calculated from the date of study entry until documented PD; overall survival time was calculated from the date of study entry to the date of death or the date of the last follow-up. Median probability of survival and the median time to progression were estimated by the Kaplan-Meier method. Compliance was calculated for all the courses using the ratio of the total dose actually administered to the scheduled dose. Analysis was planned to be carried out when 19 patients were enrolled. In this study, the threshold rate was defined as 5% and the expected rate was set as 15%. If the lower limit of the 90% confidence interval exceeded the 5% threshold (objective response in 4 or more of the 19 patients), S-1 was judged to be effective and we would proceed to the next large-scale study. If the upper limit of the 90% confidence interval did not exceed the expected rate of 15% (no objective response in the 19 patients), S-1 was judged to be ineffective and the study was to be ended. If response was confirmed in 1–3 of the 19 patients, whether to proceed to the next study or not was judged based on the safety and survival data from the present study.

Results

Patients

Nineteen consecutive patients with metastatic pancreatic cancer were enrolled in this study between June 2000 and January 2001 at the National Cancer Center Hospital. All patients were eligible and assessable for responses and adverse events. The patient characteristics are shown in table 1. The Karnofsky performance status was 80–100 points in all patients, and 18 of the 19 showed a Karnofsky performance status of ≥90. Before chemotherapy, morphine was prescribed for 7 patients due to abdominal and/or back pain.

Treatments

A total of 56 courses were administered to the 19 patients with a median of 2 courses per patient (range, 1–12). The initial administered dose of S-1 was 100 mg/day in 8 patients and 120 mg/day in 11 patients. Dose reduction was required in one patient because of grade 3 nausea, vomiting, and anorexia. The compliance rate of the patients taking S-1 during all the courses was as good as 90%.

Response and Survival

Out of the total of 19 evaluable patients, although no complete response was seen, partial response was obtained in 4 patients, resulting in an overall response rate of 21.1% (95% CI, 6.1–45.6%). No change was noted in 10 patients (52.6%), and PD in 5 patients (26.3%).

Table 2. Characteristics of responding patients (n = 4)

Patient No.	Gender	Age	KPS	History of pancreatectomy	Sites of metastasis	Symptomatic benefits	Response duration days	Survival time days
7	Female	65	90	No	Liver	Not assessable	78	463+
17	Female	61	90	No	Liver	No change	205	253
18	Female	68	90	No	Lung	No change	418	452+
19	Male	63	90	Yes	Abdominal lymph node	Improved[a]	213	448+

[a] Morphine consumption was decreased to ≥ 50% from baseline for 27 weeks without any deterioration of the KPS.

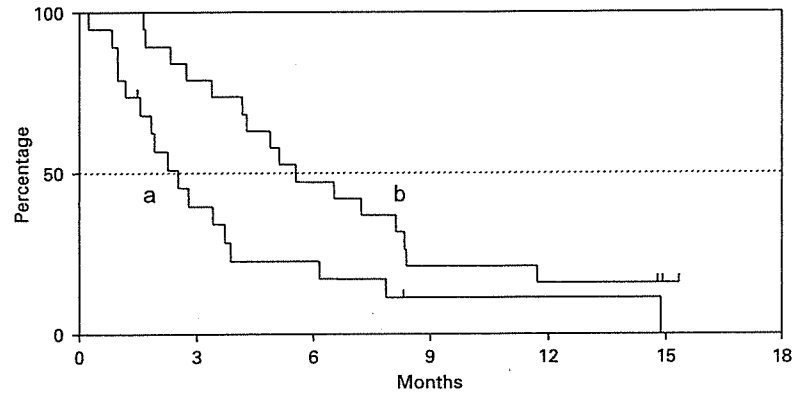

Fig. 1. Time to progression (a), and overall survival time (b).

Responses for each of the target sites were 20.0% (3/15) in liver, 33.3% (1/3) in the distant lymph nodes, and 33.3% (1/3) in lung metastases, respectively. The median time from the date of study entry to the day of the first demonstration of response was 34.5 days (range, 31–35 days) and the median response duration was 7.0 months (range, 2.6–13.9 months). The characteristics of all responders are shown in table 2. The median time to progression was 2.6 months, and the overall median survival was 5.6 months with a one-year survival rate of 15.8% (fig. 1). The serum CA 19-9 level was reduced to less than half in 7 (43.8%) of 16 patients who had a pretreatment level of 100 U/ml or greater.

Safety

S-1 was tolerated in this study. Treatment-related adverse events are listed in table 3. The most common adverse events were nausea (grade ≥ 1, 68.4%) and anorexia (grade ≥ 1, 57.9%), though most of them were tolerable and reversible. Vomiting, stomatitis, diarrhea, and skin rash were generally mild and less frequent, and no serious hepatic or renal toxicities were observed. As to hematological toxicities, grade ≥ 3 neutropenia was noted in only one patient (5.3%), and no grade ≥ 3 thrombocytopenia was observed. Although most patients could be treated as an outpatient without severe adverse events, 3 patients required hospitalization due to grade 3 ileus. Ileus occurred in the first course of treatment in 2 patients, and the remaining one had this event in the sixth course of treatment. However, all of them recovered from ileus after interruption of the S-1 with appropriate treatment. No other severe or unexpected adverse events were noted. Although 2 patients died within 2 months due to rapid disease progression, no treatment-related deaths were observed.

Table 3. Treatment-related adverse events (n = 19): worst grade reported during treatment period

Toxicity	Grade				Grade 1–4	Grade 3–4
	1	2	3	4	%	%
Hematological						
Leukopenia	1	1	0	0	10.5	0
Neutropenia	1	1	1	0	15.8	5.3
Hemoglobin	1	5	1	0	36.8	5.3
Thrombocytopenia	6	0	0	0	31.6	0
Nonhematological						
Nausea	10	0	3	0	68.4	15.8
Vomiting	4	1	1	0	31.6	5.3
Anorexia	6	2	2	1	57.9	15.8
Stomatitis	5	0	0	0	26.3	0
Diarrhea	2	1	1	0	21.1	5.3
Abdominal distension	3	0	2	0	26.3	10.5
Ileus	0	0	3	0	15.8	15.8
Colitis	0	0	2	0	10.5	10.5
Fatigue	3	1	1	0	26.3	5.3
Skin rash	2	1	0	0	15.8	0
Pigmentation	2	2	0	0	21.1	0
Aspartate aminotransferase	3	0	0	0	15.8	0
Alanine aminotransferase	1	2	0	0	15.8	0
Creatinine	0	0	0	0	0	0

Table 4. Pharmacokinetic parameters of FT, 5-FU, CDHP, and Oxo after administration of S-1 (n = 8)

	C_{max} ng/ml	T_{max} h	$AUC_{0-\infty}$ ng·h/ml	$T_{1/2}$ h
FT	1,705±383	2.9±1.2	23,846±9,848	8.9±2.4
5-FU	125.7±46.8	4.0±1.1	680.5±252.1	1.9±0.3
CDHP	217.3±100.6	3.0±1.1	1,139.3±335.7	2.9±0.4
Oxo	48.7±51.1	2.4±1.1	253.3±277.6	2.4±0.8

Parameters are represented as mean ± SD.

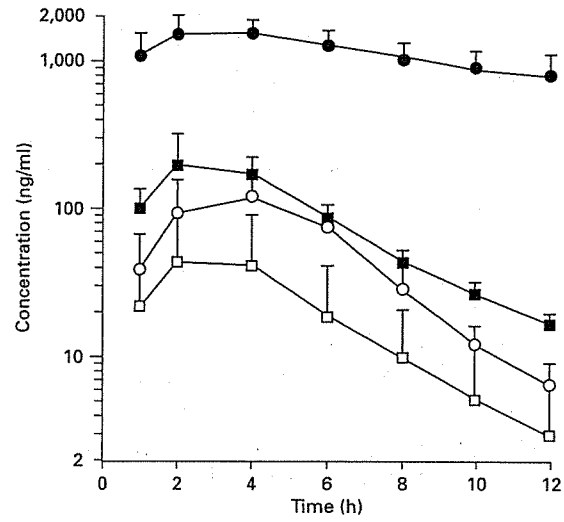

Fig. 2. Plasma concentration-time profiles of FT (●), 5-FU (○), CDHP (■), and Oxo (□) after administration of S-1 (n = 8). The values are expressed as the mean ± SD.

Pharmacokinetics

The pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0-\infty}$, and $T_{1/2}$) for FT, 5-FU, CDHP, and Oxo are listed in table 4. Plasma concentrations of all compounds peaked between 2 and 4 h after administration. The plasma concentration of FT reached a plateau after C_{max}, which was maintained for 12 h, while 5-FU, CDHP, and Oxo were more rapidly eliminated from the systemic circulation (fig. 2).

Discussion

5-FU, first synthesized 40 years ago, is still one of the most widely used agents for digestive system cancers including pancreatic cancer. Since 5-FU shows a short half-life and a time-dependent effect, its continuous infusion is known to result in a better antitumor effect than bolus injection [23]. A meta-analysis of six randomized trials has demonstrated that the continuous infusion 5-FU is superior to bolus 5-FU with respect to tumor response and survival in metastatic colorectal cancer [24]. As for pancreatic cancer, a recent study by Maisey et al. [25] has reported that the continuous infusion of 5-FU for the treatment of advanced pancreatic cancer results in a response rate of 8.4% and a median survival time of 5.1 months. However, continuous infusion of 5-FU requires a catheter, and is associated with complications, such as infections, and a reduced quality of life. Moreover, patients receiving continuous infusion of 5-FU show disturbance of their circadian rhythms and intraindividual variations in plasma 5-FU levels caused by dihydropyrimidine dehydrogenase, which contribute to limiting the effect of 5-FU. In addition, continuous infusion of 5-FU may cause severe gastrointestinal toxicities such as diarrhea and stomatitis. To overcome these problems, an oral fluoropyrimidine derivative, S-1, was developed on the basis of the biochemical modulation by CDHP, a dihydropyrimidine dehydrogenase inhibitor, and Oxo, a protector against 5-FU-induced gastrointestinal toxicity. Since the antitumor effects of S-1 on various solid cancers have been reported [12–18], we considered that the efficacy of S-1 on pancreatic cancer should also be investigated.

S-1 showed a good objective response rate of 21.1% with a good tumor growth control rate (objective responses plus no change) of 73.7% for metastatic pancreatic cancer patients. In the reported phase II and III studies for pancreatic cancer, single-agent gemcitabine showed response rates ranging from 5.4 to 16.0%, mostly below 15%, and tumor growth control rates ranging from 25.1–72.0%, mostly below 50% [2–8]. Our study also demonstrated a median survival time of 5.6 months with a one-year survival rate of 15.8%, which was comparable to the results of the gemcitabine studies. S-1 was easily administered, and most patients could be treated as outpatients. These results suggest that S-1 has an antitumor effect on metastatic pancreatic cancer.

A pharmacokinetic study of S-1 has already been conducted by Hirata et al [26]. They administered S-1 twice daily at a dose of 80 mg/m^2/day in 12 patients with gastric, colorectal, and breast cancer, and reported that C_{max}, T_{max}, AUC_{0-14}, and $T_{1/2}$ of 5-FU after a single administration of S-1 were 128.5 ± 41.5 ng/ml, 3.5 ± 1.7 h, 723.9 ± 272.7 ng·h/ml, and 1.9 ± 0.4 h, respectively. The pharmacokinetic parameters of 5-FU observed in our study (C_{max}, 125.7 ± 46.8 ng/ml; T_{max}, 4.0 ± 1.1 h; $AUC_{0-\infty}$, 680.5 ± 252.1 ng·h/ml; $T_{1/2}$, 1.9 ± 0.3 h) were similar to those in Hirata's study. The pharmacokinetic parameters of other compounds, FT, CDHP, and Oxo, also did not show a large difference between the two studies. Therefore, our data suggest that there were no large differences between the pharmacokinetic parameters of S-1 in patients with pancreatic cancer and those in patients with other cancers.

Toxicity of S-1 was acceptable in our study. Hematological toxicities were mild, similar to the results of clinical studies of S-1 for other cancers. However, gastrointestinal toxicities such as anorexia and vomiting tended to occur more frequently in our study. Grade ≥3 anorexia and vomiting were observed in 4.8 and 1.6% of colorectal cancer patients [12], while grade ≥3 anorexia and vomiting were seen in 15.8 and 5.3% of pancreatic cancer patients. Since the pharmacokinetic parameters of S-1 did not differ between subjects with pancreatic cancer and those with other cancers, we speculate that anorexia and vomiting were observed more frequently partly because many patients with pancreatic cancer had disease-related symptoms such as anorexia before treatment. Although phase I studies for S-1 from the Netherlands and the United States described diarrhea as a dose-limiting factor [27, 28], diarrhea was mild and low in incidence in this study, similar to the results of other cancer studies conducted in Japan. However, 3 patients in the current study required hospitalization because of ileus, an observation different from the past Japanese reports. In the United States, an 80-year-old female with gallbladder cancer was reported as developing grade 4 ileus with grade 3 diarrhea after administration of S-1 [28]. In the current study, 1 of the 3 patients had concomitant colitis, while the remaining 2 had no colitis. Although the causes of the ileus were unknown, S-1 may have been the underlying cause, because all patients recovered from ileus after cessation of S-1 with appropriate treatment. Two of the 3 patients had been put on morphine, and showed a tendency towards constipation before the onset, suggesting that the administration of S-1 requires attention to bowel movements.

In this study, since no serious adverse events occurred except the above-described ileus, most patients could be treated as outpatients. The compliance rate of the patients receiving S-1 was as good as 90%. S-1 is an oral anticancer

drug, and has the advantage of being able to treat patients while maintaining their quality of life. Since the prognosis of patients with advanced pancreatic cancer is generally poor, the demonstration in this study of the effectiveness and safety of S-1 (which allows treatment on an outpatient basis) for pancreatic cancer is highly significant. As the toxicity of S-1 is relatively mild, S-1 can be used in combination with other anticancer drugs. Combination therapy with S-1 and cisplatin has already been conducted for gastric cancer, and an excellent response rate of 76% was reported in a phase II study [29], which encourages the expectation of a future combination therapy with S-1 and other anticancer drugs including gemcitabine for advanced pancreatic cancer as well.

In conclusion, although this study had a small patient population, S-1 showed a promising antitumor activity with tolerable toxicity in metastatic pancreatic cancer patients. As an oral medication, S-1 offers a potential advantage as far as patient convenience is concerned, especially in terms of the patients' quality of life. We are currently conducting a multi-institutional late phase II study of S-1 for metastatic pancreatic cancer to confirm the results in this study.

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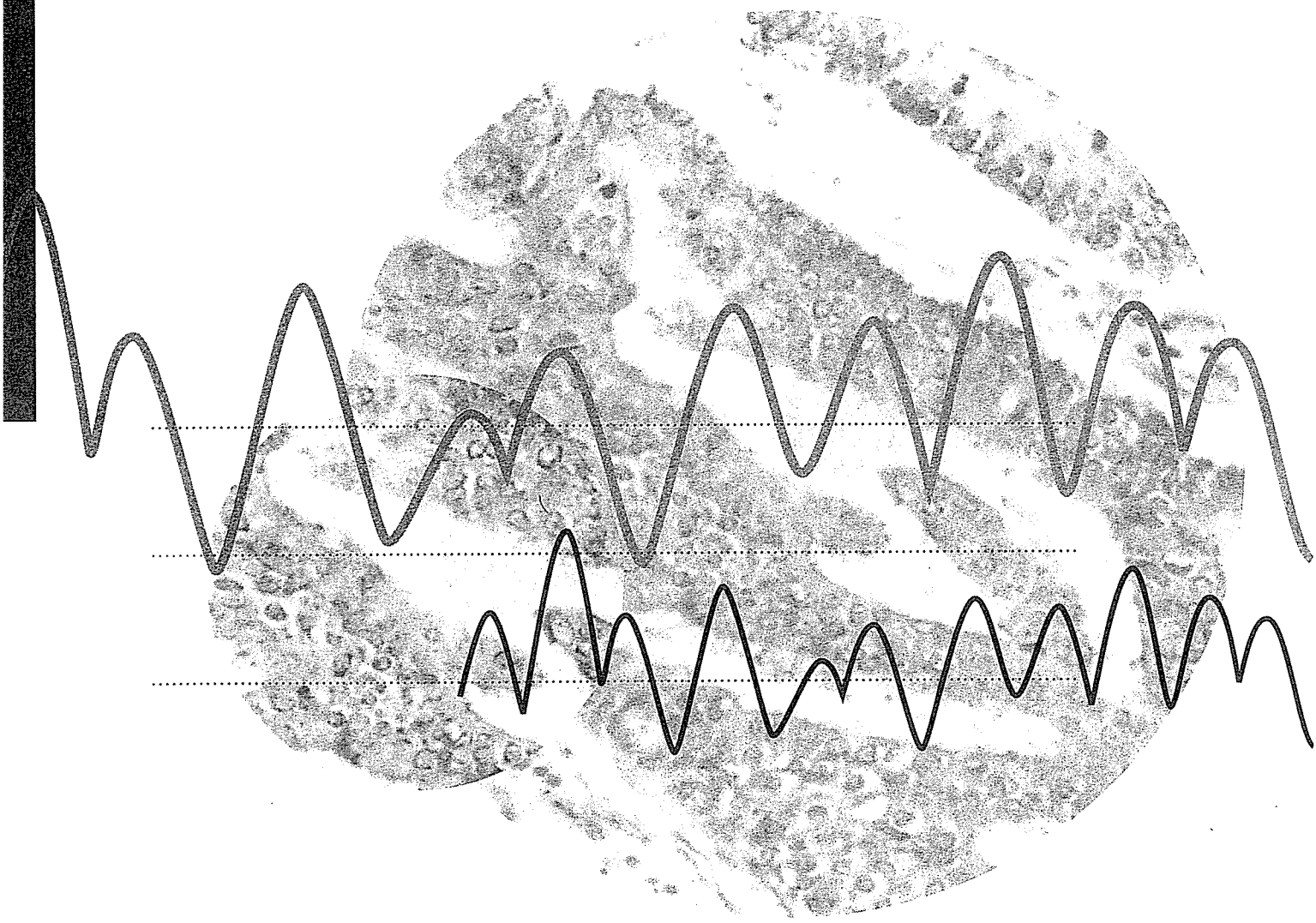

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Laboratory Investigations

Clinical Studies

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A Phase I Study of Combination Chemotherapy with Gemcitabine and Oral S-1 for Advanced Pancreatic Cancer

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Key Words
Pancreatic cancer · 5-Fluorouracil · Gemcitabine · S-1

Abstract
Objective: The aim of this study was to determine the maximum-tolerated dose and dose-limiting toxicity (DLT) of combination therapy with gemcitabine and S-1 in patients with advanced pancreatic cancer. ***Methods:*** Chemotherapy-naive patients with histologically or cytologically proven unresectable or metastatic pancreatic cancer were enrolled. The patients received gemcitabine intravenously over 30 min on days 1 and 8 and S-1 orally twice daily from days 1 to 14. Cycles were repeated every 21 days until disease progression. Patients were scheduled to receive gemcitabine (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels: 800/60 (level 1), 1,000/60 (level 2), 1,000/70 (level 3) and 1,000/80 (level 4). ***Results:*** Eighteen patients were enrolled in this study. The maximum-tolerated dose was not reached even at the highest dose level (level 4) because only 2 of the 6 patients at this level experienced DLT. The DLTs were neutropenia and rash. Six (33%) of the 18 patients achieved a partial response and median overall survival time was 7.6 months. ***Conclusions:*** Combination chemotherapy with gemcitabine and S-1 was well tolerated and showed good antitumor activity in the treatment of pancreatic cancer. We recommend a gemcitabine dose of 1,000 mg/m^2/week and an S-1 dose of 80 mg/m^2/day in further studies with this schedule.

Introduction

Pancreatic cancer is a fatal disease, with a 5-year survival rate of less than 5% [1]. Surgery remains the only curative option for patients with this disease, but the vast majority of patients unfortunately present with advanced, unresectable tumors. Effective non-surgical treatment is therefore needed to improve the outcome in patients with pancreatic cancer.

A randomized controlled study demonstrated that gemcitabine, a nucleoside analogue, is effective in palliating symptoms and prolonging survival in patients with advanced pancreatic cancer: gemcitabine showed a statistically significant advantage both in clinical benefit response (23.8 vs. 4.8%, p = 0.0022) and in median survival (5.65 vs. 4.41 months, p = 0.0025) compared with weekly bolus 5-fluorouracil (5-FU) [2]. Single-agent gemcitabine is currently accepted worldwide as first-line therapy for advanced pancreatic cancer. Nevertheless, there is substantial room for improvement in chemotherapy for pancreatic cancer, because single-agent gemcitabine pro-

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vides only limited benefit, with objective response rates of less than 15% and a median survival of less than 6 months [2–5].

S-1 is an oral fluoropyrimidine derivative that combines tegafur with two modulators of 5-FU metabolism, 5-chloro-2,4-dihydroxypyridine and potassium oxonate [6]. 5-Chloro-2,4-dihydroxypyridine 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 [7]. Potassium oxonate, 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 [8]. The efficacy of S-1 has already been demonstrated in a variety of solid tumors: the response rates for advanced gastric cancer, colorectal cancer and non-small cell lung cancer in the phase II studies conducted in Japan were 49, 35 and 22%, respectively [9–11]. Recently, the clinical efficacy of S-1 against pancreatic cancer has also been investigated. We conducted an early phase II study of S-1 for metastatic pancreatic cancer and reported that 4 (21.1%) of 19 patients achieved a partial response, with mild toxicity [12]. Hayashi et al. [13] performed a pilot study of single-agent S-1 or S-1 plus cisplatin combination therapy in patients with advanced pancreatic cancer and reported that 3 (20.0%) of the 15 patients or 8 (57.1%) of the 14 patients showed a partial response.

Since S-1 shows a favorable toxicity profile and activity in various solid tumors, including pancreatic cancer, we decided to investigate whether combination therapy with gemcitabine and S-1 is an effective chemotherapeutic regimen for pancreatic cancer. Although many clinical studies of gemcitabine in combination with fluoropyrimidines such as 5-FU, uracil/tegafur and capecitabine have been reported [14–22], little information is available on the combination of gemcitabine and S-1. Thus, we conducted a phase I study to determine the maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of gemcitabine and S-1 combination therapy in patients with unresectable or metastatic pancreatic cancer.

Patients and Methods

Patient Selection

Patients were considered eligible if they met the following criteria: histologically or cytologically proven pancreatic adenocarcinoma, unresectable locally advanced or metastatic disease, naive to chemotherapy, Eastern Cooperative Oncology Group performance status of 0–2, age between 20 and 74 years, life expectancy of ≥8 weeks, and adequate organ function defined as white blood cell count ≥4,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.0 g/dl, serum creatinine ≤the upper limit of normal, serum albumin ≥3.0 g/dl, total bilirubin ≤2.0 mg/dl, and aspartate aminotansferase and alanine aminotransferase levels ≤2.5 times the upper limit of normal or ≤5 times the upper limit of normal if liver metastases or biliary drainage were present. The exclusion criteria were severe complications, such as infection, heart disease and renal disease (in this study we did not define in detail the exclusion criteria in relation to severe complications), metastasis to the central nervous system, marked pleural effusion or ascites, and watery diarrhea. 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 and conducted in accordance with the Declaration of Helsinki.

Treatment Plan

This was an open-label, two-center, single-arm phase I study. Gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) was administered as a 30-min intravenous infusion weekly for 2 weeks followed by a 1-week rest. S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally twice daily from day 1 to day 14 followed by a 1-week rest. The treatment cycles were repeated every 3 weeks until disease progression or unacceptable toxicity occurred. If patients experienced leucopenia <2,000/mm^3, neutropenia <1,000/mm^3, thrombocytopenia <70,000/mm^3, total bilirubin >2.0 mg/dl or aspartate aminotansferase and alanine aminotransferase levels >5 times the upper limit of normal, both gemcitabine and S-1 were withheld until recovery. If patients experienced DLT, the dose of gemcitabine was reduced by 200 mg/m^2/week and the dose of S-1 was reduced by 10 mg/m^2/day in the subsequent cycle. If a rest period of more than 3 weeks was required because of toxicity, the patient was withdrawn from the study.

Patients were scheduled to receive gemcitabine and S-1 at four dose levels (table 1). At the first dose level (level 1), gemcitabine was administered at a dose of 800 mg/m^2/week and S-1 was administered at 60 mg/m^2/day. At the next dose level (level 2), gemcitabine was increased to 1,000 mg/m^2/week with S-1 kept at the same dose. At each of dose levels 3 and 4, S-1 was increased by 10 mg/m^2/day with gemcitabine kept at 1,000 mg/m^2/week. At least 3 patients were enrolled at each dose level. If DLT was observed in the initial 3 patients, a maximum of 3 additional patients was entered into the same dose level. The MTD was defined as the highest dose level that did not cause DLT in 3 of the 3 or ≥3 of the 6 patients treated at that level during the first two cycles of treatment. DLT was defined as grade 4 leucopenia or neutropenia, febrile neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenia requiring transfusion, ≥grade 3 non-hematological toxicity excluding nausea, vomiting, anorexia and fatigue, or any toxicity that necessitated a treatment delay of more than 3 weeks. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Patient Evaluation

Physical examinations, complete blood cell counts, biochemistry tests and urinalyses were performed at least once weekly. Tumor assessment with computed tomographic scan or magnetic resonance imaging and measuring of tumor marker CA 19-9 was performed every two cycles, and tumor response was evaluated by the

Table 1. Dose escalation scheme and DLT

Dose level	Gemcitabine mg/m²/week	S-1 mg/m²/day	Patients	DLT events	DLT
1	800	60	3	0	
2	1,000	60	3	0	
3	1,000	70	6	1	grade 4 neutropenia
4	1,000	80	6	2	grade 4 neutropenia grade 3 rash and grade 4 neutropenia

criteria of the Japan Society for Cancer Therapy [23], which are similar to those of the World Health Organization. Briefly, a complete response was defined as the disappearance of all clinical evidence of the tumor for a minimum of 4 weeks. A partial response was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for 4 weeks or longer without any evidence of new lesions. No change was defined as a reduction of less than 50% or a less than 25% increase in the sum of the products of two perpendicular diameters of all lesions for a minimum of 4 weeks. Progressive disease was defined as an increase of 25% or more in the sum of the products of two perpendicular diameters of all lesions, the appearance of any new lesion, or deterioration in clinical status that was consistent with disease progression. The response duration was calculated from the day of the first sign of a response until disease progression; progression-free survival was calculated from the date of the initiation of treatment until documented disease progression or death due to any cause (whichever occurred first); overall survival time was calculated from the date of treatment initiation to the date of death or the last follow-up. The median probabilities of the progression-free or overall survival periods were estimated by the Kaplan-Meier method.

Results

Patient Characteristics

Between September 2003 and July 2004, 18 patients were enrolled in this study. All of them received at least two cycles of chemotherapy and were evaluable for toxicity and response. Patient characteristics are listed in table 2. All patients had good performance status (0 and 1). Two patients had locally advanced unresectable disease and the remaining 16 had metastatic disease. Before the start of the study, 1 patient had received surgical resection and 3 had undergone biliary drainage for obstructive jaundice. Twelve patients had abdominal and/or back pain at study entry. A total of 125 cycles of chemotherapy was administered, with a median of 6 treatment cycles per patient (range 2–22). It was possible to treat all patients as outpatients after one or two cycles of observation in hospital.

Table 2. Patient characteristics

Characteristics		Patients
Patients enrolled		18
Sex		
Male		13
Female		5
Age, years		
Median	61	
Range	43–72	
ECOG performance status		
0		10
1		8
Body surface area, m^2		
Median	1.58	
Range	1.46–1.97	
Disease stage		
Locally advanced		2
Metastatic		16
Sites of metastatic disease		
Liver		13
Lung		2
Distant lymph nodes		5
Pleura		1

ECOG = Eastern Cooperative Oncology Group.

DLT and Recommended Dose

No DLT was observed at dose levels 1 or 2 (table 1). At dose level 3, 1 patient developed grade 4 neutropenia, which was considered DLT, but the remaining 5 did not develop DLT. At dose level 4, the highest dose level, 2 of the 6 patients exhibited DLTs: 1 had grade 4 neutropenia and the other had grade 3 rash concomitant with grade 4 neutropenia. All DLTs occurred in the first cycle of treatment. The MTD was not reached because only 2 of the 6 patients experienced DLT at dose level 4. Therefore, dose level 4 (gemcitabine dose of 1,000 mg/m^2/week and S-1

Table 3. Toxicities across first two cycles by dose level (patient number)

Toxicity	Dose level 1 (n = 3)				Dose level 2 (n = 3)				Dose level 3 (n = 6)				Dose level 4 (n = 6)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leucopenia	1	2	0	0	0	2	1	0	1	4	1	0	1	2	3	0
Neutropenia	1	1	0	0	0	1	2	0	0	5	0	1	0	3	1	2
Anemia	2	0	0	0	3	0	0	0	4	1	0	0	4	2	0	0
Thrombocytopenia	2	0	0	0	1	2	0	0	4	1	0	0	3	0	0	0
Nausea	2	0	0	0	1	0	1	0	2	2	0	0	2	0	0	0
Vomiting	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0
Anorexia	1	0	0	0	0	0	1	0	2	1	0	0	2	1	0	0
Diarrhea	1	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0
Stomatitis	2	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Rash	0	1	0	0	1	2	0	0	2	0	0	0	3	1	1	0
ALT elevation	1	0	0	0	2	0	0	0	3	2	0	0	1	0	0	0
Creatinine elevation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fever	0	0	0	0	0	1	0	0	0	0	0	0	3	0	0	0
Fatigue	1	0	0	0	1	0	0	0	1	1	0	0	2	1	0	0

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. ALT = Alanine aminotransferase.

dose of 80 mg/m^2/day) was considered the recommended dose in further studies with this schedule.

Toxicity

All 18 patients were assessable for toxicity. The major toxicities observed during the first two cycles are summarized in table 3. Hematological toxicity, particularly neutropenia, was the most pronounced toxicity of gemcitabine and S-1 with this schedule of administration. Although 3 patients experienced grade 4 neutropenia during the first two cycles of treatment, all of them recovered quickly without any severe complications. The neutrophil nadir typically occurred on day 15, and neutrophil counts recovered to baseline values by day 22. The non-hematological toxicities commonly observed with our regimen were gastrointestinal toxicities, such as nausea (≥grade 1; 55.6%) and anorexia (≥grade 1; 44.4%), although most of them were mild and transient. Although 1 patient at dose level 2 experienced grade 3 anorexia and grade 3 nausea in the first cycle, he recovered from the toxicities with the use of antiemetic agents and could continue treatment without reducing the doses of gemcitabine and S-1. Skin rash was also frequently seen in the current study (≥grade 1; 61.1%). The rash typically appeared on the arms and legs and spread to the trunk within 10 days of the initiation of chemotherapy. Most rashes were mild and resolved promptly with appropriate medical treatment such as antihistamines and steroids, although 1 patient at dose level 4 exhibited grade 3 rash that required temporary treatment discontinuation and dose reduction in the next cycle. Although 125 cycles of chemotherapy have been administered, there was no indication of cumulative toxicity.

Table 4. Objective tumor response

Dose level	Patients	Response				Response rate, %
		CR	PR	NC	PD	
1	3	0	2	1	0	66.7
2	3	0	0	1	2	0
3	6	0	3	3	0	50
4	6	0	1	4	1	16.7
Total	18	0	6	9	3	33.3

CR = Complete response; PR = partial response; NC = no change; PD = progressive disease.

Efficacy

The objective tumor responses at each dose level are shown in table 4. A partial response was seen even at the lowest dose level, and across all dose levels, 6 of the 18 patients achieved a partial response, resulting in an over-