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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.

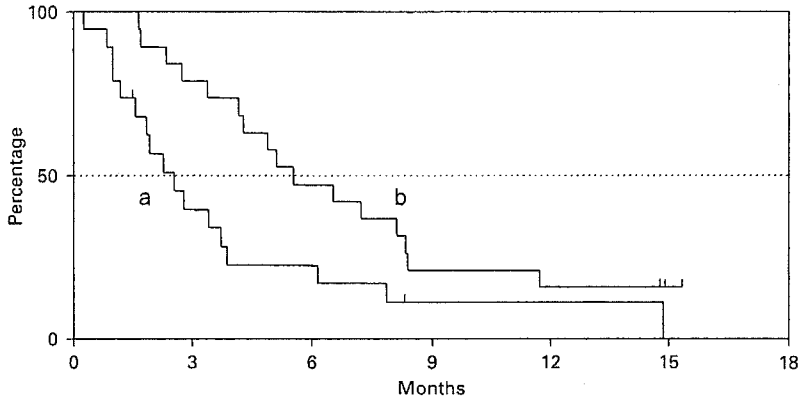

Fig. 1. Time to progression (a), and overall survival time (b).

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.

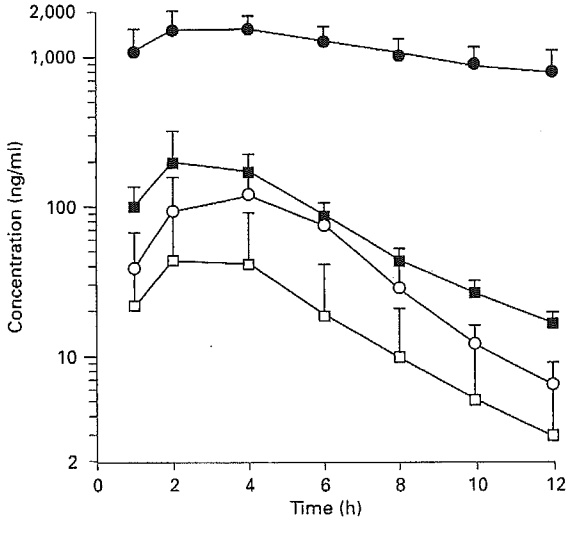

Fig. 2. Plasma concentration-time profiles of FT (●), 5-FU (○), CDHP (■), and Oxo (□) after administration of S-1 (n = 8). The values are expressed as the mean ± SD.

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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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/m^2/week	S-1 mg/m^2/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-

all response rate of 33.3 (95% confidence interval, 13.3–59.0%). No change was noted in 9 patients (50%) and progressive disease in 3 patients (16.7%). The mean response duration was 4.8 months (range 2.8–15.9). The serum CA 19-9 level was reduced to less than half from baseline values in 8 (61.5%) of the 13 patients who had a pretreatment level greater than the upper limit of normal (37 U/ml). At the time of analysis, 9 patients had died because of disease progression. The median progression-free and the median overall survival times were 5.0 and 7.6 months, respectively.

Discussion

To improve the prognosis of patients with advanced pancreatic cancer, gemcitabine-based combination chemotherapy has been actively investigated, although many phase III trials have failed to demonstrate any survival benefit of combination chemotherapy in comparison with gemcitabine as a single agent. 5-FU has been selected as a candidate to be investigated in combination with gemcitabine in patients with pancreatic cancer because of its favorable toxicity profile and modest but substantial activity in this disease. Gemcitabine is considered to enhance the effect of the 5-FU metabolite 5-FdUMP by reducing the concentration of its physiological competitor via inhibition of ribonucleotide reductase [24]. Preclinical studies have demonstrated synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells [25, 26]. Clinical studies have reported activity of gemcitabine in pancreatic cancer patients with refractoriness to 5-FU [27], suggesting the lack of cross-resistance between the two agents. Several phase I and II studies of combination therapy with gemcitabine and 5-FU for advanced pancreatic cancer have demonstrated relatively good response rates of around 20% with acceptable toxicity profiles [14–18]. A phase III study comparing gemcitabine alone with gemcitabine plus weekly bolus 5-FU showed that median progression-free survival was significantly longer in the combination arm compared with gemcitabine alone (3.4 vs. 2.2 months, $p = 0.022$); however, median overall survival was not significantly prolonged (6.7 vs. 5.4 months, $p = 0.09$) [5].

The novel oral anticancer agent S-1 was developed to improve the tumor-selective toxicity of 5-FU and has shown efficacy in a variety of solid tumors, including pancreatic cancer [9–13]. With the aim of developing a more effective chemotherapeutic regimen for pancreatic cancer, we decided to conduct a clinical study of combination therapy with gemcitabine and S-1. Since this combination has not previously been investigated, a phase I study was carried out to determine MTD and DLT.

In the present study, MTD was not reached because only 2 of the 6 patients experienced DLT at the highest dose, level 4. Although the 6 patients at level 4 have received a total of 34 cycles of treatment (average 5.7, range 2–12), there was no indication of cumulative toxicity. Therefore, dose level 4 (gemcitabine 1,000 mg/m^2/week, S-1 80 mg/m^2/day) was considered the recommended dose in further studies of this combination regimen. Because 2 of the 6 patients experienced DLT at this level, it goes without saying that more large-scale studies will be necessary to confirm the safety of our recommended dose. The overall toxicity of this regimen was mild, and neither unexpected nor life-threatening toxicities were observed during the study, indicating that S-1, like other fluoropyrimidines, can be safely combined with gemcitabine.

Neutropenia was the major DLT of this combination regimen: 1 of the 6 patients at dose level 3, and 2 of the 6 patients at dose level 4, experienced grade 4 neutropenia. Neutropenia as the DLT was to be expected because myelosuppression, especially neutropenia, is one of the most common toxicities of each individual drug. The neutrophil nadir typically occurred on day 15, but in most cases, the neutrophil count spontaneously recovered to baseline values within a week. Furthermore, no febrile neutropenia was observed during any of the 125 cycles of treatment, suggesting that the myelosuppression caused by this combination regimen is manageable on an outpatient basis.

The non-hematological toxicities commonly observed with our regimen were gastrointestinal toxicities such as nausea and anorexia. Although 1 patient at dose level 2 experienced transient grade 3 nausea and grade 3 anorexia, no DLTs associated with gastrointestinal toxicities were observed. Diarrhea was also mild and rare in the current study, similar to previous reports from Japanese studies of single-agent S-1; however, relatively severe diarrhea induced by S-1 has been reported in studies from Europe and the United States [28–30]. For example, Hoff et al. [28] reported that severe diarrhea occurred in all of the 3 patients who received S-1 at a dose of 40 mg/m^2 b.i.d. It is not clear why the toxicity profile and MTD of S-1 in Western studies differ from those in studies with Japanese populations, although a pharmacokinetic study suggested that the conversion of tegafur to 5-FU may occur more slowly in Japanese patients than in patients from other ethnic groups [31]. In any event, it may be dangerous to apply the results of our study directly to

treatment of Western patients, particularly from the viewpoint of gastrointestinal toxicity.

In the present study, 11 (61.1%) of the 18 patients experienced grade 1 or greater rash. This toxicity was mild and manageable, although 1 patient at dose level 4 developed grade 3 rash, requiring temporary treatment discontinuation. The reason for the enhanced cutaneous toxicity during combination therapy with gemcitabine and S-1 is unknown, although cutaneous toxicity has already been reported in patients receiving gemcitabine and 5-FU combination regimens. Hidalgo et al. [14] reported grade 1 or greater cutaneous toxicity in 11 (42.3%) of the 26 patients in a phase I–II study with gemcitabine and 5-FU. One of these patients developed a severe cutaneous reaction, manifested as generalized exfoliative dermatitis, after the first cycle of chemotherapy.

Combination therapy with gemcitabine and S-1 was associated with promising activity in advanced pancreatic cancer. Six (33.3%) of the 18 patients achieved an objective response. Of the 13 patients who had a pretreatment serum CA 19-9 level greater than 37 U/ml, the CA 19-9 level decreased more than 50% in 8 patients (61.5%). In addition, the median progression-free survival time of 5.0 months and the median overall survival time of 7.6 months are encouraging. These efficacy data in this study, which compare favorably with those reported for single-agent gemcitabine, support further studies of this regimen.

In conclusion, our combination regimen of gemcitabine and S-1 was well tolerated up to dose level 4. The major toxicities were myelosuppression, gastrointestinal toxicity and skin rash, although most of these toxicities were mild and reversible. Six of the 18 patients showed a partial response, suggesting a promising antitumor activity of this regimen against pancreatic cancer. A multicenter phase II study of this regimen, 1,000 mg/m^2/week gemcitabine on days 1 and 8 and 80 mg/m^2/day S-1 from days 1 to 14 every 3 weeks, is under way in patients with metastatic pancreatic cancer.

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Chemoradiotherapy for Locally Advanced Pancreatic Carcinoma in Elderly Patients

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Key Words
Chemoradiotherapy · Pancreatic carcinoma · Elderly

Abstract
Objectives: Chemoradiotherapy, which is one of the standard treatments for locally advanced pancreatic carcinoma, is considered a high-risk procedure in elderly patients. This study investigated the outcome and tolerability of this treatment in elderly patients. ***Methods:*** We reviewed our database from November 1993 to March 2003 and retrospectively examined the clinical data of patients with histologically confirmed exocrine pancreatic carcinomas that were nonresectable but confined to the pancreatic region, who were treated with protracted 5-fluorouracil infusion (200 mg/m^2/day) and concurrent radiotherapy (50.4 Gy in 28 fractions over 5.5 weeks). We evaluated the outcome of patients ≥70 years and those <70 years. ***Results:*** There were 19 patients ≥70 and 39 patients <70. On pretreatment evaluation, the elderly patients showed lower serum albumin levels, lower transaminase levels, better ECOG performance status, more frequent body weight loss and less frequent abdominal and/or back pain with the administration of morphine than the younger patients. There were no significant differences in the frequency of severe toxicity. Neither the response rate nor the incidence of treatment discontinuation differed significantly between the two groups. The median survival time was longer in the elderly patients than in the younger patients (11.3 vs. 9.5 months, p = 0.04). ***Conclusions:*** With careful patient selection, chemoradiotherapy can be one of the treatment options for locally advanced pancreatic carcinoma in elderly patients.

Introduction

The prognosis of patients with pancreatic carcinoma is extremely poor because of difficulty in the early detection of this disease and the ineffectiveness of nonsurgical treatments. For patients with locally nonresectable disease, the results of previous randomized trials indicated that concurrent external beam radiation therapy (EBRT) and 5-fluorouracil (5-FU) therapy resulted in significantly better survival compared with EBRT alone [1, 2] or chemotherapy alone [3]. However, this combination treatment sometimes induces intolerable toxic effects, and approximately 10–20% of patients cannot complete the scheduled course of treatment [4, 5]. Consequently, this treatment is considered to be frequently contraindicated in elderly patients, who are thought to be less likely to tolerate its potential toxicity than younger patients.

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Furthermore, many physicians believe that pancreatic carcinoma is less treatable in the elderly because of the presence of comorbid illnesses. On the other hand, it was reported that elderly patients often tolerate aggressive chemotherapy or radiotherapy for other carcinomas as well as their younger counterparts [6–16].

Some studies have shown that for resectable pancreatic carcinoma, pancreatic resections can be performed for the elderly with acceptable morbidity and mortality rates and possible long-term outcome [17–25]. However, in locally advanced pancreatic carcinoma treated with chemoradiotherapy, the tolerability, efficacy of treatment and long-term outcome have not been discussed extensively.

The current retrospective analysis examines the outcome and tolerability of elderly patients (i.e. those aged ≥70 years) within our database. The main purposes of this examination were to determine if the outcome for elderly patients was different from that for younger patients and to characterize the toxicity experienced by the elderly patients.

Methods

We reviewed the database of the Hepatobiliary and Pancreatic Oncology Division of the National Cancer Center Hospital from November 1993 to March 2003. In this retrospective analysis, we examined the clinical data of all patients who met the following requirements: (1) histological diagnosis of exocrine pancreatic carcinoma, (2) nonresectable disease confined to the pancreatic region, (3) treatment with protracted 5-FU infusion and concurrent radiotherapy, and (4) absence of prior treatment for pancreatic carcinoma. We divided the patients into two groups according to age, those ≥70 years and those <70 years. We evaluated the patient characteristics, toxicities, efficacies and survival in both groups.

Treatment was performed according to the treatment protocol of our division; radiotherapy was delivered via a microtron (MM22, Scanditronix, Upsala, Sweden) with 10- or 14-MV X-rays or a racetrack microtron (MM50, Scanditronix) with 25-MV X-rays. A total dose of 50.4 Gy was delivered in 28 fractions over 5.5 weeks. All patients had treatment planning computed tomography (CT) scans (X-vision, Toshiba, Tokyo, Japan), and FOCUS (Computerized Medical Systems, St. Louis, Mo., USA) was used as a radiotherapy treatment planning system. The clinical target volume included the primary tumor, nodal involvement detected by CT scan, and regional draining and para-aortic lymph nodes, which included the peripancreatic nodes, celiac and superior mesenteric axes. The planning target volume was defined as the clinical target volume plus a 10-mm margin. Four field techniques (anterior, posterior and opposed lateral fields) were used. The spinal cord dose was maintained below 45 Gy, ≥50% of the liver was limited to ≤30 Gy, and ≥50% of both kidneys was limited to ≤20 Gy. 5-FU was given from the first day of radiation and continued through the entire course of radiation at a dose of 200 mg/m^2/day through a central venous catheter. Patients were admitted to the hospital during chemoradiotherapy. Within 8 weeks after the completion of chemoradiotherapy, maintenance chemotherapy was delivered on an outpatient basis and continued until disease progression. For the maintenance chemotherapy, we used a weekly administration of 5-FU (500 mg/m^2, 30-min infusion) before the approval of gemcitabine for pancreatic carcinoma in Japan (April 2001), and thereafter, we used weekly administration of gemcitabine (1,000 mg/m^2, 30-min infusion) 3 times every 4 weeks.

During chemoradiotherapy, the toxicity of the treatment was scored weekly according to the World Health Organization criteria [26]. Both radiotherapy and chemotherapy were suspended when ≥grade 3 toxicities other than anorexia, fatigue, nausea/vomiting, constipation and hyperglycemia occurred and were resumed when recovery to grade 2 toxicity levels was achieved. If there was a total delay of 2 weeks due to toxicity for any reason, the combined treatment was discontinued. In this retrospective analysis, we obtained the information regarding adverse events about the subjective symptoms from the doctor's record in as much detail as possible. As a rule, follow-up CT was performed within 1 week after the completion of chemoradiotherapy and every 2 months thereafter to evaluate the objective tumor response with reference to the World Health Organization criteria.

Statistics

Frequencies in 2 × 2 and larger contingency tables of the patient characteristics, response rates and toxicities were compared with the χ^2 or Fisher's exact test. Distributions of continuous variables were compared with the Mann-Whitney test. Overall survival was measured from the first day of treatment, and the survival curves were calculated according to the Kaplan-Meier method. The log rank test was used to detect differences between the curves. All p values in this study were of the two-tailed type. Significance was defined as a p value of 0.05 or less. Statistical analyses were performed with Stat View version 5.0.

Results

One hundred and ninety-nine patients with locally advanced pancreatic carcinoma admitted to the Hepatobiliary and Pancreatic Oncology Division of the National Cancer Center Hospital from November 1993 to March 2003. Thirty-nine patients were ≥70 years and 160 were <70 years. Nineteen (49%) of the 39 patients ≥70 and 39 (24%) of the 160 of those <70 met the above-mentioned conditions. The remaining 141 patients were excluded from this analysis. One hundred and thirty-eight received other anticancer treatments including chemoradiotherapy using other regimens (130), systemic chemotherapy (7) and radiotherapy alone (1). Three patients underwent only the best supportive care. The patient characteristics are shown in table 1 and the pretreatment laboratory data are shown in table 2. The male-to-female ratio was 1.7:1 in the elderly patients and 1.4:1 in the younger patients.

Table 1. Patient characteristics

	≥70 years	<70 years	p
Patients	19	39	
Age			
Median	75	60	
Range	70–86	35–69	
Sex			0.78
Male	12 (63)	23 (59)	
Female	7 (37)	16 (41)	
ECOG PS			0.004
0	6 (32)	1 (3)	
1	11 (58)	36 (92)	
2	2 (11)	2 (5)	
Diabetes mellitus	9 (47)	10 (26)	0.14
Abdominal and/or back pain[a]	3 (16)	19 (49)	0.02
Biliary drainage	4 (21)	8 (21)	>0.99
Regional lymph node	11 (58)	22 (56)	>0.99
Body weight loss[b]	14 (74)	24 (62)	0.20
Tumor location			0.42
Uncus	1 (5)	5 (13)	
Head	12 (63)	25 (64)	
Body	5 (26)	9 (23)	
Tail	1 (5)	0 (0)	
Treatment start			>0.99
Before April 2001[c]	10 (53)	21 (54)	
After April 2001[c]	9 (47)	18 (46)	

Figures in parentheses are percentages. ECOG = Eastern Cooperative Oncology Group.

[a] Abdominal and/or back pain: with consumption of morphine.

[b] Body weight loss: more than 7% of previous body weight within 6 months.

[c] April 2001: approval of gemcitabine.

Table 2. Pretreatment laboratory data

	≥70 years	<70 years	p
Albumin, g/dl	3.6 (3.0–4.3)	3.8 (3.1–4.5)	0.002
AST, IU/l	19 (11–66)	23 (10–274)	0.04
ALT, IU/l	17 (9–136)	32 (6–332)	0.01
Total bilirubin, mg/dl	0.7 (0.3–1.3)	0.6 (0.2–3.7)	0.20
CA19-9, U/ml	769.5 (3–27,000)	624.0 (4–6,310)	0.06
CEA, ng/ml	6.9 (2.1–76.4)	4.9 (0.7–1,620)	0.11

AST = Aspartate aminotransferase; ALT = alanine aminotransferase; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen.

Table 3. Response to chemoradiotherapy

	≥70 years	<70 years	p
Complete response	0 (0)	0 (0)	
Partial response	2 (11)	2 (5)	
No change	14 (74)	28 (72)	
Progressive disease	3 (16)	7 (18)	
Not evaluable	0 (0)	2 (5)	0.60

Figures in parentheses are percentages.

In the elderly patients, there were 6 patients (32%) who had an ECOG performance status (PS) of 0, but there was only 1 such patient (3%) among the younger patients ($p = 0.004$). The incidence of patients who had abdominal or back pain with consumption of morphine was smaller in the elderly patients ($p = 0.02$). There was no significant difference between the younger and elderly patients with regard to the period prior to treatment initiation (before or after the gemcitabine approval) ($p > 0.99$). The serum albumin level and transaminase levels were lower in the elderly patients. The other patient characteristics of those ≥ 70 years were generally similar to those of the younger patients.

The results of the treatment outcome are shown in table 3. Even though this study was conducted retrospectively, the antitumor response in CT was obtained in all but 2 younger patients who were transferred to another hospital before the completion of treatment. The laboratory data were also maintained for all patients, whose blood examinations were performed at least weekly. Four subjects among the elderly patients (21%) suspended the chemoradiotherapy during the schedule, as did 11 (28%) among the younger patients. One elderly patient (5%) discontinued chemoradiotherapy, as did 5 (13%) of the younger patients. Chemoradiotherapy was discontinued because of patient request due to unacceptable toxicities such as fatigue (1 younger patient), nausea/vomiting (3 younger patients and 1 elderly patient) and patient refusal (1 younger patient). A partial response was obtained in 2 (11%) elderly and 2 (5%) younger patients. Fourteen (74%) elderly patients and 28 (72%) younger patients showed no change. The survival curves are shown in figure 1. The median survival time was longer for the elderly patients than for younger patients (11.3 months in the elderly patients, 9.5 months in the younger patients, $p = 0.04$). The longest survivor in both groups was a 71-year-old male who survived 60.1 months (5.0 years) after the initiation of treatment.

Table 4. Toxicity in patients receiving chemoradiotherapy

	Grades 1–4		p	Grades 3 and 4		p
	≥70 years	<70 years		≥70 years	<70 years	
Leukocytes	9 (47)	20 (51)	>0.99	1 (5)	2 (5)	>0.99
Hemoglobin	8 (42)	16 (41)	>0.99	0 (0)	0 (0)	–
Neutrophils	3 (16)	12 (31)	0.37	0 (0)	0 (0)	–
Platelets	4 (21)	4 (10)	0.48	0 (0)	0 (0)	–
Albumin	10 (53)	16 (41)	0.58	0 (0)	0 (0)	–
AST	4 (21)	8 (21)	>0.99	0 (0)	2 (5)	0.81
ALT	3 (16)	15 (38)	0.15	0 (0)	3 (8)	0.54
Total bilirubin	2 (11)	3 (8)	>0.99	0 (0)	1 (3)	>0.99
Creatinine	2 (11)	0 (0)	0.2	0 (0)	0 (0)	–
Nausea	11 (58)	34 (87)	0.03	2 (11)	13 (33)	0.12
Vomiting	4 (21)	19 (49)	0.07	0 (0)	1 (3)	>0.99
Anorexia	16 (84)	35 (90)	0.9	6 (32)	22 (56)	0.13
Stomatitis	3 (16)	2 (5)	0.85	1 (5)	0 (0)	0.71
Diarrhea	4 (21)	13 (33)	0.47	0 (0)	2 (5)	0.81
Fatigue	3 (16)	13 (33)	0.28	0 (0)	1 (3)	>0.99

Figures in parentheses are percentages. AST = Aspartate aminotransferase; ALT = alanine aminotransferase.

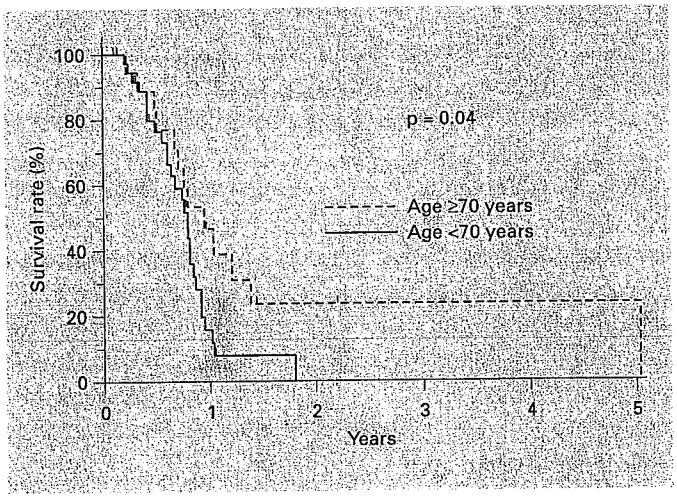

Fig. 1. Overall survival curves for patients ≥70 years (n = 19) and those for patients <70 years (n = 38).

The percentages of overall toxicities (grades 1–4) and severe toxicities (grades 3 and 4) are listed in table 4. Although the incidence of nausea (grades 1–4) was significantly higher in the younger patients, there were no significant differences in the incidence of other overall toxicities or all severe toxicities. The toxicities of both groups were generally mild and reversible. One younger patient died from a fungal infection of the lung due to pneumothorax which occurred as a complication of the insertion of a central venous catheter. There was no conspicuous late toxicity in either group.

Discussion

Based on previous randomized trials [1–3], concurrent EBRT and 5-FU result in significantly better survival compared with EBRT alone or chemotherapy alone and are generally accepted as the standard treatment for locally advanced pancreatic carcinoma. However, this treatment restrains patients for more than 1.5 months during treatment. Furthermore, the life expectancy for the majority of these patients is still short, with a median survival of approximately 10–11 months. The poor prognosis and long duration of treatment makes us hesitant to indicate chemoradiotherapy for patients with locally advanced pancreatic carcinoma, especially for patients at high risk for complications. Elderly patients have been generally considered a high-risk population for chemoradiotherapy due to a number of physiological and pharmacological reasons. For example, diminished bone marrow cellularity can potentially result in decreased tolerance to myelosuppressive therapies. In addition, a decrease in hepatic and renal function may reduce the efficiency of drug metabolism and excretion, resulting in greater toxic potential.

However, in this study, no differences were found in the response rate, incidence of treatment discontinuation and toxicity profile, except for nausea, between the two groups. The median survival time was significantly longer in the elderly patients than in the younger patients. The most important reason for the favorable results of the elderly patients may be the careful selection of patients. Ikeda et al. [27] reported that a good PS was one of the independent favorable prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. In our study, 32% of the patients ≥70 had an ECOG PS of 0, as opposed to 3% of those <70. Since this was a retrospective analysis, indication according to a physician's decision might have been different for younger and for elderly patients, only allowing the elderly patients in very good condition to receive chemoradiotherapy. As a result, this may be a comparison of elderly patients with a very good PS and younger patients with a less good or average PS.

An imbalance in the incidence of patients with abdominal pain between the two groups might also have affected the treatment outcome in our study. According to the report of Kelsen et al. [28], unresectable pancreatic carcinoma patients with abdominal pain had a median survival of 4.7 months, whereas the median survival among patients without such pain was 8.3 months.

In this study, there was no significant difference between the younger patients and the elderly patients with regard to the ratio of the patients who received maintenance chemotherapy using gemcitabine. Although it is possible that maintenance therapy had some effect on survival, the survival time did not differ significantly between the gemcitabine maintenance chemotherapy group and the 5-FU maintenance chemotherapy group in this study (data not shown).

The mild toxicity of this treatment may be another favorable factor for elderly patients [4]. This study showed that severe toxicities except anorexia were observed infrequently in both groups and that discontinuation of the treatment was required in only 1 elderly patient. Protracted 5-FU infusion with concurrent radiotherapy, which is considered a less toxic treatment than radiotherapy and bolus 5-FU [29, 30], is feasible even in elderly patients.

Krzyzanowska et al. [31] reported an attractive retrospective cohort study in 1,696 patients diagnosed with locally advanced pancreatic carcinoma. According to the report, older age was associated with a lower likelihood of receiving carcinoma-directed therapy, much less of a combined therapy such as chemoradiotherapy. However, Cox proportional hazard models showed that carcinoma-directed therapy, including chemoradiotherapy, has the potential to prolong the survival of elderly patients with locally advanced pancreatic carcinoma. These findings, which suggest that chemoradiotherapy can be an optimal treatment option for locally advanced pancreatic carcinoma in elderly patients, are supported by the results of our study.

Since this study was conducted retrospectively, the results do nothing more than suggest possibilities of the efficacy of the 5-FU-based chemoradiotherapy for selected elderly patients with locally advanced pancreatic carcinoma. To identify the benefit of the treatment in elderly patients, we must design a large prospective study. In summary, this study demonstrates that chemoradiotherapy for locally advanced pancreatic carcinoma is well tolerated and does not lead to an increase in treatment interruption or discontinuation in elderly patients. We conclude that, with careful patient selection, chemoradiotherapy can be considered an appropriate treatment for elderly patients.

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