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ORIGINAL ARTICLE

Phase II study of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer

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Abstract
Purpose The primary objective of this study was to assess the efficacy and safety of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer.
Methods Patients with histologically or cytologically proven, advanced pancreatic cancer who had received first-line chemotherapy with gemcitabine were eligible for this study. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for 28 days, followed by 14 days' rest. Treatment was repeated every 6 weeks until disease progression.
Results Twenty-one patients were enrolled in this study. Grade 3 and 4 toxicities included anorexia in 14% of the patients, abdominal pain in 4.8% and infection without neutropenia in 4.8%. S-1 was discontinued in two patients because of toxicity. Of the 21 eligible patients, 2 (9.5%) achieved a partial response and 9 (43%) had stable disease. A marked decrease ($\geq$50%) in tumor marker (CA19-9) was observed in 5 (28%) of the 18 evaluable patients. The median progression-free survival and the median survival time from the first day of S-1 therapy were 4.1 months (95% CI, 1.3–6.9 months) and 6.3 months (95% CI, 3.6–8.9 months), respectively.
Conclusions Second-line chemotherapy with S-1 was tolerated with acceptable toxicity and resulted in a relatively high disease control rate in patients with gemcitabine-resistant advanced pancreatic cancer. As an oral agent, S-1 may be a feasible treatment option for this patient population.

Keywords Pancreatic cancer · S-1 · Second-line therapy · Phase II study

Introduction

Pancreatic cancer is one of the most prevalent gastrointestinal tumors and its prognosis is extremely poor. A previous randomized trial of gemcitabine in patients with advanced pancreatic cancer has shown this drug is superior to 5-fluorouracil (5-FU) in terms of overall survival and clinical benefit [1], and treatment with gemcitabine alone has been accepted as the only approved therapy for unresectable pancreatic cancer. In an effort to improve therapeutic efficacy, various studies have investigated gemcitabine-based combination regimens. However, most of those studies have found a low impact on survival, and gemcitabine monotherapy is still considered as the standard treatment for this disease.

There is no accepted second-line treatment for advanced pancreatic cancer after gemcitabine failure. Although several studies have shown the efficacy and safety of second-line chemotherapy in a selected patient population [2], second-line strategies are often hard to implement due to the poor condition and prognosis of the patients. Thus,

This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. All study participants provided written informed consent. This manuscript has not been published and is not under consideration for publication elsewhere.

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there is an urgent need to develop effective therapies for tumors refractory to treatment with gemcitabine.

S-1 is an oral fluorinated pyrimidine, which was designed to improve the antitumor activity of 5-FU while reducing gastrointestinal toxicity, based on a hypothetical biochemical modulation of 5-FU. S-1 contains tegafur, 5-chloro-2, 4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a molar ratio of 1:0.4:1 [3]. Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU by hepatic microsomal enzymes. Gimeracil inhibits the degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD) and it is 180 times more potent than uracil, a DPD inhibitor included in UFT; thus, an efficacious concentration of 5-FU is maintained both in plasma and tumor tissues [4]. Oteracil is a competitive inhibitor of orotate phosphoribosyltransferase that inhibits phosphorylation of 5-FU in the gastrointestinal tract. Because oteracil preferentially acts in the gastrointestinal tract after oral administration, it reduces the gastrointestinal toxicity associated with 5-FU [5].

S-1 has shown favorable antitumor activity in several phase II studies in patients with various solid tumors [6–9], and a recent phase II study of S-1 in patients with metastatic pancreatic cancer yielded a good response rate of 37.5% and median survival of 9.2 months [10]. Furthermore, recent studies of combination chemotherapy with S-1 and gemcitabine for metastatic pancreatic cancer yielded a promising response rate of 44–48% and a median survival time of 10.1–12.5 months [11, 12]. Based on currently available data, S-1 seems to have significant activity against advanced pancreatic cancer; thus, we selected S-1 to treat patients with gemcitabine-resistant pancreatic cancer.

Patients and methods

Eligibility

Patients with histologically or cytologically proven, advanced adenocarcinoma of the pancreas who had received first-line chemotherapy with gemcitabine were eligible for this study. Participants were required to be at least 20 years old and to have an Eastern Cooperative Oncology Group performance status of 2 or less and adequate organ function defined by the following parameters: leukocytes $\geq$3,500/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dL, normal serum creatinine, a serum glutamic oxaloacetic transaminase (GOT) <150 IU/L, a serum glutamic pyruvic transaminase (GPT) <150 IU/L and serum bilirubin $\leq$2.0 mg/dL.

Patients were excluded if they had interstitial pneumonitis, active inflammatory bowel disease, active infection, mental disorder, or other severe concurrent disease. Patients with other malignancies and pregnant or lactating women were also excluded.

This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. Written informed consent was obtained from all patients before their inclusion into the study.

Treatment

S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily after a meal for 28 consecutive days, and the course was repeated after 14 days' rest, until disease progression or unacceptable toxicities. Three initial doses were established according to the body surface area (BAS) as follows: BSA $<$ 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA $<$ 1.50 m^2, 100 mg/day; 1.50 m^2 $\leq$ BSA, 120 mg/day.

Dose modification

S-1 was temporally discontinued when any of the following conditions were encountered: leukocytes <2,000/mm^3, neutrophils <1,000/mm^3, hemoglobin <8.0 g/dL, platelets <75,000/mm^3, serum GOT/GPT $\geq$ 150 IU/L, serum total bilirubin $\geq$3.0 mg/dL, serum creatinine $\geq$1.5 mg/dL, or when grade 3 non-hematological toxicity was observed. Administration was resumed when the toxicity resolved. When grade 4 hematological toxicity or grade 3 or greater non-hematological toxicity occurred, the dose of S-1 was reduced by 20 mg/day. If it was difficult to administer S-1 for 28 consecutive days because of tumor-related symptoms or non-severe toxicity, which did not meet the dose reduction criteria (e.g. grade 2 anorexia or nausea), a regimen consisting of S-1 administration for 14 consecutive days followed by 7 days' rest (2-week administration regimen) was permitted, since this regimen was recently reported to be more feasible and did not require a change in dose intensity, when compared to the standard 4-week administration regimen (28 consecutive days followed by 14 days' rest) [13].

Follow-up evaluation

Pretreatment evaluation included a medical history and physical examination, complete blood count and biochemistry test, a chest radiogram, and CT of the abdomen and pelvis. Complete blood counts and serum biochemistry tests were performed weekly during the first course of S-1 and every other week after the second course. Biochemistry

tests included standard serum tests such as total protein, albumin, bilirubin, GOT, GPT, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, creatinine, and C-reactive protein. Treatment-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Follow-up CT was performed every 2 months to assess objective tumor response according to the Response Evaluation Criteria in Solid Tumors. Serum CA 19-9 levels were measured monthly using a commercially available chemiluminescent enzyme immunoassay kit based on the two-step sandwich method (CL-EIA). A value of 39.5 U/mL was defined as the upper normal limit.

Statistics

The primary end-point was the objective response rate (complete response or partial response), with secondary end-points including overall and progression-free survival, disease control rate (complete response, partial response or stable disease), and safety of S-1. The number of patients required for this study was calculated according to the optimal two-stage design. The threshold response rate and expected response rate were 5% and 20%, respectively. The number of patients was 19 (α- and β-error probabilities 0.05 and 0.2). Both survival and tumor response were determined according to the intention-to-treat principle in all enrolled patients. Overall survival and progression-free survival were calculated with the Kaplan–Meier method.

Results

Patient characteristics

From March 2005 to July 2006, 21 patients entered this study. The patients' characteristics are listed in Table 1. All patients had been treated with gemcitabine alone. The median progression-free survival with first-line gemcitabine was 3.2 months. At the time of enrollment, most patients (95%) had evidence of metastatic disease and one patient had locally advanced unresectable disease. Seventy-one percent of the patients had an ECOG performance status of 0 or 1.

A total of 66 cycles were delivered (median, 3; range, 0–13). Based on the dose modification guidelines, the 2-week administration regimen was adopted in ten patients (48%).

Toxicity

All treated patients ($n = 21$) were assessed for toxicities. The toxicities observed during treatment are listed in Table 2. Generally, hematological toxicity was mild, and no grade 3 or higher toxicity was observed. As for non-hematological toxicity, grade 3 anorexia (14%), grade 3 abdominal pain (4.8%), and grade 3 infection (4.8%) was experienced. One patient developed duodenal bleeding 54 days after the beginning of S-1 treatment requiring embolization under angiography. This was considered to be tumor bleeding unrelated to the medication. Second-line chemotherapy with S-1 was feasible with acceptable toxicity and no treatment-related deaths occurred.

Table 1 Patient characteristics

Number of patients	21
Gender	
Men	13
Women	8
Age, years	
Median (range)	64 (32–75)
ECOG performance status	
0	4
1	11
2	6
Disease status	
Locally advanced	1
Metastatic	20

ECOG Eastern cooperative oncology group

Table 2 Toxicity ($n = 21$)

Toxicity	No. of patients (%)		
	Grade 1/2	Grade 3	Grade 4
Hematological toxicity			
Leukocytopenia	6 (29)	0	0
Neutropenia	4 (19)	0	0
Anemia	4 (19)	0	0
Thrombocytopenia	7 (33)	0	0
Non-hematological toxicity			
Anorexia	4 (19)	3 (14)	0
Nausea	5 (24)	0	–
Vomiting	2 (9.5)	0	0
Diarrhea	3 (14)	0	0
Stomatitis	2 (9.5)	0	0
Elevation of GOT/GPT	5 (24)	0	0
Elevation of creatinine	1 (4.8)	0	0
Hyperbilirubinemia	1 (4.8)		
Abdominal pain	2 (9.5)	1 (4.8)	0
Infection without neutropenia	2 (9.5)	1 (4.8)	0

GOT glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase

Response and survival

Partial response was achieved in 2 patients, and the disease remained stable in 9, with a response rate of 9.5% (95% CI, 0–22%) and a disease control rate of 52%. Eighteen patients had elevated serum levels of CA 19-9 (median/range, 1998/42-49420 U/mL) without jaundice before treatment. The CA 19-9 level after treatment decreased more than 50% in 5 (28%) of those 18 patients and showed a normal value in 2 (11%).

The median progression-free survival and the median survival time from the first day of S-1 therapy were 4.1 months (95% CI, 1.3–6.9 months) and 6.3 months (95% CI, 3.6–8.9 months), respectively (Fig. 1).

Discussion

There is no accepted second-line treatment for patients with advanced pancreatic cancer who do not respond to treatment with gemcitabine. This study evaluated the use of S-1, a novel oral fluoropyrimidine preparation. As first-line treatment for metastatic pancreatic cancer, S-1 has shown favorable efficacy in clinical trials, but the efficacy and safety of S-1 as a second-line therapy has not been fully evaluated as yet.

In the current study, S-1 showed a modest activity against gemcitabine-resistant pancreatic cancer, yielding a response rate of 9.5%. Although it is difficult to compare our results with those of other studies (Table 3) because of differences in patients' backgrounds, the response rate compares with that (15%) obtained in a previous phase II study of S-1 for gemcitabine-refractory metastatic pancreatic cancer reported by Morizane et al. [14]; and it was equivalent to that of other second-line regimens such as rubitecan (7%) [15], irinotecan (9%) [16], 5FU + celecoxib (12%) [17] or 5FU + paclitaxel (10%) [18]. On the other hand, the disease control rate (52%) of S-1 in the current study was relatively high and comparable to that observed in other active combination regimens for gemcitabine-resistant pancreatic cancer, such as gemcitabine + oxaliplatin (PR 22.6%, SD 38.7%) [19], 5FU + leucovorin + oxaliplatin (PR 23.3%, SD 30%) [20] or irinotecan + raltitrexed (PR 16%, SD 37%) [21]. The median survival time (6.3 months) in this study was also comparable to that (6–6.5 months) reported with other active combination regimens [19–21].

Most patients in the current study had some symptoms related to disease progression or prior chemotherapy at the study entry. It was often difficult to administer S-1 for 28 consecutive days because of tumor-related symptoms or toxicity. To improve therapeutic compliance, the 2-week administration regimen was adopted in ten patients (48%) based on the guidelines for dose modification, since this regimen was recently reported to be more feasible without changing dose intensity compared to the standard treatment schedule [13]. Hematological toxicity of S-1 was mild, and the occurrence of grade 3 or higher hematological toxicity seemed to be lower when compared to other combination regimens. The most common grade 3 non-hematological toxicity of second-line S-1 was anorexia (14%). In the current study, second-line chemotherapy with S-1 was feasible with acceptable toxicity in patients with gemcitabine-resistant advanced pancreatic cancer.

Although the response rate (9.5%) to S-1 in the current study was modest, we consider that the relatively high disease control rate, favorable survival data and toxicity profile may support the use of S-1 as second-line treatment. Furthermore, S-1 has the clinical advantage of being orally administered when compared with infusion regimens. Oral administration of S-1 reduces hospital visits for outpatients and has advantages in terms of quality of life. Considering the extremely poor prognosis of patients with gemcitabine-resistant pancreatic cancer, treatment should be more concerned with their quality of life.

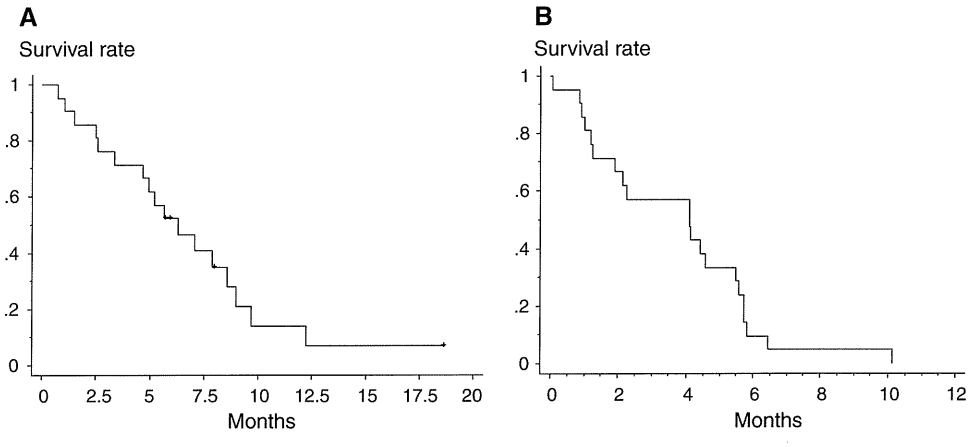

Fig. 1 Overall survival time curve (**a**) and progression-free survival (**b**) from the first day of S-1 therapy

Table 3 Clinical trials in patients with gemcitabine-pretreated advanced pancreatic cancer

Treatment	Number of patients	Response rate (%)	Disease control rate (%)	Progression-free survival	Median overall survival
Oxaliplatin	18	0	16.7	2 months	N/A
Capecitabine	39	0	39	2.3 months	7.6 months
Rubitecan	58	7	23	59 days	92 days
Irinotecan	33	9	48	2 months	6.6 months
S-1	40	15	58	2 months	4.5 months
Oxaliplatin + 5FU + leucovorin	30	23.3	53.3	22 weeks	25 weeks
Xelox (oxaliplatin + capecitabine)	41	2.6	28	9.9 weeks	23 weeks
FDR-GEM + oxaliplatin	33	22.6	61	4.2 months	6 months
5FU + celecoxib	17	12	24	8 weeks	15 weeks
5FU + paclitaxel	28	10	30	2.5 months	7.6 months
Docetaxel + gefitinib	41	2.4	49	1.8 months	4.5 months
Irinotecan + raltitrexed	19	16	53	4 months	6.5 months

FDR fixed dose rate, *N/A* not available

In conclusion, this study has shown that second-line chemotherapy with S-1 is tolerated with acceptable toxicity, and yields a relatively high disease control rate in patients with gemcitabine-resistant pancreatic cancer. As an oral agent, S-1 is a feasible treatment option considering QOL. Our data warrant further studies regarding second-line treatment using S-1 after gemcitabine failure.

Conflicts of interest statement No financial support for this study was provided. The authors report no conflicts of interest.

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CLINICAL INVESTIGATION **Pancreas**

PHASE II STUDY OF ORAL S-1 AND CONCURRENT RADIOTHERAPY IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED PANCREATIC CANCER

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Purpose: S-1 is an oral fluoropyrimidine derivative that has demonstrated favorable antitumor activity in patients with metastatic pancreatic cancer. The aim of this study was to evaluate safety and efficacy of S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer.

Methods and Materials: Patients with histopathologically proven, unresectable, locally advanced pancreatic cancer were eligible. Radiotherapy was delivered in 1.8 Gy daily fractions to a total dose of 50.4 Gy over 5.5 weeks. S-1 was administered orally twice a day at a dose of 80 mg/m^2/day from day 1 to 14 and 22 to 35. Two weeks after the completion of chemoradiotherapy, maintenance chemotherapy with S-1 was administered for 28 days every 6 weeks until progression.

Results: Thirty-four patients were enrolled in this study. The most common Grade 3 toxicities during chemoradiotherapy were anorexia (24%) and nausea (12%). The overall response rate was 41% (95% confidence interval, 25%–58%) and overall disease control rate (partial response plus stable disease) was 97%. More than 50% decrease in serum CA 19-9 was seen in 27 of 29 evaluable patients (93%). The median progression-free survival was 8.7 months. The median overall survival and 1-year survival rate were 16.8 months and 70.6%, respectively.

Conclusions: Oral S-1 and concurrent radiotherapy exerted a promising antitumor activity with acceptable toxicity in patients with locally advanced pancreatic cancer. This combination therapy seems to be an attractive alternative to conventional chemoradiotherapy using 5-fluorouracil infusion. © **2011 Elsevier Inc.**

Pancreatic cancer, S-1, Radiotherapy, Phase II study.

INTRODUCTION

Radiotherapy combined with 5-fluorouracil (5-FU) has been the mainstay in the treatment of locally advanced, unresectable pancreatic cancer on the basis of previous randomized trials (1–3). However, prognosis remains poor, with a reported median survival time of only approximately 10 months. Distant metastases were the main cause of treatment failure after chemoradiotherapy with 5-FU (4). Although the potent radiosensitizing property of 5-FU is the rationale for chemoradiotherapy using 5-FU, this therapy is unlikely to be effective against systemic metastases of pancreatic cancer. A more effective systemic treatment might be essential to control distant metastases and subsequently prolong patient survival.

S-1 is a novel oral fluoropyrimidine preparation that was designed to improve the antitumor activity of 5-FU while reducing gastrointestinal toxicity. In S-1, tegafur is combined with 5-chloro-2, 4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a 1:0.4:1 molar concentration ratio (5). Generally, when administered intravenously, more than 85% of 5-FU is rapidly catabolized by dihydropyrimidine dehydrogenase (DPD) (6). Gimeracil is a competitive inhibitor of DPD and 180 times more potent than uracil, which is the DPD inhibitor included in UFT; thus, an effective concentration of 5-FU is maintained both in plasma and tumor tissues (7). Oteracil inhibits the phosphorylation of 5-FU in the gut and thereby reduces the gastrointestinal toxicity of 5-FU (8).

Recently, S-1 has shown favorable antitumor activity in several Phase II studies for various solid tumors including

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pancreatic cancer. In a recent Phase II study of S-1 for metastatic pancreatic cancer, S-1 demonstrated promising antitumor activity with a response rate of 37.5% and median survival time of 9.2 months (9). Furthermore combination chemotherapy with S-1 and gemcitabine has shown excellent efficacy with a response rate of 44%–48% and a median survival of 10.1–12.5 months in patients with metastatic pancreatic cancer (10, 11). S-1 is regarded as a promising agent for the management of unresectable advanced pancreatic cancer (12), and a randomized Phase III study is ongoing to evaluate the efficacy of S-1 versus gemcitabine vs. S-1 plus gemcitabine.

Although no randomized trials have been performed, the antitumor activity of S-1 for metastatic pancreatic cancer seems to be better than that of 5-FU infusion, which has been used to treat locally advanced pancreatic cancer. Oral S-1 also has a great clinical advantage because the risks of complications associated with intravenous administration are avoided. Moreover, a recent preclinical study has shown that gimeracil, the DPD inhibitor included in S-1, is a potent radiosensitizer (13). Preclinical studies showed that S-1 and fractionated radiotherapy was more effective than either agent alone (14).

We considered oral S-1 to be an attractive alternative to 5-FU infusion in the treatment of locally advanced pancreatic cancer and performed a Phase I study (15). In that study, we suggested that the daily dose of S-1 recommended for systemic chemotherapy could be combined with the conventional dose radiotherapy with acceptable toxicity. This combination therapy was well tolerated and showed outstanding antitumor effect. Thus, we planned a Phase II study to further evaluate the safety and efficacy of S-1 combined with radiotherapy in patients with unresectable locally advanced pancreatic cancer.

METHODS AND MATERIALS

Eligibility

Patients with histopathologically proven, unresectable, locally advanced adenocarcinoma of the pancreas were eligible for this study. Computed tomography (CT) criteria for unresectability was defined as invasion of the superior mesenteric artery or celiac axis or the bilateral stenosis of the portal vein. Patients with distant metastases were excluded. Eligible patients were at least 20 years old with an Eastern Cooperative Oncology Group performance status of $\leq$2 and had adequate organ function (leukocytes $\geq$4000/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.5 g/dL, normal serum creatinine and blood urea nitrogen, a serum glutamic oxaloacetic transaminase (GOT) $\leq$2.5 times the upper normal limit (UNL), a serum glutamic pyruvic transaminase (GPT) $\leq$ 2.5 times the UNL and serum bilirubin $\leq$ 2.0 mg/dL.) Patients with jaundice caused by biliary obstruction were required to have a total bilirubin concentration of 3.0 mg/dL or less after biliary drainage.

Patients were excluded if they had received systemic therapy or radiotherapy, had a concomitant malignancy, active inflammatory bowel disease, active gastric/duodenal ulcer, active infection, severe heart disease, mental disorder, or other severe concurrent disease. Pregnant or lactating women were also excluded.

This prospective Phase II study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000, and the protocol was approved by the Institutional Review Board of Chiba Cancer Center and Chiba University Graduate School of Medicine. All patients gave their written informed consent before entry into this study.

Treatment

Radiotherapy was initiated on Day 1 of the study using 10-MV photons. A fractional daily dose of 1.8 Gy (5 days/week) at the isocenter, up to a total dose of 50.4 Gy, was prescribed. Treatment planning was performed using a CT simulator for all patients. CT images were acquired using a 3-mm-slice thickness with free breathing. The dose distribution and dose–0volume histogram were calculated with a three-dimensional (3D) treatment planning system. The gross tumor volume was taken to be the primary tumor and metastatic lymph nodes identifiable on CT scan. The clinical target volume was defined as the gross tumor volume plus a 0.5-cm margin and the planning target volume was defined as the clinical target volume plus 1–1.5 cm for daily patient setup variation. No prophylactic nodal irradiation was performed. The clinical target volume was encompassed within the 95% isodose line. To avoid renal toxicity, we allowed a maximum of 50% of both kidneys to be exposed to 20 Gy. The dose to the liver was limited to 50% of the volume receiving <30 Gy. Radiation to the spinal cord was limited to 40 Gy.

S-1 (Taiho Pharmaceutical, Tokyo, Japan) was administered orally twice a day at a dose of 80mg/m^2/day from Day 1–14 and 22–35 in concurrent with radiotherapy. 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 $\leq$ BSA < 1.50 m^2, 100 mg/day; and 1.50 m^2 $\leq$ BSA, 120 mg/day. Two weeks after the completion of chemoradiotherapy, maintenance chemotherapy with S-1 was administered for 28 days every 6 weeks until progression.

Dose modification

S-1 was temporally discontinued until recovery when any of the following conditions were encountered: leukocytes <2,000/mm^3, neutrophils <1,000/mm^3, hemoglobin <8.0 g/dL, platelets <75,000/mm^3, serum GOT/GPT $\geq$150 IU/L, serum total bilirubin $\geq$3.0 mg/dL, serum creatinine $\geq$1.5 mg/dL, or when Grade 3 nonhematologic toxicity was observed. The dose of S-1 was reduced by 20 mg/day if Grade 4 hematologic toxicity or Grade 3 nonhematologic toxicity occurred. Radiation therapy was withheld when Grade 4 hematologic or Grade 3 nonhematologic toxicity occurred, until resolution of the toxicities.

Pretreatment and follow-up evaluation

The pretreatment evaluation included a medical history and physical examination, complete blood cell counts, routine chemistry tests, electrocardiogram, chest X-ray, ultrasonography, and CT of the abdomen and chest with intravenous contrast.

Physical examination, complete blood cell counts and serum biochemistry tests were performed at least weekly during chemoradiotherapy. Upper gastrointestinal endoscopy was performed before study entry and within 2 weeks after completing treatment to evaluate acute gastrointestinal toxicities. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Follow-up CT was performed at the completion of radiotherapy, and then repeated every 2 months. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors by three independent radiologists. The best overall response was recorded for each patient. The overall response rate was defined as the percentage of patients achieving either complete response (CR) or partial response (PR). Disease control rate was defined as

the proportion of patients who achieved CR, PR, or stable disease (SD) as the best overall response. Serum CA 19-9 levels were evaluated monthly using a commercially available chemiluminescent enzyme immunoassay kit based on the two-step sandwich method (CL-EIA). A value of 39.5 U/mL was defined as the upper normal limit. Progression-free survival and overall survival were calculated from the first day of treatment.

Statistical analysis

The primary objective of this study was to evaluate the response rate of S-1 concurrent with radiotherapy in patients with locally advanced pancreatic cancer. The secondary objectives were to evaluate toxicity, progression-free survival, and overall survival.

The number of patients required for the study was calculated according to the optimal two-stage design. The threshold response rate and expected response rate were 10% and 30%, respectively. The sample size was 29 patients with a type I error of 5% and a test power of 80%.

An intent-to-treat analysis was performed for all included patients. Time-related parameters were analyzed using Kaplan–Meier method.

RESULTS

Patient characteristics

Thirty-four patients from two institutions were enrolled in this study between September 2004 and July 2008 (Fig. 1). The characteristics of the eligible patients are summarized in Table 1. Eighteen of the patients were men and 16 were women, with a median age of 63 years. Most patients (82%) had an Eastern Cooperative Oncology Group performance status of 0 or 1. The most common tumor site was the pancreatic head (59%), with a median tumor size of 3.9 cm.

Twenty-nine patients (85%) completed the planned chemoradiotherapy without a dose reduction of S-1 or radiation. Four patients required a dose reduction of S-1 because of adverse events: Grade 4 neutropenia in one patient, nausea, and anorexia in one patient, skin rash in one, and urinary tract infection in one patient. The remaining patient discontinued the protocol treatment because of withdrawal of consent.

Thirty-three patients (97%) received maintenance chemotherapy with S-1 after chemoradiotherapy, for a total of 173 cycles (median, 4; range, 0–16). When tumor progressed, most patients (28/31, 90%) received a second-line treatment with gemcitabine.

Toxicity

All treated patients (n = 34) were assessed for toxicities. Toxicity during chemoradiotherapy is listed in Table 2. Hematologic toxicity was relatively mild, and the most common Grade 3 toxicity was anorexia (24%). Other Grade 3 or 4 nonhematologic toxicities included nausea (12%), skin rash (3%), and urinary tract infection (3%). There was no life-threatening toxicity, and no treatment-related deaths occurred. We performed upper gastrointestinal endoscopy after the combination therapy in 29 patients: 6 had gastric or duodenal ulcers and 17 had gastritis or duodenitis. Most of these patients had few symptoms except for anorexia and recovered with medical treatment. No Grade 3 or 4 gastrointestinal ulcers were observed.

Grade 3 or 4 toxicity during maintenance chemotherapy is summarized in Table 3. The most common Grade 3 or 4 toxicity was anemia. Grade 3 nonhematologic toxicities were observed in five patients: hemorrhagic gastritis in three, acute cholecystitis in one, and liver abscess in one. Although one of the three patients who experienced hemorrhagic gastritis recovered with conservative treatment, the remaining two patients required endoscopic hemostasis. The patient who experienced acute cholecystitis 12 months after radiotherapy required surgical treatment and 2 months' hospitalization. The patient who developed a liver abscess 12 months after chemoradiotherapy recovered with conservative treatment.

Response and survival

All treated patients (n = 34) were evaluable for tumor response. At the initial evaluation immediately after chemoradiotherapy, partial response was seen in four patients (12%). Stable disease was seen in 29 patients, and progressive disease in only one patient (3%). Subsequently, 10 additional patients with stable disease at the initial evaluation achieved partial response during maintenance chemotherapy. Thus, 14 (41%) of the 34 patients (95% confidence interval [CI], 25%–58%) showed partial response during the follow-up period. Disease control rate (partial response plus stable disease) was 97% (33/34).

Twenty-nine patients had elevated CA 19-9 levels (median, 1008; range, 83–7184 U/mL) without jaundice before treatment. The minimal CA 19-9 level after treatment (median, 52; / range, 3–4,140 U/mL) decreased more than 50% in 27 (93%) of these 29 patients and showed a normal value in 13 (45%).

At the time of analysis, disease progression was noted in 31 patients. The pattern of initial disease progression was distant metastases in 13 patients (38%), local progression of the pancreatic tumor in 9 (26%), both in 6 (18%), and deterioration of general condition in 3 patients (9%; Table 4). Among the patients, regional lymph nodes recurrence was seen in two patients. Both patients had concurrent distant metastases. The median progression-free survival was 8.7 months (95% CI, 7.0–10.4 months). The median survival time and 1-year survival rate were 16.8 months (95% CI, 12.9–20.7 months) and 70.6% (95% CI, 55.3%–85.9%), respectively (Fig. 2).

DISCUSSION

Chemoradiotherapy using 5-FU has been the mainstay treatment for unresectable, locally advanced pancreatic cancer. We used S-1 instead of 5-FU infusion, in combination with radiotherapy, because of its favorable antitumor activity against metastatic pancreatic cancer and convenient oral administration. In our protocol, the standard daily dose of S-1 for systemic chemotherapy was combined with concurrent radiotherapy based on our Phase I study (15). Maintenance chemotherapy with S-1 was administered to delay or reduce the development of distant metastases in responding or stable patients after S-1 and radiotherapy. In addition, second-line chemotherapy with gemcitabine was delivered in most cases after treatment failure. The rationale of our protocol was to

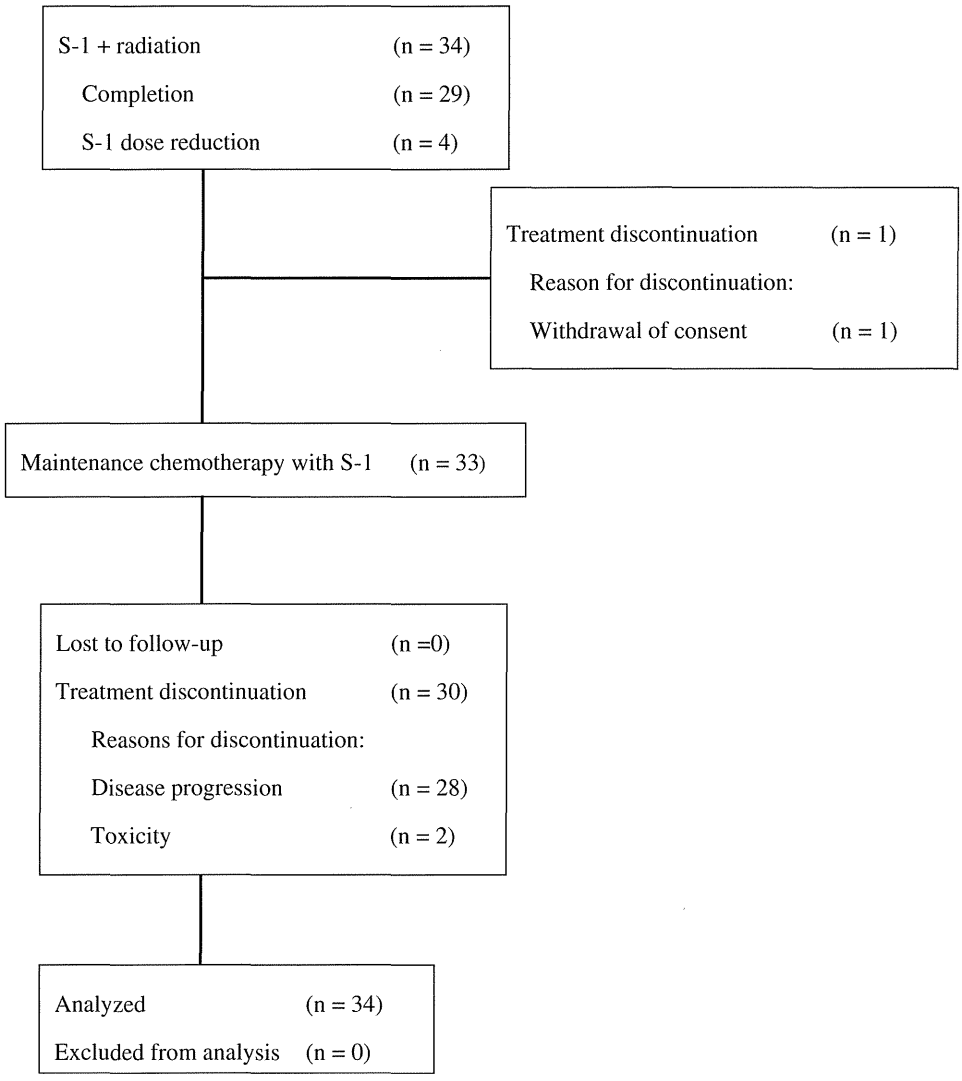

Fig. 1. Study schema.

intensify systemic activity while maintaining the patient's quality of life by using an oral anticancer agent.

To date, there is little information on the safety and efficacy of this combination therapy not only in patients with pancreatic cancer, but in those with other types of tumors as well. In this study, S-1 at the dose recommended for systemic chemotherapy and the standard dose of radiotherapy were well tolerated and feasible in patients with locally advanced pancreatic cancer. The most common toxicity during chemoradiotherapy was anorexia, with Grade 3 toxicity occurring in 24% of the patients. Hematologic toxicity was relatively mild. No life-threatening toxicity was experienced. We performed upper gastrointestinal endoscopy after chemoradiotherapy to assess acute gastrointestinal toxicity but did not detect Grade 3 or 4 ulcers. As for radiation late toxicity, hemorrhagic gastritis was considered to require special attention. Acute cholecystitis and liver abcess were considered to be caused mainly by biliary stent occlusion.

Table 1. Patient characteristics

No. of patients	34
Sex	
Men	18
Women	16
Age, years	
Median (range)	63 (42–78)
ECOG performance status	
0	9
1	19
2	6
Site of tumor	
Head	20
Body-tail	14
Largest dimension, cm	
Median (range)	3.9 (2.9–6.6)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

In this study, S-1 combined with radiotherapy showed promising antitumor effect in patients with locally advanced pancreatic cancer. Although it is difficult to compare our results with those of other studies, the response rate of 41%, the disease control rate of 97%, the CA 19-9 response rate of 93% and the median survival time of 16.8 months compare well with the outcomes of other chemoradiotherapy regimens (Table 5) (4, 16–20). One possible explanation for these

Table 2. Toxicity during chemoradiation (n = 34)

Toxicity	Grade 1 or 2	Grade 3	Grade 4
Hematological toxicity			
Leukocytopenia	26	3	0
Neutropenia	15	2	1
Anemia	15	0	0
Thrombocytopenia	21	1	0
Nonhematological toxicity			
Anorexia	19	8	0
Nausea	18	4	0
Vomiting	7	0	0
Diarrhea	5	0	0
Elevation of GOT/GPT	11	0	0
Elevation of creatinine	1	0	0
Skin rash	7	1	0
Urinary tract infection	0	1	0
Gastric/duodenal ulcer*	6	0	0
Gastritis/duodenitis*	17	0	0
GI hemorrhage	0	0	0

Abbreviations: GI = gastrointestinal; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

* Twenty-nine patients received GI endoscopy after chemoradiotherapy.

promising results, we suppose, may be the use of an agent that has demonstrated high response rate for metastatic pancreatic cancer from the beginning of radiotherapy. Indeed, only one patient developed distant metastases at the initial evaluation after chemoradiotherapy. In addition, it also seemed important that the compliance of our regimen was relatively good because of the acceptable toxicity profile and convenient oral administration of S-1. As a result, most patients received the planned chemoradiotherapy and following maintenance chemotherapy. Moreover, 90% of the patients received second-line chemotherapy with gemcitabine after treatment failure.

In this study, to reduce toxicity and improve therapeutic compliance, radiotherapy was performed using 3D treatment planning without conducting prophylactic nodal irradiation. The clinical target volume (CTV) of conventional chemoradiotherapy for pancreatic cancer usually includes the regional lymph nodes irrespective of the presence or absence of nodal metastases, which may result in severe gastrointestinal toxicity and limit the delivery of the prescribed dose of radiotherapy or following maintenance chemotherapy. In an attempt to reduce toxicity and combine radiotherapy with full-dose gemcitabine, McGinn *et al.* (21) investigated the usefulness of 3D conformal radiotherapy not including prophylactic nodal irradiation. Our group has also reported the feasibility of involved-field irradiation with a 15-20 mm margin where only the primary tumor and clinically enlarged lymph nodes were included in the CTV without using prophylactic nodal irradiation (22). The rationale for reducing the irradiation field size is to reduce radiation toxicity and subsequently to deliver sufficient systemic chemotherapy. In this study, as described earlier, severe acute gastrointestinal mucositis was rare and treatment compliance was satisfactory. Locoregional lymph nodes recurrence was seen in only two patients, and we therefore suggest that the reduction of the radiation field size did not result in excess locoregional failure.

To date, in an attempt to prolong the survival of patients with locally advanced pancreatic cancer, many studies using novel agents such as gemcitabine (16, 17), capecitabine (18), paclitaxel (19), oxaliplatin (20), or bevacizumab (23), as well

Table 3. Grade 3–4 toxicity during maintenance chemotherapy (n = 33)

Toxicity	Grade 3	Grade 4
Leukocytopenia	2	0
Neutropenia	3	0
Anemia	2	2
Thrombocytopenia	0	0
Anorexia	1	0
Nausea/vomiting	0	0
Diarrhea	0	0
Elevation of GOT/GPT	0	0
Skin rash	0	0
Hemorrhagic gastritis	3	0
Acute cholecystitis	0	1
Liver abscess	1	0

Abbreviations: GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

Table 4. Patterns of initial disease progression (n = 34)

	No. of patients (%)
None	3 (9%)
Distant metastases	13 (38%)
Liver	3
Peritoneum	4
Liver and peritoneum	1
Lung	2
Pleura	2
Bone	1
Local progression of the pancreatic tumor	9 (26%)
Local progression of the pancreatic tumor and distant metastases	6 (18%)
Liver	1
Peritoneum	4
Lung	1
Deterioration of general condition	3 (9%)

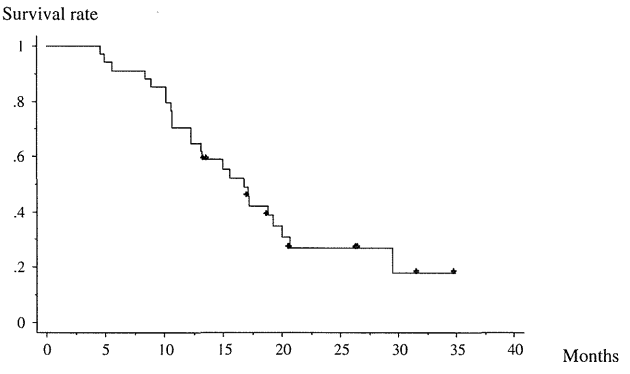

Fig. 2. Kaplan–Meier overall survival.

Table 5. Clinical trials involving patients with locally advanced pancreatic cancer

Author	Chemotherapy	RT	Response rate (CR + PR)	Disease control rate (CR + PR + SD)	CA 19-9 response	MST (months)	1-year survival
Ishii (4)	5-FU	50.4 Gy	10%	90%	83%	10.3	41.8%
Saif (18)	Capecitabine	50.4 Gy	20%	85%	No data	17.2	58%
Moureau-Zabotto (20)	5-FU+oxaliplatin	55 Gy	26%	62%	No data	12.2	52.1%
Okusaka (16)	GEM 250 mg/m^2/w	50.4 Gy	21%	83%	76%	9.5	28%
Small (17)	GEM 1,000 mg/m^2/w	36 Gy	5.1%	84.6%	No data	No data	73%

Abbreviations: CR = complete response; GEM = gemcitabine; MST = median survival time; PR = partial response; RT = radiation therapy; SD = stable disease; w = week.

as modified radiotherapy approaches such as hyperfractionated (24) or intensity-modulated radiation therapy (25) have been conducted. Especially, gemcitabine-based chemoradiotherapy has been investigated in many studies because this agent has shown significant survival benefit compared with 5-FU in patients with metastatic pancreatic cancer. However, the combination of gemcitabine and radiotherapy is often related with severe toxicity, and therefore, Phase I studies have indicated the need to reduce the dose of gemcitabine when combined with standard-dose radiotherapy (26, 27). No regimens have achieved survival benefit over conventional chemoradiotherapy with 5-FU infusion.

On the other hand, in recent clinical trials, the feasibility of chemoradiotherapy using oral fluoropyrimidines such as UFT or capecitabine instead of 5-FU infusion has been reported for various solid tumors, including pancreatic cancer (18, 28). Capecitabine is an oral fluoropyrimidine carbamate that was designed to generate 5-FU preferentially at the tumor site. Tumor-selective generation of 5-FU could potentially improve the therapeutic ratio for capecitabine. To achieve tumor selectivity, capecitabine was designed to exploit the high concentrations of thymidine phosphorylase in the tumor compared with normal tissues (29, 30). Saif et al. (18) conducted a Phase II study of capecitabine and radiotherapy in patients with locally advanced pancreatic cancer. Twenty patients were treated with 50.4 Gy of radiotherapy and capecitabine, with a response rate of 20% and a 1-year survival rate of 58%. The authors emphasized the convenience and safety of oral administration. Oral administration is more convenient for patients than infusion regimens, and it avoids the risks of complications associated with intravenous administration. Considering the poor prognosis of patients with locally advanced pancreatic cancer, this approach seems to be an important option in terms of patients' quality of life.

In this treatment strategy, S-1 is an attractive candidate because it showed favorable antitumor effect in metastatic pancreatic cancer. To date, three Phase I studies of S-1 and concurrent radiotherapy in locally advanced pancreatic cancer have been reported including our regimen (15, 31, 32). Ikeda *et al.* (31) reported that the recommended dose of S-1 with concurrent radiotherapy (50.4 Gy in 28 fractions) was 80 mg/m^2/day on the day of irradiation. Shinchi *et al.* (32) investigated a regimen of S-1 and concurrent radiotherapy at a total dose of 50 Gy per 40 fractions for 4 weeks, and the recommended dose of S-1 was 80 mg/m^2/day given on Days 1–21. However, the efficacy and safety of this combination have not been fully evaluated in Phase II trials. Although the current Phase II study involved a small number of patients, the safety and efficacy results are promising. Recently, Kim *et al.* conducted a Phase II study, in which 25 patients were treated with S-1 and concurrent radiotherapy using a similar dose and schedule to those recommended in our Phase I study. In that study, this combination had a low toxicity profile and showed favorable efficacy with a response rate of 24% and a median survival of 12.9 months. The main difference between Kim's study and our Phase II study lies in maintenance chemotherapy. In Kim's study, 75% of the patients received gemcitabine-based chemotherapy after completion of radiotherapy, whereas most patients received maintenance chemotherapy using S-1 (97%) and salvage chemotherapy using gemcitabine (90%) in our study.

In summary, this study showed that oral S-1 at the dose recommended for systemic chemotherapy plus concurrent radiotherapy exerted a promising antitumor activity with acceptable toxicity in patients with locally advanced pancreatic cancer. S-1 has a great clinical advantage of oral administration, and thus this combination therapy is attractive alternative to conventional chemoradiotherapy using 5-FU infusion. This regimen should be further studied and its survival benefit in comparison with gemcitabine monotherapy or conventional chemoradiotherapy using 5FU infusion needs to be confirmed in a randomized controlled trial.

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膵・胆道癌薬物療法：臨床試験を読む！—最新の動向と実地診療へのインパクト—

膵・胆道癌化学療法の動向—臨床試験の読み方

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要約：膵・胆道癌に対する化学療法は，これまでゲムシタビンを中心に第Ⅲ相試験が実施され，標準治療が確立してきた。切除不能膵癌において，海外ではゲムシタビン＋エルロチニブ併用療法およびFOLFIRINOXにおいて，ゲムシタビン単独療法に比べ有意な生存期間の延長が得られ，一般臨床で用いられている。また，最近では，ゲムシタビン＋ナブパクリタキセル併用療法の有用性が報告されたところである。我が国では日本と台湾で実施されたゲムシタビン，S-1，ゲムシタビン＋S-1併用療法の大規模な第Ⅲ相試験の結果，ゲムシタビンに対するS-1の非劣性が証明され，S-1も標準治療のひとつと位置付けられている。膵癌の術後補助療法もゲムシタビンが標準治療として用いられているが，最近我が国で行われたS-1とゲムシタビンによる第Ⅲ相試験の結果，S-1が新たな標準治療と位置付けられつつある。切除不能胆道癌では，ゲムシタビン＋シスプラチン併用療法がゲムシタビンとの比較試験の結果，標準治療として国際的にも認知されている。膵神経内分泌癌は希少疾患であり，大規模な臨床試験が難しく，これまで有効な薬剤がなかったが，エベロリムスおよびスニチニブが相次いでプラセボ対照第Ⅲ相試験において有意な無増悪生存期間の延長を示し，保険適用に承認されている。これらの標準治療の確立には質の高い臨床試験の実施が必要である。臨床試験の結果を十分理解した上で実地診療への適応が求められる。

Key words：膵癌，胆道癌，化学療法，術後補助療法

はじめに

膵・胆道癌は，切除例と非切除例を合わせた5年生存率がそれぞれ，5～10%，20～30%と極めて予後不良の疾患である。これらの疾患は従来，化学療法抵抗性の癌腫とされていたが，ゲムシタビン（GEM）を始めとして効果の実感できる薬剤が登場し，さらにさまざまな新規薬剤やレジメンが試みられてきている。現在，膵・胆道癌の標準化学療法は，切除不能例だけでなく術後補助療法を含め，GEM単独療法から新しい治療法に変わりつつある。

実地診療においては，臨床試験の結果に基づいて設定された標準治療を適応していくことが求められるが，臨床試験の結果は厳格な選択基準により設定された限られた症例によるものである。臨床試験の目的や対象も治療法に応じて異なり，標準治療をそのまますべての症例に適応できるものではない。治療選択を適切に行うには臨床試験を十分理解し，解釈した上で決定していくことが重要である。本項では膵・胆道癌における化学療法の最近の動向と，臨床試験を理解する上でのポイントを概説する。

Update of Chemotherapy for Biliary Tract and Pancreatic Cancer
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Ⅰ．膵　癌

1．切除不能膵癌に対する化学療法

5-FUとの比較試験の結果，GEMの有効性が確認されて以来[1)]，GEMと新規治療法の比較試験が欧米を中心に数多く行われてきた。その中でGEM＋エルロチニブ併用療法（GE療法）が唯一，統計学的に有意な生存期間の延長を示し，標準治療のひとつとして位置

表 1 膵・胆道癌における主な比較試験

試験	対象	新規治療	参照治療	試験デザイン	主要評価項目
5-FU vs. ゲムシタビン	切除不能膵癌	ゲムシタビン	5-FU	第Ⅲ相試験	臨床症状の改善
PA.3	切除不能膵癌	ゲムシタビン＋エルロチニブ	ゲムシタビン	第Ⅲ相試験	全生存期間
GEST	切除不能膵癌	S-1	ゲムシタビン	第Ⅲ相試験（非劣性試験）	全生存期間
		ゲムシタビン＋S-1	ゲムシタビン	第Ⅲ相試験	全生存期間
Prodige 4/ACCORD11	転移を伴う膵癌	FOLFIRINOX	ゲムシタビン	第Ⅲ相試験	全生存期間
MPACT	転移を伴う膵癌	ゲムシタビン＋ナブパクリタキセル	ゲムシタビン	第Ⅲ相試験	全生存期間
CONKO-01	術後補助療法	手術＋ゲムシタビン	手術単独	第Ⅲ相試験	無病生存期間
ESPAC-03	術後補助療法	手術＋ゲムシタビン	手術＋5-FU/ FA	第Ⅲ相試験	全生存期間
JSAP-02	術後補助療法	手術＋ゲムシタビン	手術単独	第Ⅲ相試験	全生存期間
JASPAC-01	術後補助療法	手術＋S-1	手術＋ゲムシタビン	第Ⅲ相試験（非劣性試験）	全生存期間
RADIANT-3	切除不能膵神経内分泌腫瘍	エベロリムス	プラセボ	第Ⅲ相試験	無増悪生存期間
	切除不能膵神経内分泌腫瘍	スニチニブ	プラセボ	第Ⅲ相試験	無増悪生存期間
ABC-02	切除不能胆道癌	ゲムシタビン＋シスプラチン	ゲムシタビン	第Ⅲ相試験	全生存期間
BT-22	切除不能胆道癌	ゲムシタビン＋シスプラチン	ゲムシタビン	ランダム化比較試験	全生存期間
JCOG0805	切除不能胆道癌	ゲムシタビン＋S-1	S-1	ランダム化第Ⅱ相試験	全生存期間

づけられた[2]。我が国ではGEMの第Ⅰ相試験が行われ[3]，2001年保険適用に承認されている。その後，S-1の第Ⅱ相試験により2006年適用が承認され[4]，さらにGEM＋S-1併用療法（GS療法）が有望な治療として期待されていた（表1）[5]。

GEM，S-1，GS療法の3群による第Ⅲ相試験（GEST試験）は日本と台湾の共同試験として実施された大規模なランダム化比較試験である。S-1単独治療とGS療法はいずれも単アームの第Ⅱ相試験の成績であり，大規模な比較試験による検証が求められていた。GEST試験は，標準治療GEM対し，経口薬の簡便性からS-1の非劣性とGS療法の優越性をそれぞれ検証する目的で計画された。すなわち，主要評価項目をOSとし，OS中央値がGEM群7.5ヵ月に対してS-1群8.0ヵ月（ハザード比≦1.33），GS群10.5ヵ月（ハザード比0.71）と仮説が設定された。その結果，S-1はハザード比の上限が1.18と非劣性が証明されたが，GS療法はGEMに対する優越性は示されなかった[6]。有害事象は，GEMでは骨髄抑制，ALT，AST上昇，間質性肺炎が比較的高率であったのに対し，S-1では食欲低下，疲労，下痢が目立ち，GS療法では骨髄抑制，発熱性好中球減少，悪心・嘔吐，下痢，皮疹などが他に比べて高頻度と，それぞれ特徴がみられた。これらより，S-1はGEMに並んで生存期間に関するエビデンスが確立したことから，我が国の切除不能膵癌に対する標準治療の一つと位置づけられている。一方，GS療法ではGEMに対する優越性が示されなかったことから，標準治療としての位置づけは難しいものと考えられている。

海外では，GEM＋エルロチニブ併用療法（GE療法）がGEM単独治療に比べ初めて有意な生存期間の延長を示した。しかし，GEM単独のOS中央値5.9ヵ月に対し，GE療法のOS中央値は6.4ヵ月とその差はわずかであり，間質性肺炎など重篤な有害事象も報告された[2]。つまり，コストや副作用を考慮するとそのままGEMに完全に置き換わる標準治療として受け入れられておらず，選択肢の一つとなっている。我が国では，間質性肺炎のリスクが懸念され，106例という多数例での第Ⅱ相試験が行われ，8.5％と高率に間質性肺炎の合併が報告された[7]。幸い死亡例はなく，厳しい施設要件と間質性肺炎に対する対応を行うことで，2011年，保険適用が承認された。以上の臨床試験から，現在我が国における切除不能膵癌に対する標準治療はGEM単独，S-1単独，GE療法の三つが同様のエビデンスレベルで推奨されている。

2010年以降，GEM単独治療に対し，有意な生存期間の延長を示した治療法が二つ報告された。ひとつはフランスで行われたFOLFIRINOX療法であり，大腸癌で用いられているFOLFOXとFOLFIRIを併せた強力な治療法である。GEM単独のOS中央値6.8ヵ月に対し，FOLFIRINOX療法のOS中央値は11.1ヵ月，ハザード比0.57（95%信頼区間0.45～0.73；$P<0.001$）と大きな差をつけて生存期間の延長が得られている[8]。しかし，骨髄抑制，発熱性好中球減少，下痢，末梢神経障害など毒性も強く，modified FOLFIRINOXも検討されつつある。もう一つはGEM＋ナブパクリタキセル併用療法であり，861例という大規模な第Ⅲ相試験が行われ，ナブパクリタキセル併用群で有意な生存期間の延長が報告された[9]。この試験でのOS中央値はGEM単独群6.7ヵ月に対し，ナブパクリタキセル併用群8.5ヵ月ハザード比0.72（95%信頼区間0.617～0.835；$P=0.000015$）と，有意な差が得られたが，FOLFIRINOX療法に比べるとやや劣る印象がある。骨髄抑制，下痢，末梢神経障害が主な有害事象であるが，忍容性は高く，今後，FOLFIRINOX療法との使い分けも課題となっていくものと考えられる。これら二つの第Ⅲ相試験には日本は参加しておらず，オキサリプラチン，イリノテカンはもちろんナブパクリタキセルも膵癌に適用は承認されていない。現在，日本人での安全性と有効性を確認する治験が進められており，近い将来日本でも使えるようになるものと期待されている。

一方，膵癌に対する分子標的薬は数多くの新規薬剤が開発されているものの，エルロチニブ以降，全く結果が残せていない。分子標的薬の国際治験として，日本もアキシチニブ（血管内皮細胞増殖因子受容体VEGFR阻害薬）やガニツマブ（抗インスリン様成長因子-1型受容体IGF-1R抗体薬）などの国際第Ⅲ相試験に参加しているが，いずれもネガティブな結果となっている。

2．術後補助療法の動向

切除成績の向上を目指した取り組みは早くから行われ，とくに術後補助療法の臨床試験は数多く計画されてきた。GEMが切除不能例での標準治療となった後，ドイツを中心に実施されたGEMと切除手術単独との比較試験（CONKO-001試験）により[10]，GEMが標準的術後補助療法として確立した。我が国でも小規模ながらGEMを用いた比較試験（JSAP-02試験）が実施され，CONKO-001試験と同様の結果が得られている[11]。ヨーロッパを中心に日本も参加したGEMと5-FU/フォリン酸との比較試験（ESPAC-3試験）では，従来から行われていた5-FU/フォリン酸に比べGEMによる生存期間の改善は得られなかったと報告された[12]。しかし，重篤な有害事象の発生はGEMで有意に少なかったとされている。これらの3試験におけるGEM群のOS中央値は22.1～23.6ヵ月とほぼ同等の成績が得られており[10～12]，これらの結果から，現在術後補助療法としてはGEMが標準的治療法として汎用されている。

その後，GEMを参照治療とした大規模な比較試験がいくつか行われている。その中で，我が国で実施されたS-1とGEMとの比較試験（JASPAC-01試験）の結果が2013年1月公表され，大きな注目を集めた。本試験は，術後補助療法としてGEMに対するS-1の非劣性を検証する目的で実施されたが，全生存期間および無再発生存期間ともS-1群で有意に改善することが証明された[13]。この結果は中間解析によるものであるが，生存期間のハザード比が0.56と大きな差を認めており，今後，我が国の術後補助療法はS-1が中心となっていくものと考えられる。

現在，国内外でGEM＋S-1，GEM＋カペシタビン，FOLFIRINOXなどの術後補助療法の比較試験が行われており，さらに術前補助療法への関心も高まっている。今後，より有効な切除手術の補助療法の確立が期待される。

3．膵神経内分泌腫瘍

神経内分泌腫瘍（NET）は神経内分泌細胞から発生する腫瘍であり，人体のどの臓器からも発生しうる腫瘍である。とくに膵臓に発生したNETが膵神経内分泌腫瘍（P-NET）である。NETの病理組織学的分類はこれまで幾度か改訂されており，現在2010年WHO分類が用いられている。これによると，核分裂像数とKi-67指数から，NETのG1，G2と神経内分泌癌（NEC）に分類されている。NETは比較的進行が緩徐であるのに対し，NECは進行が速く，極めて予後不良である。また，切除や化学療法の適応など治療選択や化学療法の方法も異なる。NETでは最近，エベロリムスやスニチニブの分子標的薬が用いられるのに対し，NECに対する化学療法は小細胞肺癌に準じてシスプラチンとイリノテカンあるいはエトポシドの併用療法が用いられている。

P-NETに対する化学療法は，分子標的薬を用いたプラセボ対照第Ⅲ相試験の結果，大きく変わってきている。mTOR阻害薬のエベロリムス[15]と血管内皮細胞増殖因子受容体（VEGFR）や血小板由来増殖因子受容体（PDGFR）など複数の受容体を阻害するスニチニブ[16]の単独治療で，それぞれ有意に無増悪生存期間を延長させる結果が得られ，保険適用が承認されてい

る。また海外で以前から使用されていたストレプトゾシンも我が国で治験が実施され，一般臨床でも使用できる見込みが出てきている。

一方，ソマトスタチンアナログであるオクトレオタイドは以前より，P-NETを含む消化管ホルモン産生腫瘍の症状改善を目的とした適応に承認されていた[17,18]。その後，消化管NETを対象としてプラセボ対照第Ⅲ相試験が行われ，オクトレオタイド群で有意な無増悪期間の延長が得られている[19]。しかし，この試験にはP-NETは含まれておらず，非機能性P-NETへの保険適用は承認されていない。

Ⅱ．胆道癌

1．切除不能胆道癌に対する化学療法

これまで胆道癌に対して大規模な比較試験はもちろん，保険適用承認に向けた治験もほとんど行われず，20年以上にわたって有効性の確認された薬剤は全く開発されてこなかった。2000年以降，我が国で行われたGEMあるいはS-1の第Ⅱ相試験（治験）の結果から[20,21]，保険適用が承認されていたが，質の高い第Ⅲ相試験による標準治療の確立が望まれていた。

切除不能胆道癌に対する化学療法では，国内外ともGEMを基本薬剤とした併用療法が試みられ，GEM＋フッ化ピリミジン系薬剤，GEM＋プラチナ系薬剤などの第Ⅱ相試験が行われてきた。その中で，英国においてGEM単独療法とGEM＋シスプラチン（GC療法）の大規模なランダム化第Ⅲ相試験（ABC-02）によりGC療法の有意な生存期間の延長が得られ[22]，初めてエビデンスに基づく標準治療が確立した。また，我が国でも同じ治療レジメンを用いたGEM単独療法とGC療法のランダム化比較試験（BT-22試験）が実施され，ほぼ同様の治療成績が確認された[23]。これらの結果から，我が国でも，2012年2月，シスプラチンがGEMとの併用により胆道癌に適応が承認され，切除不能胆道癌に対する標準治療として用いられている。

2．胆道癌化学療法の今後の動向

切除不能胆道癌の1次治療ではS-1も第Ⅱ相試験で高い奏効率と生存期間が得られており，またGS療法も効果が期待されていた。そこで，S-1の位置づけを明らかにし，今後の第Ⅲ相試験を検討する目的で，S-1とGS療法のランダム化第Ⅱ相試験がJCOG試験として実施された（JCOG0805試験）。その結果，主要評価項目の1年生存割合はGS療法群52.9%，S-1群40.0%とGS療法が良好であり，OS中央値も12.5ヵ月とGC療法を上回る成績が得られている[24]。GS療法はGC療法に比べ，治療成績だけでなく，簡便性，悪心など消化器毒性が少ないなどの利点も期待され，現在，切除不能胆道癌に対するGS療法とGC療法による第Ⅲ相試験が開始されている（JCOG1113試験）。さらにGEM，S-1，シスプラチンの3剤併用も次の興味として試みられており，第Ⅰ相あるいは第Ⅱ相試験が進められている[25]。今後，3剤併用の強力な治療法の有効性が検証されていくものと考えられる。

一方，1次治療耐性後も治療継続が可能な患者も多くなってきているが，これまで2次治療として有用性が確認された薬剤は確立していない。胆道癌の組織を用いたバイオマーカーの検索も行われており，それに基づいた分子標的薬の開発が期待されている。

胆道癌では，これまで術後補助療法に関する大規模な臨床試験は行われておらず，術後補助療法の意義や有用性も確認されていなかった。我が国ではGEMによる術後補助療法の比較試験がすでに登録が終了し，結果待ちの状態である。また，膵癌で高い有効性が得られたS-1も試みる価値があり，第Ⅲ相試験が計画されている。海外では，英国でカペシタビンを用いた切除単独との比較試験が進められている。これらの試験から早急に胆道癌術後補助療法の確立が望まれる。

Ⅲ．臨床試験のポイント

臨床試験の結果を解釈する際には，まずその試験の目的や試験デザインを確認することが大切である。臨床試験は新たな治療開発，標準治療の確立を目的に行われるが，第Ⅰ相試験からⅡ相，Ⅲ相試験とその目的は異なる。第Ⅰ相試験は薬物動態や次相での推奨用量を決めるものであり，通常20～30例の少数例で実施される。第Ⅱ相試験は決定した推奨用量により，一定の疾患における有効性と安全性を探索的にみるものであり，それで標準治療が決まるものではない。治療の有用性を判断するには比較試験が求められるが，比較試験にはランダム化第Ⅱ相試験と第Ⅲ相試験があり，目的も意義も異なる。つまり，ランダム化第Ⅱ相試験はあくまでⅡ相試験であり，どちらの治療がより有望か，を探索的に調べるものであり，第Ⅲ相試験に続く予備的なものである。したがって，標準治療は最終的な検証試験である第Ⅲ相試験によって決められるべきものである。

第Ⅲ相試験は通常，優越性あるいは非劣性を検証することでデザインされる。新しい治療が毒性などの不利益があっても，リスク/ベネフィットバランスからみて，不利益を超えた有効性が得られれば，新しい標

準治療として受け入れられるものとして，優越性試験が組まれる。また，毒性が少なく，利便性や経済性などを含めた利点があれば，治療効果が一定以上劣らないという条件で標準治療としてよいという考え方が非劣性試験である。どの程度の優越性を見込むか，またどの程度の劣性を許容するか，新治療の効果や毒性などから総合的に考慮して，臨床的に妥当な仮説や検出率を決め，最終的な試験デザインが決定される。臨床試験を読み，解釈し，一般臨床への導入を検討する場合，これらの試験の背景や仮説，デザインが非常に重要であり，ポイントとなる。

臨床試験の結果に基づいて標準治療が確立し，一般診療で普及していく。しかし，臨床試験では厳格な適格規準に基づく患者選択の上で当該治療法の有用性が決定されている。その治療が一般臨床でどのように使いうるかどうかは，その臨床試験ではどんな患者を対象にしていたかを十分検証することが重要である。試験結果はあくまで適格規準に合致した患者での有効性ということであり，そこからはずれた患者での有効性は証明されていないことになる。合併症のある患者や高齢者など脆弱性を持った患者での適応は慎重に判断し，臨床応用していく必要がある。

おわりに

膵・胆道癌の化学療法は，この数年いくつかの新しいエビデンスが得られ，標準治療も変わってきている。また今後，益々多様化していくものと考えられる。エビデンスの元となった臨床試験を適切に理解し，評価した上で一般臨床に適応していくことが必要である。

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