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International Journal of
Radiation Oncology
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Clinical Investigation: Pancreatic Cancer

A Multicenter Phase II Trial of S-1 With Concurrent Radiation Therapy for Locally Advanced Pancreatic Cancer

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Received Feb 8, 2012, and in revised form Mar 24, 2012. Accepted for publication Mar 27, 2012

Summary

S-1 is the first single anticancer agent to be judged non-inferior to gemcitabine in a large-scale, randomized, phase III trial for advanced pancreatic cancer, and it can also act as a radiosensitizer. S-1 with concurrent radiation therapy showed very favorable activity, with mild toxicity in patients with

Purpose: The aim of this trial was to evaluate the efficacy and toxicity of S-1 and concurrent radiation therapy for locally advanced pancreatic cancer (PC).

Methods and Materials: Locally advanced PC patients with histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma, who had no previous therapy were enrolled. Radiation therapy was delivered through 3 or more fields at a total dose of 50.4 Gy in 28 fractions over 5.5 weeks. S-1 was administered orally at a dose of 80 mg/m^2 twice daily on the day of irradiation during radiation therapy. After a 2- to 8-week break, patients received a maintenance dose of S-1 (80 mg/m^2/day for 28 consecutive days, followed by a 14-day rest period) was then administered until the appearance of disease progression or unacceptable toxicity. The primary efficacy endpoint was survival, and the secondary efficacy endpoints were progression-free survival, response rate, and serum carbohydrate antigen 19-9 (CA19-9) response; the safety endpoint was toxicity.

Results: Of the 60 evaluable patients, 16 patients achieved a partial response (27%; 95% confidence interval [CI], 16%-40%). The median progression-free survival period, overall survival period, and 1-year survival rate of the evaluable patients were 9.7 months (95% CI, 6.9-11.6 months),

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This work was presented in abstract form on June 4-6, 2010. at the 46th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL.

This study was supported in part by grants-in-aid for cancer research from the Ministry of Health, Labor, and Welfare of Japan.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 85, No. 1, pp. 163–169, 2013
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2012.03.059

locally advanced pancreatic cancer.

16.2 months (95% CI, 13.5-21.3 months), and 72% (95%CI, 59%-82%), respectively. Of the 42 patients with a pretreatment serum CA19-9 level of ≥100 U/ml, 34 (81%) patients showed a decrease of greater than 50%. Leukopenia (6 patients, 10%) and anorexia (4 patients, 7%) were the major grade 3-4 toxicities with chemoradiation therapy.

Conclusions: The effect of S-1 with concurrent radiation therapy in patients with locally advanced PC was found to be very favorable, with only mild toxicity. © 2013 Elsevier Inc.

Introduction

Pancreatic cancer (PC), one of the most lethal human cancers, has become the fifth most common cause of death due to cancer in Japan; it has been estimated that PC was responsible for 26,791 deaths in 2009, representing approximately 3% of all deaths. PC patients have a dismal prognosis, as their 5-year survival after diagnosis is less than 5%. Of all treatment modalities available for PC, only resection offers an opportunity for a cure. However, approximately half of patients already have metastases at the time of diagnosis, and approximately one-third of patients are diagnosed as having locally advanced disease, whereas only a small proportion of patients are eligible for surgery, as a result of the lack of effective screening. Concurrent chemoradiation therapy with external beam radiation therapy and chemotherapy using 5-fluorouracil (5-FU) is often used in patients who have unresectable PC due to vascular involvement that includes the celiac artery or supra-mesenteric artery, with no distant metastases on radiological examination, because it is generally accepted as a standard therapy for locally advanced PC (1-4). A variety of anticancer agents, including gemcitabine (5) and capecitabine (6), and various radiation schedules (7-8) have been examined in clinical trials, but survival has not been significantly improved.

S-1 is a new oral fluoropyrimidine derivative in which tegafur is combined with 2 5-chloro-2,4-dihydroxypyridine modulators and oteracil potassium, a potentiator of 5-FU's antitumor activity that also decreases gastrointestinal toxicity. A multi-institutional, late-phase II trial of S-1 involving metastatic PC patients reported a good tumor response rate (38%) and improved survival (median, 9.2 months) (9). A phase III trial compared therapy with S-1, with gemcitabine alone, and with gemcitabine plus S-1 in patients with unresectable PC in Japan and Taiwan, and S-1 therapy was found to provide efficacy and toxicity similar to gemcitabine when it was used as a first-line treatment for advanced PC (median survival: S-1, 9.7 months; gemcitabine, 8.8 months [hazard ratio, 0.96; non-inferiority P value <.001]); thus, S-1 was judged to be non-inferior to gemcitabine (10). S-1 also acts as a radiosensitizer, and preclinical and clinical studies have demonstrated the radiosensitizing potency of S-1 (11). Not only is S-1 a potent radiosensitizer that has been shown to have promising antitumor activity against advanced PC, but also, since it is active orally, it is also much more convenient for patients than intravenous 5-FU infusion. Thus, concurrent raditation therapy and oral S-1 instead of 5-FU infusion may be a more efficient treatment that also improves patients' quality of life. In a phase I trial conducted in one of our hospitals, the recommended S-1 dose with concurrent radiation therapy was found to be 80 mg/m^2/day on the day of irradiation; at this dose, S-1 was found to have excellent antitumor activity with mild toxicity (12). Consequently, a multi-institutional phase II study was conducted to clarify the efficacy and safety of concomitant radiation therapy with S-1 in patients with locally advanced PC.

Methods and Materials

Patients and eligibility

Patients eligible for study entry had locally advanced nonresectable clinical stage III (T4N0-1 and M0) PC, according to International Union Against Cancer criteria. Eligibility criteria were adenocarcinoma or adenosquamous carcinoma confirmed on cytology or histology; no previous chemotherapy for PC; a square (10 cm × 10 cm) radiation field could encompass all pancreatic lesions and lymph node metastases; age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate oral intake; satisfactory hematological functions (hemoglobin concentration, ≥9.0 g/dl; leukocyte count, ≥3500/mm^3; platelet count, ≥100,000/mm^3); adequate hepatic function (serum total bilirubin ≤2.0 times the upper normal limit [UNL] or ≤3.0 mg/dl with biliary drainage); aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 times UNL or ≤5 times UNL with biliary drainage; serum albumin ≥3.0 g/dl; and normal renal function (serum creatinine ≤UNL). Written informed consent was obtained from all patients.

Exclusion criteria were active infection; active gastroduodenal ulcer; watery diarrhea; phenytoin, warfarin potassium, or flucytosine treatment; pleural effusion or ascites; severe complications such as cardiac or renal disease; psychiatric disorder; history of drug hypersensitivity; and active concomitant malignancy. In addition, pregnant and lactating women and women of childbearing age who were not using effective contraception were also excluded.

Pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast medium-enhanced computed tomography (CT) or magnetic resonance imaging of the abdomen and X-ray or CT of the chest was performed for pretreatment staging to assess the local extension of the tumor and to exclude the presence of distant metastases. The criteria for local extension surrounding the pancreas included tumor invasion to the celiac trunk or superior mesenteric artery, or both, which corresponded to clinical stage III according to the International Union Against Cancer (6th edition). All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before treatment. Laparoscopy and laparotomy to rule out occult peritoneal dissemination prior to study entry were not necessary.

Treatment schedule

The regimen consisted of S-1 with concurrent radiation therapy and maintenance S-1 chemotherapy.

S-1 with concurrent radiation therapy

Radiation therapy was delivered with >6-MV photons, using a multiple (three or more) field technique. A total dose of 50.4 Gy

was delivered in 28 fractions over 5.5 weeks. Primary tumor and metastatic lymph nodes >1 cm identified on CT were contoured as gross tumor volumes (GTV). The clinical target volume (CTV) included the primary tumor with a 0.5-cm margin and metastatic lymph nodes. Regional lymph nodes were not treated electively. The definition of planning target volume (PTV) include the CTV with a 1-cm margin laterally and a 1- to 2-cm margin in the craniocaudal direction to take into account respiratory organ motion and daily set-up errors. The reference point for the radiation dose was set at the center of the PTV. The spinal cord dose was maintained at <45 Gy. The volume of liver to receive 30 Gy was required to be <40%, and the volume to receive 20 Gy was required to be <67%. At least 75% of both kidneys was required to receive less than 18 Gy.

S-1 was administered orally at a dose of 40 mg/m^2 twice daily after breakfast and dinner on the day of irradiation (Monday through Friday) during radiation therapy. The 3 initial doses were determined according to the body surface area (BSA) as follows: patients with a BSA of <1.25 m^2 received 40 mg/dose; those with BSA of 1.25 m^2-<1.5 m^2 received 50 mg/dose; and those with BSA of ≥1.5 m^2 received 60 mg/dose. The dose of S-1, which is the standard dose when S-1 is used as a single agent for systemic therapy (15, 16), had been previously determined in our phase I trial (19).

The occurrence of grade 4 hematological toxicity, grade 3 non hematological toxicity excluding nausea, anorexia, fatigue, constipation, and hyperglycemia, or a serum AST or ALT >200 IU/l resulted in the suspension of radiation therapy and S-1 administration. When the toxicities improved by at least 1 grade compared to the suspension criteria, treatment was resumed. When suspension criteria were met, dose modification was allowed as follows: patients with a BSA of <1.25 m^2 received 25 mg/dose; those with a BSA of 1.25 m^2-<1.5 m^2 received 40 mg/dose; and those with a BSA ≥1.5 m^2 received a 50 mg/dose. Chemoradiation therapy was discontinued when the patient developed grade 4 non-hematological toxicities or other unacceptable toxicities, including gastrointestinal ulcer or bleeding, interruptions in treatment of >15 days, or unequivocal tumor progression. After treatment discontinuation, patients could receive other anticancer treatments excluding S-1 with concurrent radiation therapy at their physician's discretion.

Maintenance S-1 chemotherapy

From 2-8 weeks after completion of S-1 with concurrent radiation therapy, maintenance S-1 chemotherapy was initiated at a dose of 40 mg/m^2 twice daily orally, after breakfast and dinner, for 28 consecutive days, followed by a 14-day rest period per course. Treatment cycles were repeated until the appearance of disease progression, unacceptable toxicities, or the patient's refusal to continue treatment. If a grade 3 or higher hematological toxicity or a grade 2 or higher non hematological toxicity was observed, temporary interruption or dose reduction of S-1 administration was allowed as follows: patients with a BSA of <1.25 m^2 received 25 mg/dose; those with a BSA of ≤1.25 m^2-<1.5 m^2 received a 40 mg/dose; and those with a BSA of ≥1.5 m^2 received a 50 mg/dose. When grade 4 non hematological toxicities, unacceptable toxicities, a rest period >28 days, or an unequivocal tumor progression was observed during maintenance S-1 chemotherapy, treatment was discontinued. After treatment discontinuation, patients could be given other anticancer treatment, excluding S-1 monotherapy, at their physician's discretion.

Response and toxicity assessment

Evaluations of tumor response during chemoradiation therapy and maintenance therapy were performed at the completion of chemoradiation therapy and every 6 weeks thereafter until tumor progression or 24 weeks from the start of S-1 and radiation therapy, using the Response Evaluation Criteria in Solid Tumors version 1.0 questionnaire. Responses were evaluated centrally by 3 independent reviewers. Serum carbohydrate antigen 19-9 (CA19-9) levels were measured at least every 6 weeks. In patients with a pretreatment CA19-9 level ≥100 U/ml, the CA19-9 response was assessed; a positive response was defined as a reduction of >50% from the pretreatment level (13). Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up. Progression-free survival was defined as the time from the date of initial treatment to the first documentation of progression or death. Basic laboratory tests that included a complete blood count with differentials, serum chemistry, and urinalysis were administered at least weekly during S-1 therapy and radiation therapy and then at least once every 2 weeks during S-1 maintenance therapy. Common Terminology Criteria for Adverse Events, version 3.0, were used for the assessment of treatment-related toxicities.

Radiation therapy quality assurance

All radiation therapy treatment plans for the enrolled patients were reviewed centrally by an independent radiation committee consisting of 9 radiation oncologists. To assess radiation therapy protocol compliance, the following parameters were reviewed: fraction size, prescribed dose to the reference point, energy, relationships between GTV, CTV, PTV and radiation field, overall treatment time, isodose distributions at the transverse section of the reference points, and doses to organs at risk. The quality assurance assessment was given as per protocol (PP), deviation acceptable (DA), and violation unacceptable (VU). After parameter compliance was assessed, overall radiation therapy compliance was classified as: PPoverall, no DA or VU in any parameter; VUoverall, at least 1 VU in any parameter; or DAoverall, neither PP nor VU.

Statistical considerations

Primary endpoints of this trial were overall survival for the efficacy evaluation and frequency of adverse events for the safety evaluation; secondary endpoints were progression-free survival, response rate, and serum CA19-9 level response.

The enrollment goal was set at 60 eligible patients. The number of enrolled patients was determined using a statistical power analysis. Under the assumptions of a median survival time of 10 months for patients receiving conventional chemoradiation therapy (1-4), a 2-year registration period followed by a 2-year follow-up period and a one-sided alpha level of 5%, the statistical power of the hazard ratio test was over 70% or 90% with the expected median survival time of 14 or 16 months, respectively. Therefore, the number of planned enrolled patients, the registration period, the follow-up period, and the total research period were set at 60, 2 years, 2 years, and 4 years, respectively. The full analysis set (FAS) was defined as any patient who received at least 1 course of study medication. Overall and progression-free survival curves were calculated using the Kaplan-Meier method. This open-label, multi-institutional, single arm

phase II study was approved by the review board of each institution and was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research (Ministry of Health, Labour, and Welfare, Japan). The trial was registered at University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000486).

Patient registration and data collection were managed by the Makimoto-han datacenter. The quality of the data was ensured by a careful review performed by the data center staff and the coordinating investigator of this study (MI). All data were fixed on November 13, 2009, and all analyses in this study were performed by statisticians (NY and TS).

Results

Patient characteristics

Sixty-one patients were enrolled in this trial between July 2006 and November 2007 at 20 institutions in Japan (see the Appendix in Supplementary Material). However, 1 patient was excluded before the start of protocol treatment because distant lymph node metastases were detected during a CT examination for radiation field planning; this patient received systemic chemotherapy with gemcitabine alone. Table 1 shows the characteristics of the 60 FAS patients.

Table 1 Patient characteristics (n=60)

Characteristics	No. of patients	Value(s)	% of patients
Age (y)			
Median		64	
Range		31-80	
Sex			
Male	35		58
Female	25		42
Eastern Cooperative Oncology Group performance status			
0	34		57
1	26		43
Biliary drainage			
Present	16		27
Pathology			
Adenocarcinoma	59		98
Adenosquamous carcinoma	1		2
Tumor location			
Head	33		55
Body or tail	27		45
Maximum tumor size, cm			
Median		3.6	
Range		2.0-6.5	
Regional lymph node swelling			
N0	44		73
N1	16		27
CA19-9 (U/ml)			
Median		304	
Range		0-4400	
Planning target volume (cm^3)			
Median		240	
Range		102-442	

Abbreviation: CA19-9 = carbohydrate antigen 19-9.

Fifty-three patients (88%) completed S-1 therapy and radiation therapy but the remaining 7 patients (12%) discontinued S-1 and radiation therapy. Reasons for treatment discontinuation were disease progression (2 patients), duodenal and bile duct perforation (1 patient), acute myocardial infarction (1 patient), treatment interruption for >15 days because of cholangitis (1 patient), severe confusion (1 patient), and patient refusal to continue treatment because of grade 3 nausea and vomiting (1 patient). The treatment delay during chemoradiation therapy was observed in 20 patients (33%), and the median delay was 3 days (range, 1-17 days). Compliance with S-1 therapy was high, with a rate of 99% (1170 of 1176 doses). Of the 53 patients who completed chemoradiation therapy 47 (89%) patients received maintenance S-1 chemotherapy, but 6 patients did not for the following reasons: disease progression (3 patients); sudden death because of septic shock of unknown origin occurring 40 days after the completion of S-1 and radiation therapy (1 patient); and patient refusal to continue treatment because of grade 2 nausea and grade 2 diarrhea (1 patient) or grade 3 appetite loss and grade 2 fatigue (1 patient). The median number of S-1 maintenance chemotherapy courses was 4 (range, 1 to ≥19). At the time of the final analysis, S-1 maintenance chemotherapy had been terminated in 46 (98%) of 47 patients because of disease progression (29 patients, 63%), adverse events (12 patients, 26%), patient refusal (2 patients, 4%), or other reasons (3 patients, 7%). Treatment delay during the first and second courses of maintenance S-1 therapy was observed in 9 patients (19%) and 7 patients (18%), respectively. The rate of compliance with S-1 chemotherapy was 91% (2503 of 2744 doses) in the first course and 98% (2149 of 2184 doses) in the second course. After the completion of protocol treatment, 53 patients (88%) received subsequent therapy including gemcitabine (47 patients), S-1 (11 patients), radiation therapy for bone metastases (2 patients), and other treatments (4 patients).

Toxicity

The toxicities of S-1 and radiation therapy observed in the 60 FAS patients are listed in Table 2. Grade 3 leukocytopenia, neutropenia, and anemia occurred in 6 (10%), 3 (5%), and 2 (3%) patients, respectively; no grade 4 hematological toxicity was seen. The most common and troublesome non-hematological toxicities for patients undergoing chemoradiation therapy were usually gastrointestinal toxicities, including anorexia, nausea, and vomiting. However, grade 3 or higher cases of these toxicities were observed only in 4 (7%), 3 (5%), and 2 (3%) patients, respectively, and the toxicities were generally mild and manageable. One treatment-related death arising from perforation of the duodenum and biliary tract occurred during chemoradiation therapy.

Toxicities occurring during S-1 maintenance chemotherapy were also mild and transient (Table 3). Grade 4 leukocytopenia was the only hematological toxicity, and it was observed in only 1 patient (2%); the incidence of grade 3 or higher gastrointestinal toxicities was <6%. In addition, no serious adverse events occurred during S-1 maintenance chemotherapy. No late toxicities that could be associated with S-1 and radiation therapy were reported.

Efficacy

The response evaluation included all 60 FAS patients, but tumor response was not evaluable in 1 patient in whom contrast-enhanced CT examination could not be performed due to deterioration of her general condition following duodenal perforation.

Table 2 Toxicity during S-1 and concurrent radiation therapy (n=60)

Toxicity	No. of patients (%)*			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Leukocytes	15 (25)	28 (47)	6 (10)	0 (0)
Neutrophils	9 (15)	15 (25)	3 (5)	0 (0)
Hemoglobin	16 (27)	13 (22)	2 (3)	0 (0)
Platelets	24 (40)	3 (5)	0 (0)	0 (0)
Non hematological				
Rash	2 (3)	0 (0)	0 (0)	0 (0)
Pigmentation	6 (10)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	1 (2)	0 (0)	0 (0)	0 (0)
Gastric ulcer/gastritis	0 (0)	1 (2)	1 (2)	0 (0)
Abdominal pain	0 (0)	0 (0)	1 (2)	0 (0)
Bilirubin	4 (7)	1 (2)	1 (2)	0 (0)
Aspartate aminotransferase	11 (18)	3 (5)	0 (0)	0 (0)
Alanine aminotransferase	10 (17)	5 (8)	0 (0)	0 (0)
Alkaline phosphatase	4 (7)	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	15 (25)	7 (12)	0 (0)	-
Amylase	0 (0)	1 (2)	0 (0)	-
Creatinine	0 (0)	0 (0)	0 (0)	0 (0)
Hyperglycemia	2 (3)	4 (7)	0 (0)	0 (0)
Cholangitis	0 (0)	1 (2)	0 (0)	0 (0)

* Grading followed Common Terminology Criteria for Adverse Events version 3.0.

Tumor response was evaluated based on the best response as of 24 weeks after S-1 and radiation therapy were started. Overall, a partial response was seen in 16 patients for an overall response rate of 27% (95% confidence interval [CI], 16%-40%). The median survival in patients with partial response was 19.4 months (range, 9.8-32.6 months; 95% CI, 13.9-25.1 months), with a median duration of response of 7.3 months (range, 5.5-10.1 months). Forty patients (67%) showed stable disease, and 3 patients (5%) had progressive disease. Additionally, tumor response was evaluated for all periods because tumor shrinkage was obtained in some patients after 24 weeks. Of the 40 patients who were judged to have stable disease on the response evaluation at 24 weeks, an additional 6 patients were judged to have a partial response by the central independent reviewers. The median time to partial response was 4.7 months (range, 1.4-16.8 months) after chemoradiation therapy commenced. Therefore, the response rate for all periods was 37% (95% CI, 25%-50%). Of the 42 patients with a pretreatment serum CA19-9 level ≥100 U/ml, 34 (81%) patients had a >50% decrease compared to the pretreatment level. During this protocol treatment, 2 patients underwent surgical resection because tumor shrinkage occurred and their tumors became resectable.

Fifty-four of the 60 patients had disease progression at the time of the analysis. The median progression-free survival time and the 6-month and 1-year progression-free survival proportions for all patients were 9.7 months (95% CI, 6.9-11.6 months), 68%, and 32%, respectively (Fig.). The pattern of disease progression was distant metastases in 26 patients (46%), locoregional recurrence in 16 patients (27%), distant metastases and locoregional recurrence in 3 patients (5%), and deterioration of general condition in 9 patients (15%). At the time of analysis, 49 patients had died, and the median follow-up period was 16.3 months (range, 3.0-34.0 months). The median survival time and the 1-year and 2-year survival proportions for the 60 patients were 16.2 months (95% CI, 13.5-21.3 months), 72% (95% CI, 59%-82%), and 26%, respectively (Fig.).

Table 3 Toxicity during S-1 maintenance therapy (n=47)

Toxicity	No. of patients (%)*			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Leukocytes	4 (9)	27 (57)	4 (9)	1 (2)
Neutrophils	5 (11)	19 (40)	6 (13)	0 (0)
Hemoglobin	8 (17)	18 (38)	3 (6)	0 (0)
Platelets	8 (17)	2 (4)	1 (2)	0 (0)
Non hematological				
Malaise	13 (27)	8 (17)	2 (4)	0 (0)
Anorexia	15 (32)	11 (23)	3 (6)	0 (0)
Nausea	7 (15)	4 (9)	1 (2)	0 (0)
Vomiting	4 (9)	1 (2)	0 (0)	0 (0)
Diarrhea	3 (6)	3 (6)	0 (0)	0 (0)
Stomatitis	4 (9)	0 (0)	0 (0)	0 (0)
Alopecia	1 (2)	0 (0)	-	-
Rash	2 (4)	1 (2)	0 (0)	0 (0)
Pigmentation	11 (23)	1 (2)	0 (0)	0 (0)
Hand-foot syndrome	1 (2)	0 (0)	0 (0)	0 (0)
Duodenal ulcer	0 (0)	1 (2)	0 (0)	0 (0)
Taste alteration	1 (2)	2 (4)	-	-
Bilirubin	7 (15)	5 (11)	0 (0)	0 (0)
Aspartate aminotransferase	8 (17)	3 (6)	1 (2)	0 (0)
Alanine aminotransferase	5 (11)	2 (4)	0 (0)	0 (0)
Alkaline phosphatase	1 (2)	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	10 (21)	5 (11)	0 (0)	-
Amylase	0 (0)	1 (2)	0 (0)	-
Creatinine	3 (6)	0 (0)	0 (0)	0 (0)
Hyperglycemia	2 (4)	4 (9)	0 (0)	0 (0)

* Grading followed Common Terminology Criteria for Adverse Events version 3.0.

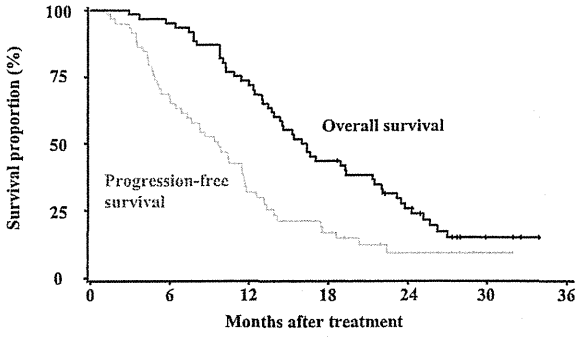

Fig. Overall survival and progression-free survival curves of the 60 locally advanced PC patients treated with S-1 with concurrent radiation therapy. Censored cases are shown by tick marks.

Radiation therapy quality assurance

Radiation therapy quality assurance was reviewed centrally by an independent radiation committee for all 60 FAS patients. DA was observed for 2 parameters in 4 patients (relationship between GTV and radiation field, 2 patients; isodose distribution, 2 patients), but no instances of VU were seen in this study. Therefore, PPoverall, DAoverall, and VUoverall were assessed in 56 (93%) patients, 4 (7%) patients, and 0 (0%) patients, respectively.

Discussion

The combination of radiation therapy and 5-FU chemotherapy has been acknowledged as a standard therapy for locally advanced PC (1-4). However, optimal chemotherapeutic regimens continue to be pursued, as the survival benefit remains modest. S-1 is the first single anticancer agent to be judged non-inferior to gemcitabine in a large-scale randomized phase III trial for advanced PC (10), and it is expected to become a first-line treatment for patients with advanced PC, at least in Asian countries. In addition, it has been shown that combined S-1 and radiation therapy has a synergistic effect against 5-FU-resistant cancer xenografts; thus, S-1 may also have a radiosensitizing effect (11). With S-1 and standard-dose radiation therapy (50.4 Gy/28 fractions), the full dose (80 mg/m^2) of S-1 can be given on the day of irradiation (12) with a reduced risk of distant metastases. Therefore, S-1 may act not only against systemic tumor spread but also a as a potent radiosensitizer to enhance local control. Furthermore, the fact that S-1 can be given orally is an additional benefit over 5-FU infusion.

In the present multicenter trial, the 24-week tumor response rate was 27%, although the overall tumor response rate for the complete period was 37%; in fact, tumor resection was possible in 2 patients after treatment. Thus, excellent tumor shrinkage appears to be an additional benefit of this treatment. Furthermore, other outcomes, including the serum CA19-9 level response (81%), progression-free survival (median, 9.7 months), and overall survival (median, 16.2 months), showed excellent results. As the subsequent therapy, most patients (78%) received gemcitabine, as it might lead to favorable overall survival. However, the outcome of S-1 and concurrent radiation therapy has been reported by other groups (14-16), which were single institutional studies with small numbers of enrolled patients and had slight differences in S-1 administration (Table 4). Similar results were obtained, although such nonrandomized data must be interpreted with caution. Given the recent reports of chemoradiation therapy (4-8, 17, 18), S-1 with concurrent radiation therapy appears to have a favorable treatment efficacy for locally advanced PC, and its survival time will approach that of resected PC patients.

During chemoradiation therapy the major troublesome adverse events were gastrointestinal toxicities (anorexia, nausea, and vomiting), which required intravenous fluid infusion and, sometimes, the termination of chemoradiation therapy (4). One approach to reducing these toxicities that has recently come to be used in chemoradiation therapy using conventional photons for the treatment of PC (4, 6), is a limited radiation field, with a PTV including gross tumor volume alone, without prophylactic nodal irradiation; this minimizes the irradiation of normal tissue and was adopted in the present study. Grade 3 or higher of the above-mentioned toxicities were observed in less than 7% of the patients, and the gastrointestinal toxicities were very mild and easily managed. Other grade 3 or higher non hematological and hematological toxicities of S-1 and concurrent radiation therapy were observed in only 10% or less of the patients and were mild, although there was one treatment-related death due to a perforated duodenum. The toxicities associated with maintenance S-1 therapy were also mild, and this regimen was considered to be well tolerated.

Regarding the results of the radiation therapy quality assurance evaluations performed in this study, 93% of the treatments were assessed as PPoverall; this result is excellent compared with that of a previous trial (5). This result was achieved thanks to the efforts made by the radiation oncologists. The radiation technique that was used in this study was thoroughly explained to all of the radiation oncologists at each institution before patient registration, and the radiation therapy records of the enrolled patients were reviewed by the radiation committee. Results of the review were returned to the radiation oncologists at each institution if any problem with the radiation technique was noted. Therefore, a high quality of radiation therapy was maintained in this study.

There continues to be debate about the role of chemoradiation therapy for patients with locally advanced PC. Prior to the 1990s, it was shown that concurrent external-beam radiation therapy and 5-FU chemotherapy offers a survival benefit over radiation therapy (1, 2) or chemotherapy alone (3). Since the introduction of gemcitabine, which is acknowledged as the first-line therapy for advanced PC, 2 randomized controlled trials comparing chemoradiation therapy with gemcitabine alone have been reported:

Table 4 Results of phase II trials of S-1 and radiation therapy for locally advanced pancreatic cancer

Study (ref.)	Y	Chemotherapy	Radiation therapy	No. of patients	Response rate	Median survival time (mo)	1-y survival rate (%)	Median progression-free survival time (mo)	Maintenance chemotherapy
Kim et al (20)	2008	S-1, 80 mg/m^2, days 1-14 and 22-35	50.4 Gy/28 fractions	25	24%	12.9	43%	6.5	Gemcitabine-based regimen
Sudo et al (15)	2011	S-1, 80 mg/m^2, days 1-14 and 22-35	50.4 Gy/28 fractions	34	41%	16.8	70.6%	8.7	S-1
Shinchi et al (16)	2011	S-1, 80 mg/m^2, days 1-21	50 Gy/40 fractions	50	30%	14.3	62%	6.7	S-1
Current study		S-1, 80 mg/m^2, on the day of irradiation	50.4 Gy/28 fractions	60	27%	16.2	72%	9.7	S-1

a French group reported an inferior outcome with radiation therapy plus 5-FU and cisplatin to chemotherapy with gemcitabine alone (17); and the ECOG study demonstrated that radiation therapy plus gemcitabine had a superior survival outcome compared with gemcitabine alone (18). Thus, these 2 recent randomized controlled trials comparing chemoradiation therapy with gemcitabine alone demonstrated opposite survival results, although both trials were terminated halfway through because of poor patient accrual. In addition, gemcitabine monotherapy for locally advanced PC has been reported to have a favorable efficacy (median survival, 15 months) according to our Japanese group (19), although the time to treatment failure (median, 6.0 months) was not optimal. Thus, in patients with locally advanced PC, it is not clear whether chemoradiation therapy or chemotherapy alone has a better outcome, and there is a need for a prospective, randomized, controlled study comparing chemoradiation therapy with chemotherapy in such patients. Recently, induction chemotherapy followed by chemoradiation therapy has been reported (20). The role of induction chemotherapy is to prevent distant metastases and to define a subset of patients who are likely to benefit from chemoradiation therapy excluding patients with chemoresistant and rapidly progressive disease. Further clinical trials are needed to elucidate the usefulness of this therapeutic strategy.

Conclusions

S-1 therapy with concurrent radiation therapy had very favorable activity, with mild toxicity in patients with locally advanced PC, and the survival time of such patients is expected to approach that of resected PC patients. This regimen appears to be a good platform for incorporation of biologic agents, and the present results should be confirmed in a prospective, randomized, controlled study to elucidate whether chemoradiation therapy or chemotherapy alone results in a better treatment outcome.

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VOLUME 31 · NUMBER 13 · MAY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study of Gemcitabine Plus S-1, S-1 Alone, or Gemcitabine Alone in Patients With Locally Advanced and Metastatic Pancreatic Cancer in Japan and Taiwan: GEST Study

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See accompanying editorial on page 1621

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Published online ahead of print at www.jco.org on April 1, 2013.

Written on behalf of the Gemcitabine and S-1 Trial Group.

Supported by Taiho Pharmaceutical and TTY Biopharm.

Presented in part at the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00498225.

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0732-183X/13/3113w-1640w/$20.00

DOI: 10.1200/JCO.2012.43.3680

ABSTRACT

Purpose
The present phase III study was designed to investigate the noninferiority of S-1 alone and superiority of gemcitabine plus S-1 compared with gemcitabine alone with respect to overall survival.

Patients and Methods
The participants were chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive only gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle), only S-1 (80, 100, or 120 mg/d according to body-surface area on days 1 through 28 of a 42-day cycle), or gemcitabine plus S-1 (gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 60, 80, or 100 mg/d according to body-surface area on days 1 through 14 of a 21-day cycle).

Results
In the total of 834 enrolled patients, median overall survival was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The noninferiority of S-1 to gemcitabine was demonstrated (hazard ratio, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority), whereas the superiority of gemcitabine plus S-1 was not (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$). All treatments were generally well tolerated, although hematologic and GI toxicities were more severe in the gemcitabine plus S-1 group than in the gemcitabine group.

Conclusion
Monotherapy with S-1 demonstrated noninferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer.

J Clin Oncol 31:1640-1648. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic cancer (PC) is currently the eighth leading cause of cancer-related mortality worldwide, with an estimated 266,000 deaths in 2008.[1] Gemcitabine became the standard treatment for advanced PC, improving overall survival (OS) compared with fluorouracil.[2] Although various gemcitabine-based combination regimens have been evaluated, only erlotinib added to gemcitabine showed a survival benefit over gemcitabine, and that was marginal.[3]

Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a gemcitabine-free combination regimen, has recently demonstrated a clear survival benefit compared with gemcitabine for patients with metastatic PC who have a performance status of 0 to 1.[4] However, because FOLFIRINOX is associated with significant toxicity, this regimen must be limited to patients with good performance status and requires close monitoring.[5]

In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. S-1

is an oral fluoropyrimidine derivative shown to be effective for gastric and various other types of cancers.[6,7] Phase II studies of S-1 as first-line therapy for metastatic PC resulted in good response rates of 21.1% to 37.5%.[8,9] Consequently, S-1 was approved for the indication of PC in Japan in 2006. Development of gemcitabine plus S-1 (GS) studies have also been initiated, mainly in Japan, and two phase II studies reported high response rates of 44.4% to 48.5% and good median OS of 10.1 to 12.5 months.[10,11]

Because S-1 and GS have shown promising activity in PC, the present randomized phase III study (GEST [Gemcitabine and S-1 Trial] study) was designed to evaluate whether S-1 alone is noninferior to gemcitabine and whether GS is superior to gemcitabine alone for locally advanced and metastatic PC with respect to OS.

PATIENTS AND METHODS

Study Design

This randomized phase III study, sponsored by Taiho Pharmaceutical in Japan and TTY Biopharm in Taiwan, was conducted as a postmarketing study in Japan and as a registration study in Taiwan and was in compliance with the Declaration of Helsinki. Data were collected by a contract research organization contracted by the sponsors and were analyzed by a bio-statistician (Y.O.). An independent data and safety monitoring committee reviewed efficacy and safety data. The study was approved by the ethics committee or institutional review board of each participating center.

Patients

All patients provided written informed consent. Enrollment criteria were locally advanced or metastatic PC, histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events), an Eastern Cooperative Oncology Group performance status score of 0 to 1, and adequate organ functions (see Appendix, online only).

Treatment

Random assignment was performed centrally with stratification by extent of disease (locally advanced disease *v* metastatic disease) and institution using the minimization method. Patients allocated to gemcitabine alone received gemcitabine at a dose of 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Patients allocated to S-1 alone received S-1 orally twice daily at a dose according to the body-surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle. Patients allocated to GS received gemcitabine at a dose of 1,000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose according to the BSA (< 1.25 m^2, 60 mg/d; ≥ 1.25 to < 1.5 m^2, 80 mg/d; ≥ 1.5 m^2, 100 mg/d) on days 1 through 14 of a 21-day cycle. The dose levels of S-1 used in the GS group were based on the results of a previous phase II study of GS, in which 1,000 mg/m^2 of gemcitabine was combined with 120 mg/d, 100 mg/d, and 80 mg/d of S-1. In that study, the rate of treatment withdrawal due to adverse events was 41% (22 of 54 patients), the rate of grade 3 or worse neutropenia was 80%, and the dose was reduced in 56% of the patients (30 of 54 patients).[11] Consequently, 20 mg/d lower doses of S-1 than those used in the S-1 monotherapy group were used in the GS group in the present study.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see Appendix).

Assessments

Physical examinations, CBCs, and biochemistry tests were usually checked at 2-week intervals in the S-1 group and at each time of administration of gemcitabine both in the gemcitabine group and in the GS group. All adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. Computed tomography or magnetic resonance imaging was performed every 6 weeks until disease progression, and response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12] Quality of life was assessed using the EuroQol 5 Dimension questionnaire[13] at baseline and 6, 12, 24, 48, and 72 weeks after the study treatment had begun.

Statistical Analysis

The primary end point was OS, defined as time from date of random assignment to date of death from any cause. Secondary end points were progression-free survival (PFS), objective response rate, safety, and quality of life. PFS was counted from the date of random assignment to the date of death without progression or of progression as confirmed by the investigator's assessment. The median OS was assumed to be 7.5 months in the gemcitabine group, 8.0 months in the S-1 group, and 10.5 months in the GS group. To maintain a one-sided significance level of .025 for the entire study while testing two hypotheses (ie, noninferiority and superiority), the one-sided significance

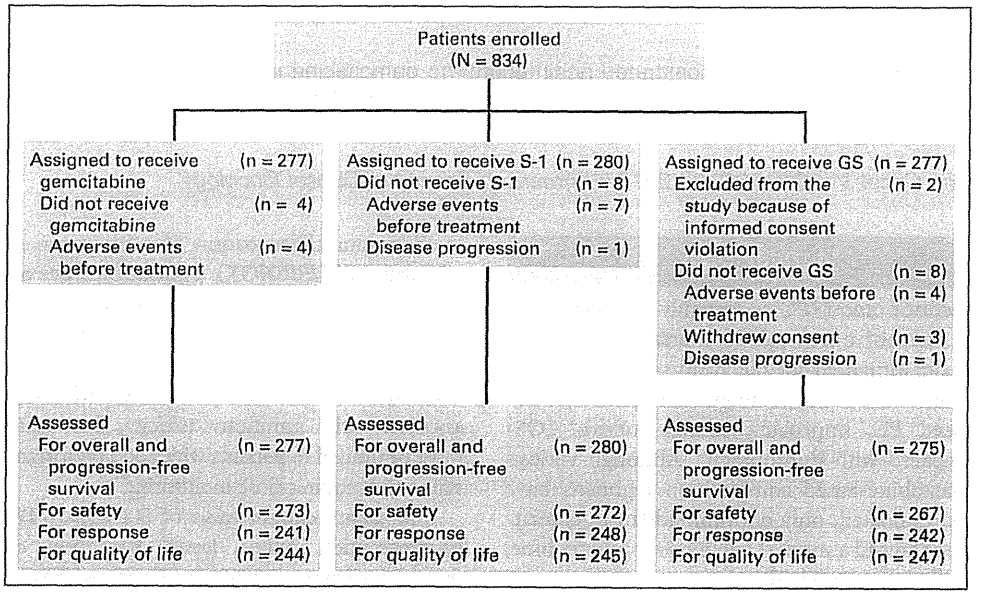

Fig 1. CONSORT diagram. GS, gemcitabine plus S-1.

level for each comparison was set at .0125. The statistical considerations are detailed in the Appendix.

The superiority of GS was evaluated by the stratified log-rank test. To assess the noninferiority of S-1, we used the Cox proportional hazards model to calculate two-sided, 97.5% CIs of the hazard ratio (HR). The noninferiority margin of S-1 was set at 1.33; that is, the null hypothesis was that the median OS with S-1 would be approximately 2 months shorter than with gemcitabine. We decided this setting was justified considering the convenience of S-1 and because there are few effective drugs for the disease. Furthermore, to interpret the obtained data, the Bayesian analysis of the log HR on the basis of the noninformative prior distribution was preplanned. Posterior probability with log HR within a stricter threshold (log 1.15) was also calculated.[14]

In each assigned group, the time-to-event distribution was estimated with the Kaplan-Meier method. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[15] In addition, the Greenwood formula[16] was used to calculate the 95% CI for survival rates. In subgroup analyses, interaction tests were performed to assess the homogeneity of the effect of treatment on OS.

The primary end point was analyzed for the full analysis set. All *P* value evaluations were two-tailed. Data analyses were done with SAS, version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patients

Between July 2007 and October 2009, a total of 834 patients were enrolled from 75 institutions in Japan and Taiwan (768 in Japan and 66 in Taiwan). Two patients in the GS group were excluded from the study because enrollment was conducted before obtaining written informed consent. The remaining 832 patients were included in the full analysis set and used to calculate OS and PFS (Fig 1). The three treatment groups were well balanced with respect to demographic and baseline characteristics (Table 1).

Study Treatment

The median duration of treatment was 2.6 months in the gemcitabine group, 2.6 months in the S-1 group, and 4.3 months in the GS group. The main reasons for treatment discontinuation were either disease progression (202 patients [72.9%] in the gemcitabine group,

Table 1. Demographics and Baseline Characteristics of Patients (full-analysis set population)

Characteristic	Gemcitabine (n = 277)		S-1 (n = 280)		GS (n = 275)		Total (N = 832)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	170	61.4	170	60.7	158	57.5	498	59.9
Female	107	38.6	110	39.3	117	42.5	334	40.1
Age, years								
< 65	134	48.4	145	51.8	137	49.8	416	50.0
≥ 65	143	51.6	135	48.2	138	50.2	416	50.0
ECOG PS								
0	181	65.3	178	63.6	172	62.5	531	63.8
1	96	34.7	102	36.4	103	37.5	301	36.2
Extent of disease								
Locally advanced	66	23.8	68	24.3	68	24.7	202	24.3
Metastatic	211	76.2	212	75.7	207	75.3	630	75.7
Type of tumor								
Adenocarcinoma	272	98.2	276	98.6	272	98.9	820	98.6
Adenosquamous carcinoma	5	1.8	4	1.4	3	1.1	12	1.4
Pancreas excision								
No	254	91.7	264	94.3	248	90.2	766	92.1
Yes	23	8.3	16	5.7	27	9.8	66	7.9
Tumor location*								
Head	122	44.0	110	39.3	116	42.2	348	41.8
Body	88	31.8	124	44.3	102	37.1	314	37.7
Tail	68	24.5	55	19.6	66	24.0	189	22.7
Biliary drainage								
No	202	72.9	217	77.5	209	76.0	628	75.5
Yes	75	27.1	63	22.5	66	24.0	204	24.5
CEA, ng/mL								
Median	5.7		5.6		5.9		5.7	
IQR	3.0-20.1		2.5-18.4		2.5-20.7		2.6-19.5	
CA19-9, U/mL								
Median	1,044		726		441		712	
IQR	52-5,002		64-5,000		45-5,090		55-5,002	
CRP, mg/dL								
Median	0.40		0.50		0.40		0.43	
IQR	0.11-1.38		0.18-1.57		0.15-1.60		0.15-1.57	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; GS, gemcitabine plus S-1; IQR, interquartile range.
*Including patients with tumors involving multiple sites.

215 [76.8%] in the S-1 group, and 162 [58.9%] in the GS group) or adverse events (40 patients [14.4%] in the gemcitabine group, 38 [13.6%] in the S-1 group, and 76 [27.6%] in the GS group). The median relative dose-intensity was 83.0% in the gemcitabine group, 96.1% in the S-1 group, and 83.3% for gemcitabine and 87.4% for S-1 in the GS group.

Survival

The median duration of follow-up for surviving patients was 18.4 months (range, 0.3 to 36.9 months) as of July 31, 2010. The analysis of OS was based on 710 deaths (85.3%) among the 832 patients. The median OS was 8.8 months (95% CI, 8.0 to 9.7) in the gemcitabine group, 9.7 months (95% CI, 7.6 to 10.8) in the S-1 group, and 10.1 months (95% CI, 9.0 to 11.2) in the GS group (Fig 2A). OS rates at 12 and 24 months were respectively 35.4% and 9.2% in the gemcitabine group, 38.7% and 12.7% in the S-1 group, and 40.7% and 14.5% in the GS group. The noninferiority of S-1 to gemcitabine with respect to OS was demonstrated (HR, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority). The Bayesian posterior probability that the HR of S-1 relative to gemcitabine would be less than 1.15 was calculated to be 98% on the basis of the noninformative prior distribution. However, GS failed to improve OS at a statistically significant level as compared with gemcitabine (HR, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$).

The analysis of PFS was based on 793 events (95.3%) among the 832 patients. The median PFS was 4.1 months (95% CI, 3.0 to 4.4) in the gemcitabine group, 3.8 months (95% CI, 2.9 to 4.2) in the S-1 group, and 5.7 months (95% CI, 5.4 to 6.7) in the GS group (Fig 2B). PFS rates at 6 and 12 months were respectively 29.8% and 9.1% in the gemcitabine group, 26.9% and 7.2% in the S-1 group, and 47.9% and 20.3% in the GS group. S-1 was shown to be noninferior to gemcitabine with respect to PFS (HR, 1.09; 97.5% CI, 0.90 to 1.33; $P = .02$ for noninferiority), and GS significantly improved PFS compared with gemcitabine (HR, 0.66; 97.5% CI, 0.54 to 0.81; $P < .001$).

Subgroup analyses of survival according to pretreatment characteristics showed no significant interaction between S-1 and gemcitabine in any subgroup (Fig 3A). However, GS showed a favorable HR compared with gemcitabine in the subsets of patients with locally advanced disease or patients with a performance status of 1 (Fig 3B).

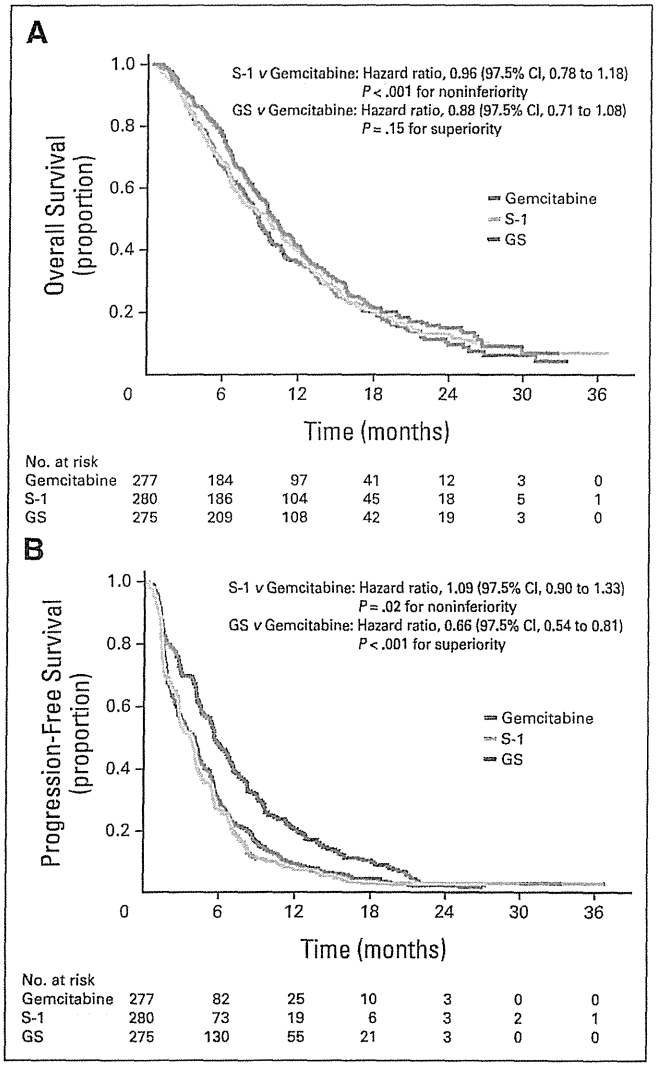

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival according to treatment group. GS, gemcitabine plus S-1.

Response to Therapy

The objective response rate was 13.3% (95% CI, 9.3 to 18.2) in the gemcitabine group, 21.0% (95% CI, 16.1 to 26.6) in the S-1 group, and 29.3% (95% CI, 23.7 to 35.5) in the GS group (Table 2). The objective response rate was significantly higher in the S-1 group ($P = .02$) and in the GS group ($P < .001$) than in the gemcitabine group.

Second-Line Chemotherapy

Second-line chemotherapy was performed in 184 patients (66.4%) in the gemcitabine group, 185 (66.1%) in the S-1 group, and 172 (62.5%) in the GS group. In the gemcitabine group, 140 patients (50.5%) received S-1 alone or S-1–based regimens, and in the S-1 group 162 (57.9%) received gemcitabine alone or gemcitabine-based regimens as second-line chemotherapy. The most common second-line regimens in the GS group were gemcitabine alone (61 patients), GS (53 patients), S-1 alone (24 patients), irinotecan (six patients), and fluorouracil/leucovorin plus oxaliplatin (four patients). In Japan and Taiwan, the use of treatments such as erlotinib, oxaliplatin, and irinotecan for PC was not approved at the time of this study; hence gemcitabine, S-1, or both were used in most patients as second-line chemotherapy.

Adverse Events and Quality-Adjusted Life-Years

The major grade 3 or worse adverse events are listed in Table 3. Patients in the gemcitabine group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, elevated AST levels, and elevated ALT levels as compared with patients in the S-1 group. However, the incidence of grade 3 or worse diarrhea was higher in the S-1 group than in the gemcitabine group. Patients in the GS group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, rash, diarrhea, vomiting, and stomatitis than patients in the gemcitabine group.

There were three deaths considered possibly related to the protocol treatment (interstitial lung disease, sepsis, and acute hepatitis B) in the gemcitabine group, one in the S-1 group (unknown cause), and

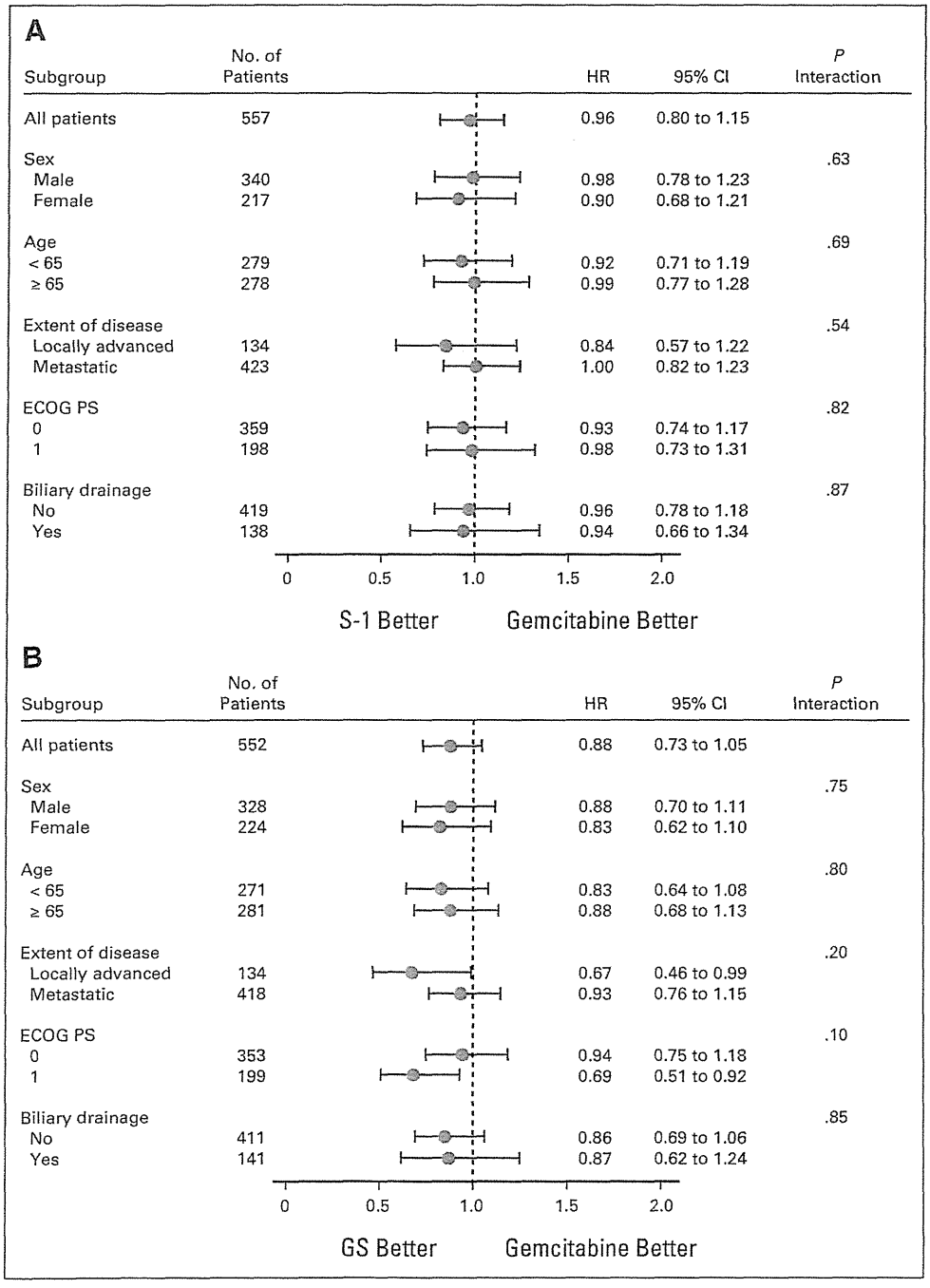

Fig 3. Forest plots of treatment effects on overall survival in subgroup analyses. Forest plots show effects on overall survival of patients in each subgroup. (A) S-1; (B) gemcitabine plus S-1 (GS). Each blue circle shows the treatment response. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

four in the GS group (unknown cause associated with myelosuppression, cerebral infarction, cerebrovascular disorder, and interstitial lung disease). The results of quality-adjusted life-years (QALYs) are in the Appendix and the details of quality-of-life assessments will be reported elsewhere.

DISCUSSION

The overall and PFS curves in the S-1 group were nearly identical to those in the gemcitabine group, confirming the noninferiority of S-1 to gemcitabine in terms of OS and PFS (Fig 2A, 2B). Toxicity profiles of these two drugs differed slightly: gemcitabine tended to show hematologic toxicity, whereas S-1 tended to show GI toxicity. However, both S-1 and gemcitabine were generally well tolerated. Furthermore, the results of QALY evaluation demonstrated that S-1 and gemcitabine were equivalent. Hence our results suggest that S-1 can be used as first-line therapy as a convenient oral alternative for locally advanced and metastatic PC. To the best of our knowledge, this is the first phase III study to demonstrate the noninferiority of a single anticancer agent to gemcitabine alone for locally advanced and metastatic PC.

Table 2. Objective Response Rates (patients with measurable lesions)

Variable	Gemcitabine (n = 241) No.	Gemcitabine (n = 241) %	S-1 (n = 248) No.	S-1 (n = 248) %	GS (n = 242) No.	GS (n = 242) %	*P* (χ^2 test) Gemcitabine *v* S-1	*P* (χ^2 test) Gemcitabine *v* GS
Response								
Complete response	1	0.4	0	0	2	0.8		
Partial response	31	12.9	52	21.0	69	28.5		
Stable disease	119	49.4	105	42.3	102	42.1		
Progressive disease	75	31.1	69	27.8	37	15.3		
Objective response rate*	32	13.3	52	21.0	71	29.3	.02	< .001
95% CI	9.3 to 18.2		16.1 to 26.6		23.7 to 35.5			
Disease control rate†	151	62.7	157	63.3	173	71.5	.88	.04
95% CI	56.2 to 68.8		57.0 to 69.3		65.4 to 77.1			

Abbreviation: GS, gemcitabine plus S-1.
*The objective response rate was defined as the proportion of patients who had a complete response or partial response.
†The disease control rate was defined as the proportion of patients who had a complete response, partial response, or stable disease.

At the time of planning this study, the participants of nearly all phase III trials included both patients with locally advanced as well as those with metastatic PC. However, because locally advanced and metastatic diseases are two clinical entities, it is recently recommended that patients with locally advanced disease should be studied separately from those with metastatic disease.[17] Although this study included locally advanced disease, subgroup analysis of extent of disease showed no significant interaction between S-1 and gemcitabine (Fig 3A). Moreover, the OS curve in the S-1 group was still similar to those in the gemcitabine group in both locally advanced and metastatic disease (Fig 4A, 4B). Regarding pathologic diagnosis, our study included adenosquamous carcinoma, although its percentage was very low (1.4% of whole population). When the data were reanalyzed after excluding patients with adenosquamous carcinoma, the results for OS for gemcitabine versus S-1 was unchanged (HR, 0.96; 95% CI, 0.81 to 1.15). The selection of one treatment over the other will depend primarily on patient preference, clinical factors, or drug costs, as biomarkers indicating effective use of S-1 or gemcitabine do not exist at this time.

Regarding GS, the OS did not differ significantly from gemcitabine, although the PFS was significantly longer in the GS group. Second-line chemotherapy mainly with S-1 in the gemcitabine group may be one reason for this discrepancy. The median OS in the gemcitabine group was 8.8 months, which is longer than those previously reported for gemcitabine in other phase III studies for locally advanced and metastatic PC.[2,3,18-24] Although the efficacy of second-line

Table 3. Grade 3 or Worse Adverse Events (safety population)

Event	Gemcitabine (n = 273) No.	Gemcitabine (n = 273) %	S-1 (n = 272) No.	S-1 (n = 272) %	GS (n = 267) No.	GS (n = 267) %	*P* (Fisher's exact test) Gemcitabine *v* S-1	*P* (Fisher's exact test) Gemcitabine *v* GS
Hematologic								
Leukocytes	51	18.7	10	3.7	101	37.8	< .001	< .001
Neutrophils	112	41.0	24	8.8	166	62.2	< .001	< .001
Platelets	30	11.0	4	1.5	46	17.2	< .001	.05
Hemoglobin	39	14.3	26	9.6	46	17.2	.11	.41
Nonhematologic								
ALT	41	15.0	16	5.9	29	10.9	< .001	.16
AST	41	15.0	21	7.7	32	12.0	.01	.32
Bilirubin	26	9.5	39	14.3	23	8.6	.09	.77
Fatigue	10	3.7	18	6.6	13	4.9	.13	.53
Rash	2	0.7	2	0.7	11	4.1	1.00	.01
Anorexia	20	7.3	31	11.4	25	9.4	.11	.44
Diarrhea	3	1.1	15	5.5	12	4.5	.004	.02
Mucositis/stomatitis	0	0.0	2	0.7	6	2.2	.25	.01
Nausea	5	1.8	5	1.8	12	4.5	1.00	.09
Vomiting	2	0.7	4	1.5	12	4.5	.45	.006
Febrile neutropenia	1	0.4	1	0.4	5	1.9	1.00	.12
Infection with normal ANC	6	2.2	7	2.6	6	2.2	.79	1.00
Pneumonitis	5	1.8	0	0.0	2	0.7	.06	.45

NOTE. Grades of adverse events were defined according to the Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviations: ANC, absolute neutrophil count; GS, gemcitabine plus S-1.

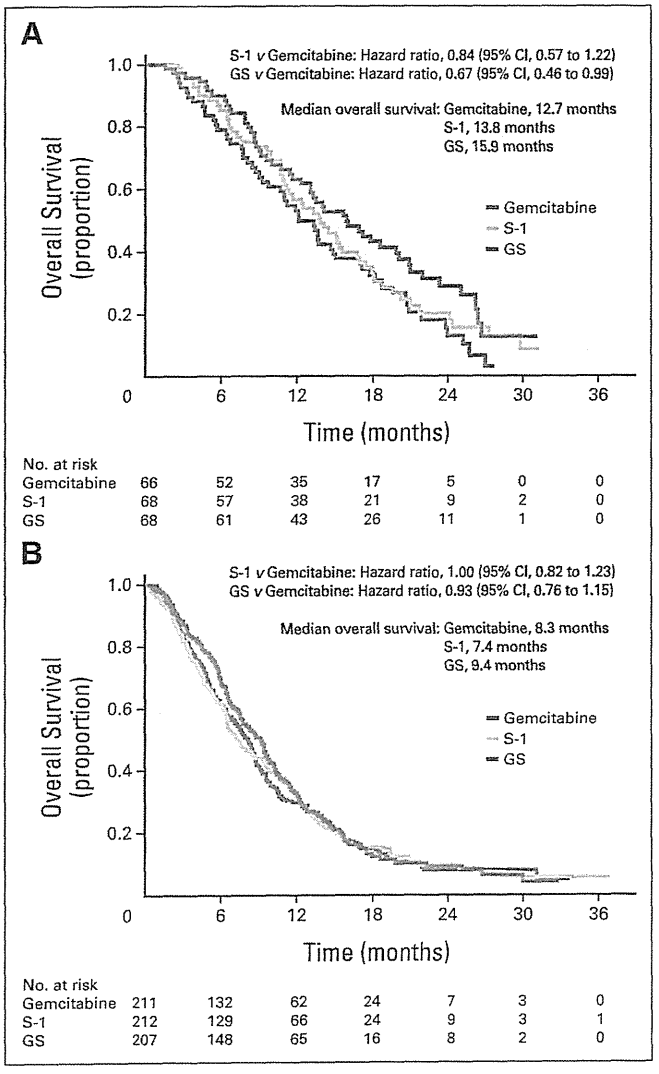

Fig 4. Kaplan-Meier estimates of overall survival in (A) locally advanced disease and (B) metastatic disease. GS, gemcitabine plus S-1.

therapy was not analyzed in this study, a phase II study of second-line S-1 in patients with gemcitabine-refractory PC showed a 15% response rate and 58% disease control rate.[25] Compared with the GS group, which had no promising second-line therapy, the use of S-1 as second-line therapy in the gemcitabine group might have contributed to prolonged survival.

The lack of a significant difference in OS between gemcitabine and GS suggests that gemcitabine and S-1 could be used sequentially rather than concurrently. However, the GS group showed a high response rate and favorable PFS, with a better HR of 0.66 compared with other gemcitabine-based combination regimens in other phase III studies (HR = 0.75 to 1.07).[3,18,20,22,24] Furthermore, the GS group showed a favorable HR for OS in patients with locally advanced disease or patients with a performance status of 1 in the subgroup analyses. Therefore, it is speculated that there may be room to select GS therapy, depending on the profile of the patients and further investigations.

Regarding oral fluoropyrimidines other than S-1, capecitabine has been studied in patients with PC, mainly in the West. In two phase III studies, a combination of gemcitabine plus capecitabine did not significantly prolong survival as compared with gemcitabine alone.[19,20] The results of a meta-analysis of these phase III studies, however, demonstrated that survival was significantly prolonged by combined treatment, with an HR of 0.86,[20] which is similar to the HR for GS in the present study (0.88).

One limitation of our study is that it is uncertain whether our results can be simply extrapolated to Western patients because pharmacokinetics and pharmacodynamics of S-1 between Westerners and East Asians may be different.[26,27] Although S-1 is available for PC only in Japan at the moment, if S-1 is used in Western patients, its effectiveness should be monitored and the dose should be carefully adjusted accordingly. Another potential limitation is that the protocol-specified noninferiority margin of 1.33 may be large. However, the result of point estimate of the HR of S-1 was 0.96 and actual upper limit of the 97.5% CI was 1.18, which was sufficiently lower than the prespecified margin of 1.33. Furthermore, Bayesian posterior probability with log HR within a stricter threshold (log 1.15) was 98%.

Given that most gemcitabine-based combination regimens have not been shown to be significantly superior to gemcitabine alone and that FOLFIRINOX has demonstrated overwhelming superiority to gemcitabine in a phase III study, reporting an HR of 0.57,[4] the development of gemcitabine-free combination regimens for first-line treatment seems to be warranted. However, because FOLFIRINOX requires the placement of a central venous access port for continuous intravenous infusion of fluorouracil, it can be expected that S-1, an oral fluoropyrimidine, will replace the continuous infusion of fluorouracil in the future.

In conclusion, this study has verified the noninferiority of S-1 to gemcitabine, thereby suggesting that S-1 can be used as first-line therapy for locally advanced and metastatic PC. Because S-1 was confirmed to be a key treatment for PC, S-1–based regimens are expected to be developed in the future to improve the management of this formidable disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Hideki Ueno, Taiho Pharmaceutical (C); Tatsuya Ioka, Taiho Pharmaceutical (U); Shinichi Ohkawa, Taiho Pharmaceutical (C); Narikazu Boku, Taiho Pharmaceutical (U); Kenji Yamao, Taiho Pharmaceutical (C); Ann-Lii Cheng, Boehringer Ingelheim (C), sanofi-aventis (C), TTY Biopharm (C); Kazuhiro Mizumoto, Taiho Pharmaceutical (C); Jen-Shi Chen, TTY Biopharm (C); Junji Furuse, Bayer (C), GlaxoSmithKline (C), Kowa (C), Novartis (C), Taiho Pharmaceutical (C); Akihiro Funakoshi, Taiho Pharmaceutical (C); Takashi Hatori, Taiho Pharmaceutical (C); Taketo Yamaguchi, Taiho Pharmaceutical (C); Atsushi Sato, Taiho Pharmaceutical (C); Yasuo Ohashi, Taiho Pharmaceutical (C); Takuji Okusaka, Taiho Pharmaceutical (C); Masao Tanaka, Taiho Pharmaceutical (C) **Stock**

Ownership: None **Honoraria:** Hideki Ueno, Taiho Pharmaceutical, Eli Lilly; Tatsuya Ioka, Taiho Pharmaceutical; Masafumi Ikeda, Taiho Pharmaceutical; Shinichi Ohkawa, Taiho Pharmaceutical, Eli Lilly, Chugai; Hiroaki Yanagimoto, Taiho Pharmaceutical; Narikazu Boku, Taiho Pharmaceutical; Akira Fukutomi, Taiho Pharmaceutical, Eli Lilly; Kazuya Sugimori, Taiho Pharmaceutical; Hideo Baba, Taiho Pharmaceutical; Kenji Yamao, Taiho Pharmaceutical, Eli Lilly; Masayuki Sho, Taiho Pharmaceutical; Jen-Shi Chen, TTY Biopharm; Junji Furuse, Taiho Pharmaceutical, Bayer, Eli Lilly; Akihiro Funakoshi, Taiho Pharmaceutical; Atsushi Sato, Taiho Pharmaceutical; Yasuo Ohashi, Taiho Pharmaceutical; Takuji Okusaka, Taiho Pharmaceutical, Eli Lilly; Masao Tanaka, Taiho Pharmaceutical **Research Funding:** Hideki Ueno, Taiho Pharmaceutical; Tatsuya Ioka, Taiho Pharmaceutical; Masafumi Ikeda, Taiho Pharmaceutical; Shinichi Ohkawa, Taiho Pharmaceutical, Eli Lilly, Chugai, Oncotherapy Science, Yakult, Abbott, Amgen; Hiroaki Yanagimoto, Taiho Pharmaceutical; Narikazu Boku, Taiho Pharmaceutical Co. Ltd; Akira Fukutomi, Taiho Pharmaceutical, Eli Lilly; Kazuya Sugimori, Taiho Pharmaceutical; Hideo Baba, Taiho Pharmaceutical; Kenji Yamao, Taiho Pharmaceutical; Tomotaka Shimamura, Taiho Pharmaceutical; Masayuki Sho, Taiho Pharmaceutical; Masayuki Kitano, Taiho Pharmaceutical; Ann-Lii Cheng, TTY Biopharm; Kazuhiro Mizumoto, Taiho Pharmaceutical; Jen-Shi Chen, TTY Biopharm; Junji Furuse, Taiho Pharmaceutical, Bayer, Pfizer, Yakult; Akihiro Funakoshi, Taiho Pharmaceutical; Takashi Hatori, Taiho Pharmaceutical; Taketo Yamaguchi, Taiho Pharmaceutical; Yasuo Ohashi, Taiho Pharmaceutical; Takuji Okusaka, Taiho Pharmaceutical, Eli Lilly; Masao Tanaka, Taiho Pharmaceutical, Eli Lilly **Expert Testimony:** None **Other Remuneration:** None

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Manuscript writing: All authors
Final approval of manuscript: All authors

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Acknowledgment

We thank all the patients, their families, the investigators and medical staff and Yuji Sato and his clinical study team, Taiho Pharmaceutical, and TTY Biopharm for their participation in the study. We also thank J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University, a remunerated consultant of Taiho Pharmaceutical, for his review of this article.

Appendix

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Details of Adequate Organ Functions in Enrollment Criteria and Main Exclusion Criteria

Adequate organ functions were defined as follows: leukocyte count $\geq$ 3,500/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, hemoglobin level $\geq$ 9.0 g/dL, serum creatinine level $\leq$ 1.2 mg/dL, creatinine clearance $\geq$ 50 mL/min, serum AST and ALT levels $\leq$ 150 U/L, and serum total bilirubin level $\leq$ 2.0 mg/dL or $\leq$ 3.0 mg/dL if biliary drainage was performed.

Main exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; and serious complications such as heart failure, peptic ulcer bleeding, or poorly controlled diabetes. Pancreatic cancers other than adenocarcinoma or adenosquamous carcinoma (eg, anaplastic carcinoma) were excluded from the study.

Dosage Adjustment Guideline for Toxicities

All treatment cycles were repeated until disease progression, unacceptable toxicity, or patient refusal. If patients had a leukocyte count of less than 2,000/μL, a neutrophil count of less than 1,000/μL, a platelet count of less than $70 \times 10^3/\mu$L, or grade 3 or worse rash, the administration of anticancer agents was postponed. S-1 was temporarily halted both in S-1 and in GS groups if patients had a creatinine level of 1.5 mg/dL or higher or grade 2 or worse diarrhea or stomatitis. Treatment was discontinued if these events did not resolve within 4 weeks after treatment suspension. In patients who experienced febrile neutropenia, grade 4 leukopenia, neutropenia, or thrombocytopenia or grade 3 or worse rash, the dose of gemcitabine was reduced by 200 mg/m^2. In patients with febrile neutropenia; grade 4

leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

FULL PAPER

BJC

British Journal of Cancer (2013) 108, 2063–2069 | doi: 10.1038/bjc.2013.174

Keywords: pancreatic cancer; gemcitabine; interleukin-1β; interleukin-6; chemotherapy

Serum levels of IL-6 and IL-1β can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer

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Background: With this study, we sought to characterise the impact of pro-inflammatory cytokines on the outcomes of gemcitabine monotherapy (GEM) in patients with pancreatic cancer (PC).

Methods: Treatment-naive patients with advanced PC and no obvious infections were eligible for enrolment. All of the patients were scheduled to undergo systemic chemotherapy. Serum pro-inflammatory cytokines were measured using an electro-chemiluminescence assay method before chemotherapy. High cytokine levels were defined as values greater than the median. Clinical data were collected prospectively.

Results: Sixty patients who received GEM were included in the analysis. High IL-6 and IL-1β levels were poor prognostic factors for overall survival in a multivariate analysis ($P=0.011$ and $P=0.048$, respectively). Patients with both a high IL-6 level and a high IL-1β level exhibited shortened overall and progression-free survival, a reduction in the tumour control rate, and a high dose intensity of GEM compared with patients with low levels of both IL-6 and IL-1β.

Conclusion: The serum levels of IL-6 and IL-1β predict the efficacy of GEM in patients with advanced PC.

An increase in inflammatory markers is associated with poor prognosis in patients receiving systemic chemotherapy for advanced pancreatic cancer (PC) (Tanaka *et al*, 2008; Morizane *et al*, 2011). C-reactive protein (CRP) is an index of systemic inflammation that is synthesised in hepatocytes by pro-inflammatory cytokines, including IL-1β (Young *et al*, 2008), IL-6 (Morrone *et al*, 1988), IL-8 (Wigmore *et al*, 1997), and TNF-α (Ganapathi *et al*, 1998), via the transcription factor nuclear factor-κB (NF-κB) and the activation of the signal transducer and activator of transcription 3 (STAT3) protein (Nishikawa *et al*, 2008). NF-κB and STAT3 represent major inflammatory pathways for pro-inflammatory cytokines and contribute to the chemoresistance of tumours (Aggarwal *et al*, 2009). An increase in the effects of pro-inflammatory cytokines is believed to attenuate the benefits of chemotherapy and to result in a poor outcome. Recently, the efficacy of anti-inflammatory therapy has been reported in several diseases: with canakinumab as an IL-1β blocker in the cryopyrin-associated periodic syndrome (Kuemmerle-Deschner *et al*, 2011), with tocilizumab as an IL-6 receptor blocker in rheumatoid arthritis (Jones *et al*, 2010), and with siltuximab as an IL-6 blocker in prostate cancer (Dorff *et al*, 2010). In the blockade of intracellular pathways, ruxolitinib is a Janus kinase inhibitor that

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Received 18 February 2013; revised 15 March 2013; accepted 24 March 2013; published online 16 April 2013