information is available about their treatment after discontinuation of FGS.

Toxicity

All patients in steps 1 and 2 were evaluated for toxicity. In step 1, grade 3/4 non-hematological toxicity was observed in two patients (grade 3 fatigue during the third course in one patient, grade 3 stomatitis during the second course in one patient). No grade 4 leukocytopenia was observed at any dose level, but grade 4 neutropenia was observed in one out of three patients at dose level 1, none of the three patients at dose level 2, two of the six patients at dose level 3 and all three of the patients at dose level 4. Grade 3 thrombocytopenia was observed in one patient at dose level 2.

Table 4 summarizes the toxicities in the 40 patients who received the RD (level 3). All 40 eligible patients were assessable for toxicities, and FGS combination therapy at the RD was generally well tolerated. The most common toxicities were leukocytopenia (60%) and neutropenia (60%), but most of these toxicities were tolerable and reversible. Grade 4 neutropenia was noted as hematological toxicity in five patients (13%). Grade 3 non-hematological toxicities consisted of fatigue (one patient), vomiting (one patient), rash (one patient) and liver abscess (one patient). The patient who developed the grade 3 liver abscesses recovered after appropriate treatment with intravenous antibiotic alone. One female patient, who had hypercholesterolemia and history of smoking of 30 cigarettes/day, experienced a grade 4 acute myocardial infarction on day 1 of the third course of treatment, after gemcitabine had been administered but before the start of oral S-1. Emergency coronary angiography showed total occlusion of the left anterior descending coronary artery. The patient recovered from the cardiogenic shock due to myocardial infarction after coronary stent implantation and appropriate supportive treatment. S-1 monotherapy for the pancreatic cancer was started about 1 month after the infarction. No other severe or unexpected toxicities were noted in any of the patients.

Table 4 Treatment-related adverse events among the 40 patients who received the recommended dosages: highest grade reported during the treatment period

	Grade				Grade 1–4	Grade 3–4
	n					
	1	2	3	4	*n* (%)	*n* (%)
Hematological toxicities						
Leukocytes	11	4	9	0	24 (60)	9 (23)
Neutrophils	10	1	8	5	24 (60)	13 (33)
Hemoglobin	5	11	1	0	17 (43)	1 (3)
Platelets	11	2	1	0	14 (35)	1 (3)
Non-hematological toxicities					(0)	
Aspartate aminotransferase	8	1	0	0	9 (23)	0 (0)
Alanine aminotransferase	8	3	0	0	11 (28)	0 (0)
Alkaline phosphatase	5	2	0	0	7 (18)	0 (0)
Total bilirubin	3	0	0	0	3 (8)	0 (0)
Fatigue	15	2	1	0	18 (45)	1 (3)
Nausea	13	4	0	0	17 (43)	0 (0)
Vomiting	8	1	1	0	10 (25)	1 (3)
Anorexia	19	6	0	0	27 (68)	0 (0)
Stomatitis	4	0	0	0	4 (10)	0 (0)
Alopecia	8	0	–	–	8 (20)	–
Diarrhea	7	2	0	0	9 (23)	0 (0)
Rash	3	4	1	0	8 (20)	1 (3)
Hyperpigmentation	9	1	–	–	10 (25)	–
Hand-foot skin reaction	1	2	0	0	3 (8)	0 (0)
Watery eye	2	0	0	–	2 (5)	0 (0)
Hoarseness	1	0	0	0	1 (3)	0 (0)
Infection liver abscess	0	0	1	0	1 (3)	1 (3)
Myocardial infarction	0	0	0	1	1 (3)	1 (3)

Three patients died within 30 days after the final dose of the study drug. All 3 of the deaths were attributed to disease progression, and there were no treatment-related deaths.

Efficacy

It was possible to assess all 40 eligible patients who received the RD for response. Thirty-four patients had died by the completion of the follow-up period. There were no complete responses, but a partial response was achieved in seven patients (18, 95% confidence interval, 7.3–32.8%). Stable disease was noted in 19 patients (48%) and progressive disease in 14 patients (35%). Tumor responses to second-line FGS therapy are classified according to the tumor responses to first-line gemcitabine in Table 5. Three of 10 patients whose best response was progression disease in first-line chemotherapy achieved partial response in FGS therapy. The median progression-free survival time was 2.8 months. The median overall survival time after the start of second-line therapy was 7.0 months (range 1.3–18.9+), and the 1-year survival rate was 18% (Fig. 1). The median overall survival time after the start of first-line therapy was 13.9 months (range 5.2–31.4).

Table 5 Objective tumor response

Response (2nd line)	*n* (%)	Response (1st line)		
		PR	SD	PD
PR	7 (18)	1	3	3
SD	19 (48)	3	12	4
PD	14 (35)	2	9	3
Total	40 (100)	6	24	10

Response rate: 18% (95% CI: 7.3–32.8)

RECIST criteria

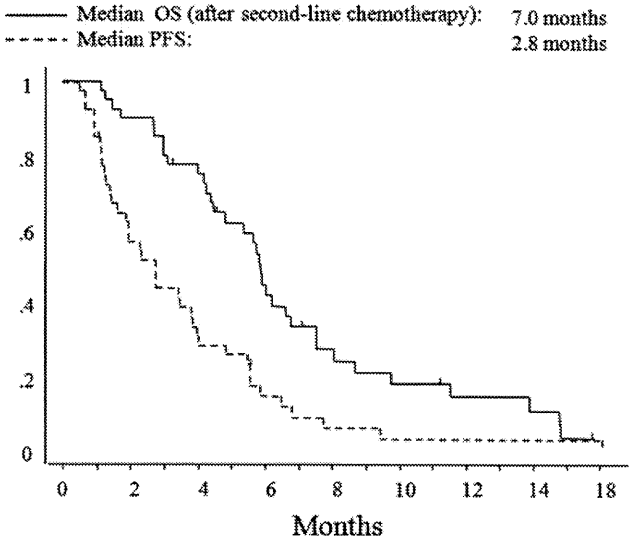

Fig. 1 Survival curves. Survival ($n = 40$). Progression-free survival (*dashed line*) and overall survival time (*solid line*) curves of patients with gemcitabine-refractory pancreatic cancer receiving systemic chemotherapy with FGS

Discussion

In the last decade, several clinical trials (mainly phase II) have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine or a gemcitabine-based combination regimen. The results of a randomized trial ($n = 168$) comparing fluorouracil and folinic acid versus oxaliplatin, fluorouracil and folinic acid (OFF) indicated that OFF improved progression-free survival and overall survival as a second-line chemotherapy. The median progression-free survival time and median survival time of OFF were 3 and 6 months, respectively [22]. In the present study, FGS yielded a median progression-free survival time of 2.8 months and a median overall survival time of 7.0 months, similar to the data mentioned above. Furthermore, the response rate of 18% in the present study was above the pre-established boundary (objective response in five or more of the 40 patients) required for the regimen to be considered effective. However, the gap between the median overall survival time and the median progression-free survival time in the present study was relatively large. Although the reason for this gap is unknown, a bias arising from the selection of patients with a good general condition or with a small tumor burden may explain these findings.

Whether gemcitabine as an FDR infusion is active even after progression during treatment with the standard 30-min administration of gemcitabine was the critical clinical question examined in this study. Differentiating between the relative roles of gemcitabine and S-1 in overcoming tumor resistance is difficult. The efficacy and survival data obtained in the present study seem to be better than those of previous studies for oral fluoropyrimidine monotherapy as a salvage chemotherapy for advanced pancreatic carcinoma (Table 6) [1, 2, 17, 28, 29]. However, since all the data were obtained in single-arm studies, a randomized study is needed to make these suggestions reliable. Furthermore, whether the combined regimen in the present study is superior to other regimens, such as the OFF regimen, remains an essential clinical question.

Safety and convenience as well as antitumor efficacy are critically important issues with regard to second-line chemotherapy. One patient experienced an acute myocardial infarction. Although she had other risk factors, such as a smoking habit and hyperlipidemia, a relation between gemcitabine and the acute myocardial infarction cannot be ruled out because gemcitabine had been administered on the day of the infarction. The toxicity profile of FGS

Table 6 Comparison between the current study and previous studies of oral fluoropyrimidine monotherapy as salvage chemotherapy for advanced pancreatic carcinoma

Study	References	Phase	Regimen	*n*	PR + CR (%)	Median PFS (months)	Median OS (months)
Morizane et al.	[12]	II	S-1	40	15	2.0	4.5
Abbruzzese et al.	[29]	II	S-1	45	0	1.4	3.1
Sudo et al.	[31]	II	S-1	21	9.5	4.1	6.3
Todaka et al.	[32]	Retrospective	S-1	52	4	2.1	5.8
Boeck et al.	[30]	II	Capecitabine	39	0	2.3	7.6
Morizane et al.	Current study	II	FGS	40	18	2.8	7.0

therapy in the other patients was acceptable, and the most common grade 1–4 adverse reactions were anorexia (68%), leukocytopenia (60%) and neutropenia (60%), although most episodes were tolerable and reversible. The safety profile in this study suggests that FGS can be safely administered to pancreatic cancer patients even in a second-line setting, at least in select populations. The biweekly schedule allows enough time to recover from myelosuppression and non-hematological toxicities before the following cycle, enabling patients to receive treatment as scheduled. Actually, the relative dose intensities of gemcitabine and S-1 in our study were high (90.8 and 90.1%, respectively). Furthermore, because of the biweekly schedule, patients do not need to come to the hospital for treatment as often compared with the first-line standard schedule of gemcitabine therapy. Our new treatment schedule may therefore improve the patients' quality of life during anticancer treatment.

We concluded that combination therapy consisting of gemcitabine as a fixed dose rate infusion and S-1 (FGS) provided a promising antitumor activity and tolerable toxicity in patients with gemcitabine-refractory metastatic pancreatic cancer. A larger randomized controlled trial is needed to confirm the clinical benefits of FGS following gemcitabine failure.

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ORIGINAL ARTICLE

Randomized phase II study of gemcitabine and S-1 combination versus gemcitabine alone in the treatment of unresectable advanced pancreatic cancer (Japan Clinical Cancer Research Organization PC-01 study)

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Abstract
Purpose To evaluate the efficacy and safety of the combination of gemcitabine (GEM) and S-1 (GS) in comparison to GEM alone (G) for unresectable pancreatic cancer.
Methods In this multicenter randomized phase II study, we randomly assigned unresectable pancreatic cancer patients to either the GS group or the G group. The GS group regimen consists of intravenous 1,000 mg/m^2 GEM during 30 min on days 1 and 8, combined with 80 mg/m^2 oral S-1 twice daily on days 1–14, repeated every 3 weeks. On the other hand, the G group regimen consists of intravenous 1,000 mg/m^2 GEM on days 1, 8, and 15, repeated every 4 weeks. The primary endpoint was objective response rate (ORR). Secondary end points included treatment toxicity, clinical response benefit, progression-free survival (PFS), and overall survival.

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Results We registered 117 patients from 16 institutions between June 2007 and August, 2010. The ORR of the GS group was 28.3%, whereas that of the G group was 6.8%. This difference was statistically significant ($P = 0.005$). The disease control rate was 64.2% in the GS group and 44.1% in the G group. Median PFS was 6.15 months in the GS group and 3.78 month in the G group. This was also statistically significant ($P = 0.0007$). Moreover, the median overall survival (OS) of the GS group was significantly longer than that of the G group (13.7 months vs. 8.0 months; $P = 0.035$). The major grade 3–4 adverse events were neutropenia (54.7% in the GS group and 22.0% in the G group), thrombocytopenia (15.1% in the GS group and 5.1% in the G group), and skin rash (9.4% in the GS group).
Conclusions The GS group showed stronger anticancer activity than the G group, suggesting the need for a large randomized phase III study to confirm GS advantages in a specific subset.

Keywords Unresectable pancreatic cancer · Chemotherapy · Gemcitabine · S-1 · Gemcitabine+S-1

Introduction

Pancreatic cancer (PC) currently is the fifth leading cause of cancer-related mortality in Japan, with an estimated 25,960 deaths attributable to the disease in 2010 [1]. Although surgical complete removal of the tumor is the only chance of cure, almost all PC patients are diagnosed at an advanced unresectable stage, despite recent improvements in diagnostic techniques. Moreover, since PC recurs in about 20% of patients even after surgical resection, development of effective chemotherapy is essential to improve the prognosis of this disease.

Gemcitabine (Gem) is widely used as a standard systemic chemotherapeutic agent for advanced PC [2]. Although some combination therapies including Gem have shown survival benefit, these are not considered as standard regimens [3, 4]. S-1 is a fourth generation oral fluoropyrimidine, which contains tegafur/gimeracil/oteracil potassium at a molar ratio of 1.0:0.4:1.0. The efficacy of S-1 has already been shown in a variety of solid tumors, particularly gastric cancer [5, 6]. A phase II trial of S-1 alone for PC metastatic to other organ has shown a response rate of 37.5% and a median survival of 9.2 months [7, 8]. Moreover, non-randomized phase II trials of a combination of Gem and S-1 (GS) therapy have demonstrated excellent results as to ORR of 44–48% and median survival of 10–12 months [9–13].

The current study (PC-01) was a randomized phase II trial to clarify the effectiveness of GS, prior to an anticipated phase III trial comparing GS with Gem alone, because there are many chemotherapy regimens that did not prove survival benefit despite the fact that one-arm phase II studies showed extremely promising results. Consequently, we, investigators of the Japan Clinical Cancer Research Organization (JACCRO), considered the current study (PC-01) could accurately elucidate the true activity of GS, because selection bias frequently seen in one-arm trials may be minimized by prospective randomization studies.

Patients and methods

Patients

The eligibility criteria for enrollment into this study (March 2007–August 2010) were patients with histologically or cytologically proven pancreatic adenocarcinoma, patients with International Union Against Cancer clinical stage III (locally advanced disease: T4N0-1 and M0) or IV (metastatic disease: T1-4N0-1 and M1), patients with measurable lesions as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines, age $\geq$20 and $\leq$80, no prior anticancer treatment for any malignancies, an Eastern Cooperative Oncology Group performance status (PS) $\leq$2, adequate bone marrow (leukocyte count $\geq$4,000/mm^3, neutrophil $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, and hemoglobin $\geq$8.0 g/dl), adequate renal function (serum creatinine concentration $\leq$1.5 mg/dl and creatinine clearance $\geq$60 ml/min), adequate hepatic function (serum bilirubin level $\leq$2.0 mg/dl, serum alanine and aspartate transaminase levels $\leq$2.5 times the upper limit of the institutional normal; if biliary drainage was performed for jaundice before registration, the former $\leq$5 times the upper limit of the institutional normal and the

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latter ≤2.5 times the upper limit of the institutional normal), oxygen saturation ≥93%, adequate nourishment, no serious complications, life expectancy of at least 8 weeks, and provision of written informed consent from the patient.

Before randomization, a complete history was obtained and physical examination, routine hematology and biochemistry, ECG, chest X-ray, and abdominal computed tomography (CT) scan were performed.

Study design

PC-01 was an open-label, screening design, randomized phase II study. The primary end point was ORR. Secondary end points included treatment toxicity, clinical response benefit, PFS, and OS.

Patients were randomly assigned to the G group or the GS group in a 1:1 ratio. Random assignment was performed centrally by a web-based assistant system (flexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure. Stratification factors were stage (III vs. IV), PS (0 or 1 vs. 2), and pain due to cancer (present vs. absent).

This study protocol was approved by the Protocol Review Committee of the JACCRO and Institutional Review Board of each institution, ClinicalTrials.gov identifier number was NCT00514163.

Protocol treatment

Eligible patients were randomly assigned to either the G group or the GS group. The G group patients received 1,000 mg/m^2 Gem intravenously during 30 min on days 1, 8, and 15, as 1 course repeated every 4 weeks. Patients with grade 4 hematological toxicities or grade 3 non-hematological toxicities underwent dose reduction to 800 mg/m^2 in the next course. The GS group patients received 1,000 mg/m^2 Gem intravenously during 30 min on days 1 and 8, and 40 mg/m^2 S-1 taken orally twice daily on days 1–14, every 3 weeks. When patients developed grade 4 hematological toxicities or grade 3 non-hematological toxicities by day 8, treatment was delayed by 1 week, and the S-1 dose was reduced to 60 mg/m^2 in the next course. In neither arms, prophylactic granulocyte-colony stimulating factor support allowed. Treatment was continued until progression, unacceptable toxicity, or patient refusal to continue the protocol treatment. The discontinuation of the protocol treatment for the reasons mentioned above was defined as protocol cessation.

Response and toxicity assessment

Toxicities were evaluated at each patient visit, according to the Common Terminology Criteria for Adverse Events version 3.0. CT or magnetic resonance imaging scans were performed at the baseline and after every 4 weeks to assess radiological response according to the RECIST version 1.0. Radiological tumor shrinkage of the primary tumor of the pancreas was assessed for all patients in the current study. ORR and DCR were set at the frequency of complete response plus partial response, in addition to stable disease among patients in each arm, respectively.

Clinical response benefit was assessed using daily analgesic consumption (measured in oral morphine-equivalent milligrams). Among patients who required opioid before the protocol treatment, patients whose opioid administration decreased to better than half of the baseline by day 1 of course 3 (8 weeks later in the G group and 6 weeks later in the GS group) were defined to be responders.

Statistical considerations

The primary endpoint was ORR. A sample size of 49 was required for a one-sided alpha value of 0.05 and a beta value of 0.20 with an expected response rate of 30% in the GS group and a threshold response rate of 10% in the G group. The protocol was activated in June 2007, and a total of 110 patients were planned for recruitment accounting for some drop-off

Table 1 Patient characteristics

Characteristics	G group (n = 59)	GS group (n = 53)	P value
	n	n	
Gender			
Male	35	32	1.00
Female	24	21	
Age			
<65	31	28	1.00
≥65	28	25	
ECOG PS			
0	45	44	0.66
1 or 2	14	9	
Locally advanced	18	13	0.53
Metastatic	41	40	
Metastatic sites			
Liver	30	28	0.85
Lymph node	10	6	0.43
Peritoneum	7	12	0.14
Lung	3	8	0.11
Ascites and/or pleural effusion			
Present	4	7	0.34
Absent	55	46	
Pain			
Present	20	17	1.00
Absent	39	36	

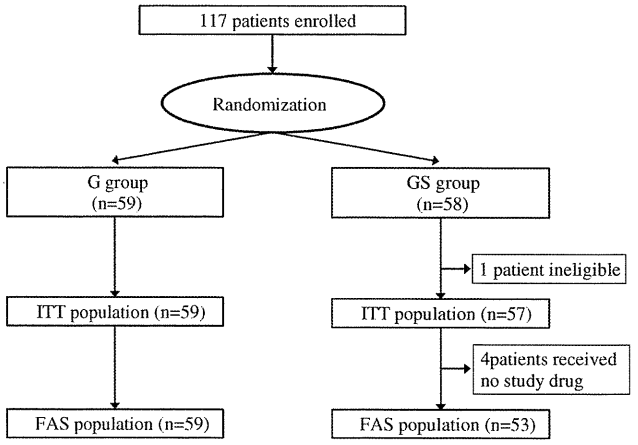

Fig. 1 Trial profile

cases within 1 year. If the null hypothesis (response rate) was not attained, the subsequent phase III trial would be designed to confirm the superiority of GS therapy to Gem alone.

The frequencies of each characteristic in Table 1 and each ORR and DCR in Table 3 were analyzed by the chi-square test.

OS was determined as the time from the date of registration to the date of death due to any cause and was censored at the date of the last follow-up for surviving patients. PFS was measured from the date of registration to the date of the first evidence of radiological or clinical progression, or death due to any cause and was censored at the date of the last follow-up CT for surviving patients with no clinical progression. OS and PFS were estimated by the Kaplan–Meier method, and the confidence interval (CI) was calculated with the Greenwood formula. Comparison of survival probability was conducted by the log-rank test. *P* values of less than 0.05 were considered to indicate statistically significant differences in the current study. The analysis was carried out with the SAS 9.2 statistical software (SAS Institute, Cary, NC, USA).

Results

Because of the poor recruitment rate, the protocol was amended twice, in January 2008 and February 2009, and a total of 117 patients were enrolled by August 2010 from 16 hospitals (see "Appendix"). One patient was judged to be ineligible after registration, because the final pathological diagnosis was not cancer. Accordingly, a total of 116 were allocated into either the G group ($N = 59$) or the GS group ($N = 57$) from among the intent-to-treat (ITT) population. Of the 116 patients, 4 in the GS group received supportive care instead of protocol treatment because of early deterioration or patient refusal. The full analysis set (FAS) consisted of 112, i.e., 59 and 53 patients in the G group and the GS group, respectively (Fig. 1).

Patient data registration was closed in June 2011, 10 months after the last patient registration. At the time of analysis, protocol treatment had been continued in 1 of 53 patients in the GS group. All analyses in comparison between the G group and the GS group were done in the FAS population, except OS.

Patient characteristics

Patient characteristics are shown in Table 1. The median age in the G group was 64 (41–79) years old, and that in the GS group was also 64 (45–77) years old. Although the protocol allowed enrollment of patients with PS 2, almost all patients were in good general condition (PS 0:1:2 was 79%:18%:3%, respectively). Metastatic disease was found in 72% of the patients. Analgesics (including opioids) were used in 33% (19%) of the patients at the baseline.

Toxicity

The major grade 3–4 adverse events are shown in Table 2. Although the frequency of grade 3–4 adverse events in the GS group was higher than that in the G group regarding both hematological and non-hematological toxicities, the toxicities were predictable and manageable. Discontinuation of the protocol treatment due to toxicity was seen in 13 (22%) of 59 protocol-cessation patients in the G group, and 14 (27%) of 52 protocol-cessation patients in the GS group. Treatment-related death was reported in 1 patient in each arm.

Clinical response benefit

At baseline, 12 and 10 patients required opioids in the G group and the GS group, respectively. There were 0 responders to opioids of 12 in the G group, and 2 of 10 in the GS group.

Objective response

Radiological responses are shown in Table 3. There was no complete response. The ORR in the GS group (28.3%) was significantly higher than that in the G group (6.8%), and the null hypothesis was rejected (two-sided $P = 0.005$). Also the DCR in the GS group was significantly higher.

In 31 patients with locally advanced disease, partial response was demonstrated in 1 (5.6%) of 18 patients in the G group, and 3 (23%) of 13 patients in the GS group. In the remaining 81 patients with metastatic disease, partial response was seen in 3 (7.3%) of 41 patients in the G group, and 12 (30%) of 40 patients in the GS group.

Table 2 Summary of maximum toxicity grades

Event	G group (n = 59)			GS group (n = 53)		
	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)
Hematological						
WBC	5.1	0	5.1	20.8	5.7	26.4
Hemoglobin	5.1	0	5.1	7.5	0	7.5
Neutrophil	20.3	1.7	22.0	41.5	13.2	54.7
Platelet	3.4	1.7	5.1	7.5	7.5	15.1
Non-hematological						
Fatigue	5.1	1.7	6.8	3.8	0	3.8
Anorexia	5.1	0	5.1	3.8	0	3.8
Nausea	1.7	0	1.7	3.8	0	3.8
Diarrhea	0	0	0	3.8	0	3.8
Stomatitis	0	0	0	3.8	0	3.8
Skin rash	0	0	0	7.5	1.9	9.4
AST	3.4	0	3.4	1.9	0	1.9
ALT	6.8	0	6.8	3.8	0	3.8
ALP	6.8	0	6.8	3.8	0	3.8
Bilirubin	6.8	0	6.8	1.9	0	1.9
Albumin	0	0	0	1.9	0	1.9
C-reactive protein	0	0	0	1.9	0	1.9
Treatment-related death	1.7			1.9		

Progression-free survival

PFS curves are shown in Fig. 2. Discontinuation of the protocol treatment due to progression was seen in 34 (58%) of 59 protocol-cessation patients in the G group, and 20 (38%) of 52 protocol-cessation patients in the GS group. The median progression survival time in the GS group (6.15 months) was significantly longer than that in the G group (3.78 months, $P = 0.0007$).

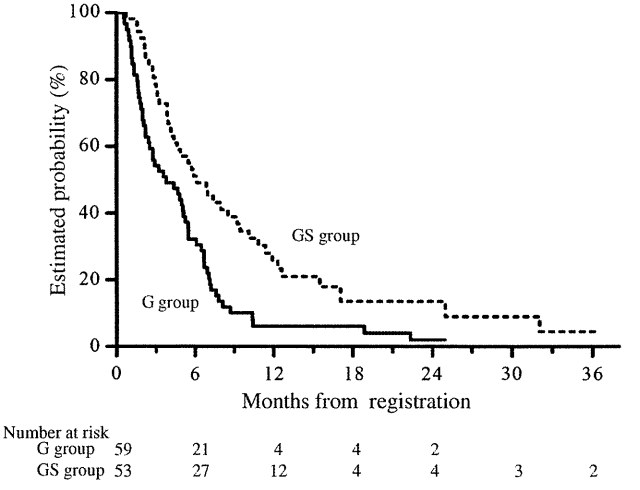

Fig. 2 Kaplan–Meier estimates of progression-free survival (n = 112)

Post-study treatment

After discontinuation of the protocol treatment, 37 (67%) of 55 patients in the G group and 23 (44%) of 52 patients in the GS group received various second-line treatments, most of which consisted of Gem or S-1 or both.

Overall survival in the ITT population

OS curves in the G group ($N = 59$) and the GS group ($N = 57$) are shown in Fig. 3. The GS group included 4 patients who deteriorated early or refused before protocol treatment, and subsequently received best supportive care without any anti-cancer treatment. The median survival time and 1-year survival probability in the G group and the GS group were 8.0 months and 29.0%, and 13.7 months and 55.9%, respectively. OS was significantly better in the GS group ($P = 0.035$), and its hazard ratio was 0.63 (95%, 0.41–0.97).

OS curves in the relation to extent of original disease are shown in Figs. 4 and 5. The median survival time in locally advanced and metastatic disease in the G group and the GS group were 8.7 and 7.7 months, and 14.6 and 12.9 months, respectively. OS in metastatic disease was significantly better in the GS group ($P = 0.029$).

Table 3 Objective response

Total (n = 112)	G group (n = 59)	GS group (n = 53)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	4 (6.8)	15 (28.3)	
Stable disease	22 (37.3)	19 (35.9)	
Progressive disease	23 (39.0)	7 (13.2)	
Not evaluable	10 (17.0)	12 (22.6)	
Objective response rate (%)	6.8	28.3	0.005
(95% CI)	(2.7–16.2)	(18.0–41.6)	
Disease control rate (%)	44.1	64.2	0.039
(95% CI)	(32.2–56.7)	(50.7–75.7)	
Locally advanced (n = 31)	G group (n = 18)	GS group (n = 13)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	1 (5.6)	3 (23.1)	
Stable disease	7 (38.9)	5 (38.5)	
Progressive disease	5 (27.8)	0	
Not evaluable	5 (27.8)	5 (38.5)	
Objective response rate (%)	5.6	23.1	0.284
(95% CI)	(1.0–25.8)	(8.2–50.3)	
Disease control rate (%)	44.4	61.5	0.473
(95% CI)	(24.6–66.3)	(35.5–82.3)	
Metastatic (n = 81)	G group (n = 41)	GS group (n = 40)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	3 (7.3)	12 (30.0)	
Stable disease	15 (36.6)	14 (35.0)	
Progressive disease	18 (43.9)	7 (17.5)	
Not evaluable	5 (12.2)	7 (17.5)	
Objective response rate (%)	7.3	30	0.011
(95% CI)	(2.5–19.4)	(18.1–45.4)	
Disease control rate (%)	43.9	65	0.075
(95% CI)	(29.9–59.0)	(49.5–77.9)	

Discussion

We set out to determine whether a combination of S-1 plus GS would obtain better results than GEM alone in a phase II study of unresectable pancreatic cancer.

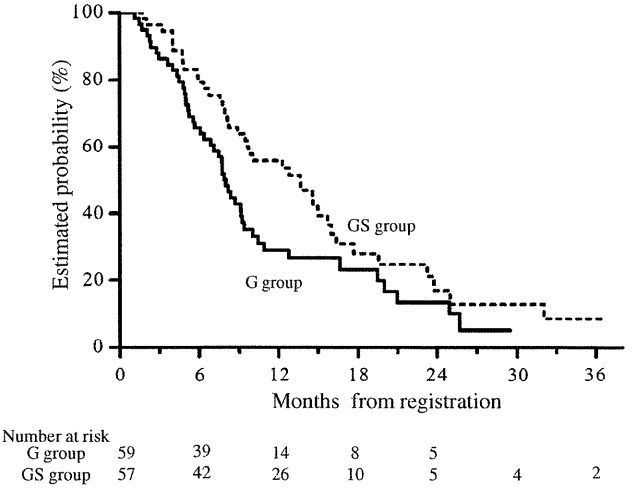

Fig. 3 Kaplan–Meier estimates of overall survival (n = 116)

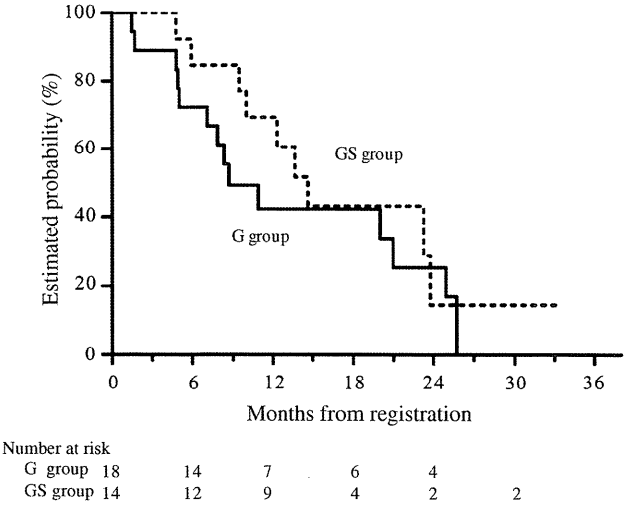

Fig. 4 Kaplan–Meier estimates of overall survival in locally advanced (n = 32)

The current PC-01 study, which was intended to screen GS as a promising investigation for a phase III trial comparing to standard Gem alone, successfully met this primary endpoint. Although the response rate obtained in the current study was lower than that in the previous one-arm phase II trials, the anticancer activity of GS was confirmed to be stronger than Gem alone [9–13]. Favorable results of GS as to PFS and OS data also encouraged us to plan a large phase III study comparing GS to standard Gem alone. However, results of large randomized phase III study of GS and Gem alone, known as the GEST trial, which was started by another Japanese cooperative group after our PC-01, were reported at the latest annual meeting of American Society of Clinical Oncology 2011 [14]. This large-scale (N = 600) GEST did not show OS superiority of GS compared to Gem alone. In terms of the survival benefit, this study seems to contradict the present PC-01 study.

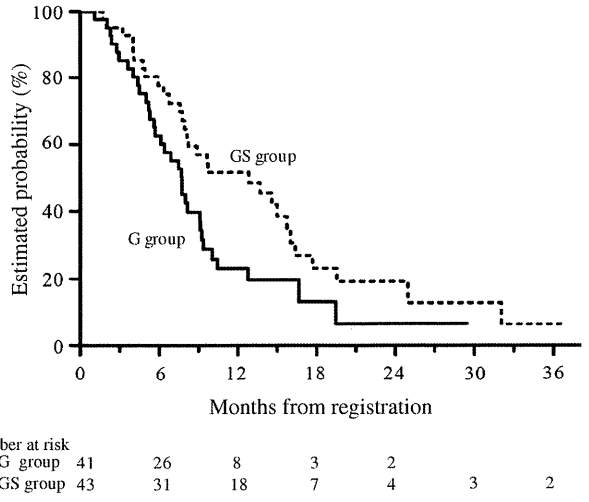

Fig. 5 Kaplan–Meier estimates of overall survival in Metastatic ($n = 84$)

Fluoropyrimidine and its derivatives have been intensively examined in combination with Gem for PC [15, 16]. All of those combinations have failed to show OS superiority compared to Gem alone in phase III settings, whereas relatively favorable results were generally reported in terms of response rate and survival. Accordingly, it may be important to explore a specific population in whom benefit would be maximized by GS therapy, though it may be difficult to develop Gem and fluoropyrimidine combination as a conventional frontline regimen for standard risk cases with advanced PC.

The main limitation of the PC-01 study derived from its inclusion of a relatively large number of patients who were found to be non-evaluable, mainly due to either the deterioration of the disease or patient refusal, which might well have affected the outcome of local response. On the other hand, randomized comparison of GS and Gem alone was one of the strengths of the current study. The ORR of GS in a previous non-randomized phase II study was extremely high, around 40%, perhaps due to selection bias [9–13]. However, in actual practice, since the response rate is usually below 30%, the PC-01 demonstrated a response rate acceptable to medical oncologists. Although PC-01 was not a phase III trial designed to confirm survival benefit, the OS and PFS data in the ITT population were impressive. The GS group showed a significant survival advantage against Gem group, even though the GS group included 3 cases of early deterioration. In the subset analysis, there was some discrepancy for the favorable population for GS between the current PC-01 and the GEST study. For example, GS was favorable in metastatic disease in PC-01; on the other hand, it was favorable in locally advanced disease in the GEST. GEMSAP, another Japanese study group, also carried out a randomized phase II trial of GEM and GS comparison and reported GS superiority to GEM in PFS in ASCO2011 [17].

Further accumulation of GEM and GS data might warrant an integrated meta-analysis to identify the population most likely to benefit from GS. Subsequently, a large randomized phase III trial to confirm GS advantages in a specific patients subset may be justified.

In conclusion, PC-01 demonstrated that GS had strong anticancer activity, and we believe that GS in some situations would be beneficial to give advanced PC patients.

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Conflict of interest No authors have any conflict of interest.

Appendix

The following investigators registered patients for this study:

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Yuki Hirose (Japan Red Cross Fukui Hospital, Fukui, Japan); Takaaki Ikari (Tobu Chiiki Hospital Tokyo Metropolitan Health and Medical Treatment Corporation, Tokyo, Japan).

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Construction and Validation of a Prognostic Index for Patients With Metastatic Pancreatic Adenocarcinoma

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Objectives: To identify prognostic factors in patients with metastatic pancreatic adenocarcinoma.

Methods: The relationship between patient characteristics and outcome was examined by multivariate regression analyses of data from 409 consecutive patients with metastatic pancreatic adenocarcinoma who had been treated with a gemcitabine-containing regimen, and we stratified the patients into 3 risk groups according to the number of prognostic factors they had for a poor outcome. A validation data set obtained from 145 patients who had been treated with agents other than gemcitabine was analyzed. The prognostic index was applied the each of the patients.

Results: The multivariate regression analyses revealed that the presence of pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value significantly contributed to a shorter survival time. The patients were stratified into 3 groups according to their number of risk factors, and their outcomes of the 3 groups were significantly different. When the prognostic index was applied to the validation data set, the respective outcomes of the 3 groups were found to be significantly differed from each other.

Conclusions: Pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value are important prognostic factors for patients with metastatic pancreatic adenocarcinoma.

Key Words: pancreatic cancer, prognostic factor, validation, chemotherapy, multivariate analyses, prognostic index

(*Pancreas* 2011;40: 415–421)

Despite the major advances in cancer management that have been achieved in recent years, pancreatic adenocarcinoma (PC) remains a challenge to clinicians because of the difficulty of early diagnosis. Most PC patients have locally advanced or metastatic disease by the time the diagnosis is made. Even when resection is performed, the recurrence rate is extremely high, and nonsurgical treatments after recurrence have largely been ineffective.[1,2] Although gemcitabine (GEM) has been demonstrated to provide a modest clinical benefit and therefore become the standard chemotherapy for advanced PC,[3,4] the median survival time of patients with advanced disease remains only around 6 months. Many clinical trials of treatments with combinations GEM and other agents have been conducted to improve treatment efficacy in patients with advanced PC, and one of them, a combination of GEM and erlotinib, has resulted in longer survival than treatment with single-agent GEM.[5] However, because the difference in median overall survival between the 2 regimens was only 0.3 months and the incidence of adverse events with GEM plus erlotinib tended to be higher, this combination has been considered a treatment option for patients in good general condition, not an alternative to GEM monotherapy. Because various treatment options according to the patient's general condition and prognosis are expected to be developed in the future, if the survival time of patients with metastatic PC could be predicted before the start of the treatment, those with an extremely poor prognosis could be offered supportive care alone or more conservative treatment, such as GEM monotherapy and spared the adverse effects of combination chemotherapy. A validated prognostic index would identify subgroups of patients for specific treatments and predict survival, and identification of prognostic factors would be helpful in designing clinical trials of systemic chemotherapy and analyzing their results. Furthermore, clinical trials of various new treatments will be conducted in the future, and because some of the candidate drug combinations for new treatment regimens may contain GEM and others may not, establishment of an accurate prognostic index that can be applied to various treatment regimens is needed. Although many possible prognostic factors, such as performance status,[6–8] the serum carbohydrate antigen (CA 19-9) level,[9–14] and the serum C-reactive protein (CRP) level[11,13,15,16] have been identified in advanced PC, most were identified in small numbers of patients, and the results were not validated, possibly making the analyses underpowered and unreliable.

The purposes of this study were (1) to identify the most helpful, readily available prognostic factors for predicting the survival time of metastatic PC patients and (2) to construct and validate a practical and universal prognostic index for metastatic PC patients.

MATERIALS AND METHODS

Cases Used as the Basis for Construction of the Prognostic Index (Construction Set)

Data from 409 consecutive patients with metastatic PC who had received GEM-containing systemic chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between March 2001 and January 2007 were reviewed to construct the prognostic index. None of the patients had been treated for their cancer before chemotherapy, except that some of them had undergone by pancreatectomy. All patients had distant metastasis based on diagnostic imaging findings obtained by various modalities, including chest radiography, ultrasonography, and computed tomography. The diagnosis of adenocarcinoma was confirmed pathologically in every case by examination of the surgical specimen or a fine-needle aspiration biopsy specimen. Whenever possible, peritoneal or pleural fluid cytodiagnosis was performed in patients with an intraperitoneal or intrapleural fluid collection. Percutaneous transhepatic or endoscopic retrograde biliary drainage was performed in all patients who had

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TABLE 1. Patient Characteristics

			Construction Set		Validation Set	*P*
Age		Median (range)	64 (21–81)		59.5 (39–75)	0.0005*
Sex	Male	n (%)	241 (59)		98 (68)	0.10†
	Female	n (%)	168 (41)		47 (32)	
Performance status	0–1	n (%)	395 (97)		138 (95)	0.40†
	2–3	n (%)	14 (3)		7 (5)	
Prior pancreatectomy	(+)	n (%)	66 (16)		16 (11)	0.24†
Abdominal and/or back pain‡	(+)	n (%)	138 (34)		62 (43)	0.074†
Diabetes mellitus	(+)	n (%)	171 (42)		46 (31)	0.037†
Location of primary tumor	Uncus and head	n (%)	191 (47)		48 (33)	0.01†
	Body or tail	n (%)	217 (53)		94 (65)	
Liver metastasis	(+)	n (%)	297 (73)		111 (77)	0.39†
Lymph node metastasis	(+)	n (%)	124 (30)		49 (34)	0.44†
Lung metastasis	(+)	n (%)	68 (17)		22 (15)	0.76†
Peritoneal dissemination	(+)	n (%)	88 (22)		37 (26)	0.40†
Pleural metastasis	(+)	n (%)	28 (7)		4 (3)	0.10†
Bone metastasis	(+)	n (%)	8 (2)		2 (1)	0.92†
Leukocytes count, /mL	(3900–6300)§	Median (range)	6100 (2100–35,500)		6800 (3400–18,000)	0.015*
Hemoglobin level, g/dL	(11.3–14.9)§	Median (range)	12.3 (6.7–16.1)		12.2 (8.6–15.9)	0.50*
Platelets count, /mL	(12.5–37.5)§	Median (range)	22.3 (9.2–57.4)		22.5 (9.5–47.1)	0.55*
Albumin level, g/dL	(3.7–5.2)§	Median (range)	3.7 (2.2–4.9)		3.7 (2.2–4.7)	0.50*
Total bilirubin level, mg/dL	(0.3–1.2)§	Median (range)	0.7 (0.2–3.1)		0.7 (0.3–3.2)	0.92*
AST level, IU/L	(13–33)§	Median (range)	27 (10–196)		26 (10–204)	0.46*
ALT level, IU/L	(6–27)§	Median (range)	29 (5–465)		28 (7–366)	0.90*
LDH level, IU/L	(119–229)§	Median (range)	188 (19–2311)		162 (15–2192)	0.001*
CRP level, mg/dL	(−0.1)§	Median (range)	0.6 (0.0–20.6)		0.8 (0–17.8)	0.15*
CEA level, ng/mL	(−5.0)§	Median (range)	6 (0.6–2090)		6.9 (0.4–9990)	0.55*
CA19-9 level, U/mL	(−37)§	Median (range)	1857 (1–1620,000)		3022 (1–1,857,600)	0.088*
Treatment		n (%)	GEM alone 302 (74)	Irinotecan	16 (11)	
		n (%)	GEM + S-1 41 (10)	Docetaxel	6 (4)	
		n (%)	GEM + 5-FU 27 (7)	S-1	29 (20)	
		n (%)	GEM + CDDP 39 (10)	UFT	22 (15)	
		n (%)		5-FU + CDDP	31 (21)	
		n (%)		MTX + 5-FU	41 (28)	

*Mann-Whitney *U* test.

†χ^2 test.

‡Abdominal and/or back pain: treated with opioid.

§Reference range.

CDDP indicates cisplatin; FU, fluorouracil; MTX, methotrexate.

obstructive jaundice before chemotherapy. All patients provided written informed consent before the start of treatment.

Factors Analyzed

The following 24 variables were selected for analysis in this study based on the results of previous investigations[12,13,15,17–23] and/or our own clinical experience: (1) age, sex, prior pancreatectomy, Eastern Cooperative Oncology Group performance status, abdominal and/or back pain treated with an opioid, diabetes mellitus, leukocyte count, hemoglobin level, platelet count, and serum level of albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin, CRP, as host-related variables, and (2) location of the primary tumor, liver metastasis, lymph node metastasis, lung metastasis, peritoneal dissemination, pleural metastasis, bone metastasis, serum level of carbohydrate antigen 19-9 (CA19-9), and CEA, as tumor-related variables. All data were obtained immediately before the start of systemic chemotherapy. Nodules more than 1 cm in diameter and/or a conspicuous volume of effusion in the abdominal or thoracic cavity observed by ultrasonography or computed tomography and cytologically proven malignant effusions were considered evidence of peritoneal dissemination or pleural metastasis in this study.

Cases Used as a Basis for Validation of the Prognostic Index (Validation Set)

A data set from 145 patients who participated in clinical trials of anticancer agents other than GEM at the National Cancer Center Hospital between August 1991 and January 2004 was used to validate the prognostic index. The treatment regimens were docetaxel,[24] irinotecan,[25] S-1,[26] UFT,[27] 5-fluorouracil + cisplatin,[28] and methotrexate + 5-fluorouracil.[29]

TABLE 2. Univariate Analysis

Categorical Variables			Continuous Variables		
	Median Survival Time, d	*P*		Coefficient (β)	*P*
Sex					
Male	209		Age, yr	−0.005	0.3542
Female	188	0.3543	Leukocytes count, /mL	7.59	<0.0001
Performance status					
0–1	207		Hemoglobin level, g/dL	−1.59	<0.0001
2–3	102	0.138	Platelets count, /mL	0.021	0.001
Prior pancreatectomy					
+	298		Albumin, g/dL	−0.867	<0.0001
−	191	<0.0001	Total bilirubin level, mg/dL	−0.088	0.3902
Abdominal and/or back pain*					
+	144		AST level, IU/l	0.008	<0.0001
−	238	<0.0001	ALT level, IU/L	0.003	0.0095
Diabetes mellitus					
+	201		LDH level, U/L	0.003	<0.0001
−	198	0.9802	CRP level, mg/dL	0.129	<0.0001
Location of primary tumor					
Uncus or head	200		CEA level, ng/mL	0.001	<0.0001
Body or tail	204	0.9885	CA19-9 level, U/mL	1.296	0.0004
Liver metastasis					
+	186				
−	243	<0.0001			
Lymph node metastasis					
+	167				
−	219	0.0584			
Lung metastasis					
+	224				
−	196	0.5835			
Peritoneal dissemination					
+	156				
−	219	0.0063			
Pleural metastasis					
+	198				
−	200	0.5435			
Bone metastasis					
+	113				
−	204	0.0336			

*Abdominal and/or back pain: treated with an opioid.

Statistical Analysis

Survival rates were calculated by the method of Kaplan and Meier.[30] All deaths regardless of cause were considered events. The stratified log-rank test was used to compare survival curves, and censored data were taken into account.[31]

Univariate Analysis

A univariate analysis was conducted to select candidate factors to adopt in the multivariable analysis. For categorical data, factors were divided into 2 categories, and the log-rank test was applied. Because dichotomizing continuous variable data, such as the serum biochemical and hematological data, by using arbitrary cutoff points might have resulted in major biases, we used the Cox proportional hazards model, which enables selection of candidate factors without dichotomization.[32,33] Differences with a $P < 0.01$ were considered significant.

Multivariate Analysis

The variables identified as having prognostic significance in the univariate analyses were included in the subsequent multivariate analysis. To construct a simple and practical prognostic index for routine clinical use, all factors were divided into 2 categories. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cutoff value to maximize both the sensitivity and the specificity of continuous variables. Each ROC curve was constructed as a predictor of death at 6.6 months, which was the median survival time of the cases in the construction set. The Cox proportional hazards model was used to identify the variables that made the most significant contribution to survival. Differences with a $P < 0.01$ were considered significant. All P values were 2 sided. All analyses were performed by using Dr SPSS statistical software (SPSS Inc, Chicago, Ill).

The numbers of risk factors present were used to construct the prognostic index. Patients were stratified into 3 risk groups on the basis of the number of risk factors present.

RESULTS

Patient Characteristics

There were 241 men and 168 women in the construction set. Their median age was 64 years (range, 21–81 years), and the performance status of 395 patients was 0 to 1. Liver metastasis had been diagnosed in 297 patients, and peritoneal dissemination had been diagnosed in 88 patients (Table 1). The treatment regimens were GEM alone in 302 patients, GEM + cisplatin, 39, GEM + 5-flurorouracil, 27, and GEM + S-1, 41.

Survival

As of the date of the survival analysis, 404 patients had died, and the median survival time and 1-year survival rate were 6.6 months and 22%, respectively.

Univariate Analysis

The following 14 of the 24 pretreatment variables evaluated were identified as significantly associated with shorter survival time (Table 2): absence of prior pancreatectomy ($P < 0.0001$), presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver metastasis ($P < 0.0001$), presence of peritoneal dissemination ($P = 0.0063$), elevated leukocyte count ($P < 0.0001$), elevated platelet count ($P = 0.001$), elevated serum AST level ($P < 0.0001$), elevated serum ALT level ($P < 0.0095$), elevated serum LDH level ($P < 0.0001$), elevated serum CRP level ($P < 0.0001$), elevated serum CA19-9 level ($P = 0.0004$), elevated serum CEA level ($P < 0.0001$), low hemoglobin level ($P < 0.0001$), and low serum albumin level ($P < 0.0001$).

Multivariate Analysis

The 14 variables found to be of prognostic significance in the univariate analysis were included in the subsequent multivariate Cox regression model. Receiver operating characteristic curve analysis was used to determine the cutoff point for continuous variables. Finally, to simplify the prognostic index, some cutoff values were approximated, thus: leukocyte count, from 7200/mL to 7000/mL; hemoglobin level, from 11.9 to 12 g/dL; platelet count, from $27.8 \times 10^4/\mu L$ to $28 \times 10^4/\mu L$; serum CRP level, from 0.9 to 1.0 mg/dL; serum CA19-9 level, from 3414 to 3000 U/mL; and serum CEA level, from 6.7 to 7 ng/mL. Originally simple values, such as serum albumin level (3.7 g/dL), serum AST level (22 IU/L), serum ALT level (28 IU/L), and serum LDH level (190U/L) were not approximated. Only 4 of the previously mentioned factors, presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver

TABLE 3. Multivariate Analysis

		Coefficient (β)	Hazards Ratio	99%CI	P
Prior pancreatectomy	−	0.297	1.346	0.906–2.000	0.530
Abdominal and/or back pain*	+	0.526	1.692	1.262–2.271	<0.0001
Liver metastasis	+	0.353	1.423	1.015–1.995	0.0071
Peritoneal dissemination	+	0.563	1.756	1.238–2.492	<0.0001
Leukocyte count	>7000 (/μL)	0.058	1.060	0.775–1.449	0.6313
Hemoglobin level	<12 (g/dL)	0.244	1.277	0.949–1.717	0.0337
Platelet count	>28 ($\times 10^4/\mu L$)	0.269	1.309	0.954–1.796	0.0285
Albumin level	<3.7 (g/dL)	0.124	1.132	0.841–1.523	0.2826
AST level	>22 (IU/L)	0.078	1.081	0.731–1.599	0.6089
ALT level	>28 (IU/L)	0.212	1.236	0.858–1.781	0.1352
LDH level	>190 (U/L)	0.259	1.295	0.951–1.764	0.0309
CRP level	>1 (mg/dL)	0.432	1.540	1.117–2.124	0.0005
CEA level	>7 (U/mL)	0.205	1.227	0.924–1.631	0.0634
CA19-9 level	>3000 (ng/mL)	0.101	1.106	0.825–1.482	0.3762

CI indicates confidence interval.

*Abdominal and/or back pain: treated with an opioid.

TABLE 4. Prognostic Index of Patients With Metastatic PC Receiving Systemic Chemotherapy

Risk Factors	
• Abdominal and/or back pain treated with an opioid	Present
• Liver metastasis	Present
• Peritoneal dissemination	Present
• Serum CRP level	>1 (mg/dL)
Risk groups	
No. risk factors	
0	Low risk
1–2	Intermediate risk
3–4	High risk

metastasis ($P = 0.008$), presence of peritoneal dissemination ($P < 0.0001$), and elevation of the serum CRP level to greater than 1.0 mg/dL ($P < 0.0007$), were identified as independent prognostic factors (Table 3).

Risk Groups Based on the Regression Model

To be able to apply the indicated prognostic factors to clinical routine use, patients were stratified into 3 risk groups according to their number of the negative prognostic factors (Table 4): a low-risk group of 47 patients with 0 risk factors, an intermediate-risk group of 276 patients with 1 to 2 risk factors, and a high-risk group of 86 patients with 3 to 4 risk factors. The survival curves of these groups are shown in Figure 1. There were significant differences between survival time in the 3 groups (median survival time: low-risk group, 11.0 months; intermediate-risk group, 7.3 months; and high-risk group, 3.2 months; $P = 0.0001$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

Validation of the Prognostic Index

The prognostic index was applied to each of the 145 cases used for validation. The patient's characteristics were similar to those of the cases in the construction set (Table 1), but the proportion of patients with diabetes mellitus and the proportion of patients whose primary tumor was in the uncus or the head were lower in the validation set. In addition, median age was younger, the median leukocyte count was higher, and the LDH value was lower in the validation set than those in the construction set. Of the 145 patients in the validation set, 141 had died. The median survival time of the 145 patients was 4.8 months, and their 1-year survival rate was 12%. We calculated the prognostic index of the 145 patients and then stratified them into 3 risk groups as described previously and compared the distribution of survival times among the 3 risk groups. Figure 2 shows a comparison of the survival curves of the 3 risk groups. There were significant differences in survival time among the 3 groups (median survival time: low-risk group, 8.6 months; intermediate-risk group, 5.2 months; and high-risk group, 2.3 months; $P = 0.03$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

DISCUSSION

In this study, we attempted to identify prognostic factors in patients with metastatic PC who had received systemic chemotherapy, and 14 of the 24 potential prognostic factors assessed were identified as significant predictors of survival by the univariate analysis. However, only 4 factors, abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and elevated serum CRP level, were found to have independent prognostic value by the multivariate analysis.

Abdominal and/or back pain is one of the most common symptoms of PC patients. Previous studies have shown correlations between pancreatic tumor size, invasion of the anterior pancreatic capsule, and lymph node metastasis and the pain intensity of patients with operable tumors.[23,34] Several studies have also shown a significant impact of preoperative pain has on the outcome after resection.[34–36] However, the pain of patients with unresectable, more advanced PC may be attributable to invasion of the retroperitoneum or extrapancreatic nerve plexus

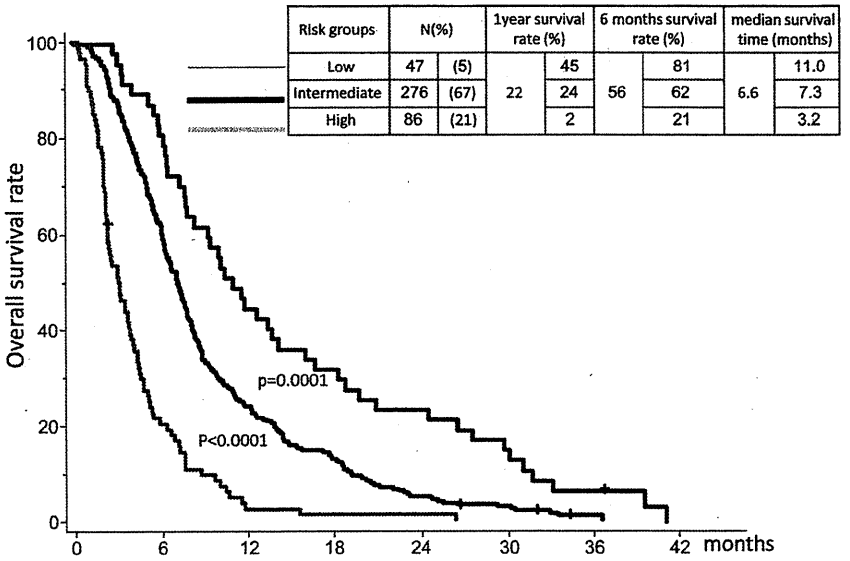
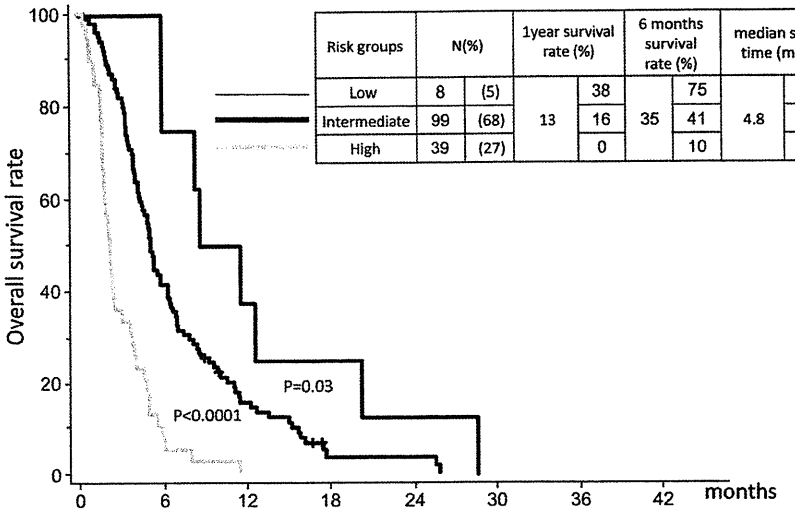


FIGURE 1. Comparison of the survival curves of patients who have received GEM-containing systemic chemotherapy and stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.0001$) and between the intermediate- and high-risk groups ($P < 0.0001$). *P* values were calculated by the log-rank test.



Risk groups	N(%)		1year survival rate (%)		6 months survival rate (%)		median survival time (months)	
Low	8	(5)	13	38	35	75	4.8	8.6
Intermediate	99	(68)		16		41		5.2
High	39	(27)		0		10		2.3

FIGURE 2. Comparison of the survival curves of patients used for validation stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.03$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.

because such advanced tumors sometimes destroy nerves more extensively than resectable tumors.

Peritoneal dissemination[37,38] and liver metastasis[39–41] have long been considered to tend to result in a fatal clinical course. Patients with peritoneal dissemination exhibit the clinical manifestations of bowel obstruction, ascites, and abdominal pain. Such complications often cause malnutrition and general deterioration. Patients with liver metastasis often have jaundice or lapse into a hepatic coma. Moreover, the dose and the schedule of chemotherapy sometimes have to be modified for patients with peritoneal dissemination or liver dysfunction because the adverse effects of chemotherapy are more severe in such patients. A previous study found that peritoneal dissemination predicts limited the effectiveness of chemotherapy in advanced PC.[42]

An elevated CRP level[13,16] has been demonstrated to be of prognostic significance in patients with PC and a variety of other gastrointestinal neoplasms.[43–45] Proinflammatory cytokines, including interleukin 6, are key signals in promoting hepatic CRP production, and there is evidence that they play a role in the genesis of cancer-associated cachexia,[46–48] which shortens the survival time of patients with metastatic PC.

Although previous studies have shown that performance status is one of the most important prognostic factors in patients with advanced PC,[13,49,50] it was not identified as a significant predictor of survival in this study. One of the main reasons for not having identified it as a significant predictor may be that proportion of patients with a performance status of 2 to 3 was extremely small in this study, only 3%.

Many models for clinical outcome prediction have been described in the medical literature, but most never find their way into clinical practice. One reason for their failure to be adopted in clinical practice may be that they have not been validated by external data and therefore lack universality and credibility. To our knowledge, this is the first report of not only construction but also validation of a practical prognostic index for patients with metastatic PC.

Some of the factors assessed in this study were continuous variables, and continuous variables are often converted into categorical variables by grouping the values into 2 or more categories. However, there is also the risk of major bias when the choice of the cutoff value is data driven, and the use of different cutoff points across multiple studies hinders direct comparisons. Dichotomizing continuous variables, on the other hand, is a reasonable method of constructing simple and practical tools for routine clinical use. To achieve a balance between convenience and credibility, we applied the Cox regression model to continuous variables in the univariate analysis to select candidates for the multivariable analysis. We then identified objective cutoff values by ROC curve analysis for the candidates, divided continuous variables into 2 categories, and applied the multivariate analysis.

Because we used a data set of patients treated with a GEM-containing regimen to construct the prognostic index and a data set of patients treated with anticancer agents other than GEM to validate it, this prognostic index may be helpful in designing clinical trials of systemic chemotherapy even if the investigational regimen does not contain GEM.

In conclusion, the presence of abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and serum CRP elevation to 1.0 mg/dL or greater were identified as significant prognostic factors in patients with metastatic PC who had received systemic chemotherapy. Accurate prediction of survival may be achieved by applying a prognostic index incorporating these 4 factors. This index facilitates stratification of patients with metastatic PC into 3 risk groups. Our index is expected to be useful for selecting treatment strategies; patients with an extremely poor prognosis could be offered supportive care alone or more conservative treatment. Furthermore, it is also expected to be useful for designing future clinical trials for patients with metastatic PC.

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ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

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ABSTRACT

BACKGROUND

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors, in two phase 2 studies. We evaluated the agent in a prospective, randomized, phase 3 study.

METHODS

We randomly assigned 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months to receive everolimus, at a dose of 10 mg once daily (207 patients), or placebo (203 patients), both in conjunction with best supportive care. The primary end point was progression-free survival in an intention-to-treat analysis. In the case of patients in whom radiologic progression occurred during the study, the treatment assignments could be revealed, and patients who had been randomly assigned to placebo were offered open-label everolimus.

RESULTS

The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval [CI], 0.27 to 0.45; P<0.001), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23% vs. 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks vs. 16 weeks).

CONCLUSIONS

Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events. (Funded by Novartis Oncology; RADIANT-3 ClinicalTrials.gov number, NCT00510068.)

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