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Concurrent Radiotherapy and Gemcitabine for Unresectable Pancreatic Adenocarcinoma: Impact of Adjuvant Chemotherapy on Survival

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Summary

This retrospective study looked at patients with unresectable pancreatic cancer treated with different combinations of chemotherapy and radiation. When concurrent chemo-radiotherapy using gemcitabine was used, a relatively favorable local control rate was seen. When adjuvant chemotherapy was given,

Purpose: To retrospectively analyze results of concurrent chemoradiotherapy (CCRT) using gemcitabine (GEM) for unresectable pancreatic adenocarcinoma.

Methods and Materials: Records of 108 patients treated with concurrent external beam radiotherapy (EBRT) and GEM were reviewed. The median dose of EBRT in all 108 patients was 50.4 Gy (range, 3.6–60.8 Gy), usually administered in conventional fractionations (1.8–2 Gy/day). During radiotherapy, most patients received GEM at a dosage of 250 to 350 mg/m^2 intravenously weekly for approximately 6 weeks. After CCRT, 59 patients (54.6%) were treated with adjuvant chemotherapy (AC), mainly with GEM. The median follow-up for all 108 patients was 11.0 months (range, 0.4–37.9 months).

Results: Initial responses after CCRT for 85 patients were partial response: 26 patients, no change: 51 patients and progressive disease: 8 patients. Local progression was observed in 35 patients (32.4%), and the 2-year local control (LC) rate in all patients was 41.9%. Patients treated with total doses of 50 Gy or more had significantly more favorable LC rates (2-year LC rate, 42.9%) than patients treated with total doses of less than 50 Gy (2-year LC rate,

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a small survival benefit became evident. Adjustments in the sequencing of chemotherapy and radiation thus have the potential to improve outcomes.

29.6%). Regional lymph node recurrence was found in only 1 patient, and none of the 57 patients with clinical N0 disease had regional lymph node recurrence. The 2-year overall survival (OS) rate and the median survival time in all patients were 23.5% and 11.6 months, respectively. Patients treated with AC had significantly more favorable OS rates (2-year OS, 31.8%) than those treated without AC (2-year OS, 12.4%; $p < 0.0001$). On multivariate analysis, AC use and clinical T stage were significant prognostic factors for OS.

Conclusions: CCRT using GEM yields a relatively favorable LC rate for unresectable pancreatic adenocarcinoma, and CCRT with AC conferred a survival benefit compared to CCRT without AC.

Keywords: Chemotherapy, Gemcitabine, Pancreatic neoplasms, Radiotherapy, Unresectable

Introduction

Pancreatic cancer is one of the leading causes of cancer death worldwide. The prognosis for patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of less than 5% (1, 2). Most patients with pancreatic cancer already have advanced disease at the time of diagnosis, and among patients with unresectable pancreatic cancer, nearly half of patients have advanced but localized disease (2).

In the 1980s, the Gastrointestinal Tumor Study Group reported the survival benefit of 5-fluorourcil (5-FU)-based concurrent chemoradiotherapy (CCRT) over that of external beam radiotherapy (EBRT) alone in patients with unresectable pancreatic cancer (3). Until recently, CCRT has been the standard approach to treating surgically unresectable, localized disease. More recently, therapy using the drug gemcitabine (GEM), a nucleoside analogue, has been reported to confer marginally superior clinical benefit and survival compared with that with 5-FU (4). GEM has also been shown to be a potent radiosensitizer in pancreatic cancer (5). Therefore, concurrent radiotherapy and GEM may be a promising strategy for treating unresectable localized pancreatic cancer. However, optimal management of concurrent EBRT and GEM for unresectable disease has not been fully investigated.

In the current study, we reviewed a retrospective and multi-institutional series of 108 patients with nonmetastatic unresectable pancreatic cancer, who were treated with concurrent radiotherapy using GEM, and evaluated the efficacy and safety of this treatment for these tumors.

Methods and Materials

The Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide questionnaire survey of patients with nonmetastatic pancreatic adenocarcinoma who were treated with radiotherapy. The questionnaire elicited detailed information regarding patient characteristics, treatment characteristics, and outcomes of treatments. Details of the JROSG survey have been described elsewhere (6–8). Briefly, 34 radiation oncology centers belonging to the JROSG agreed to participate in this survey, and detailed information for 870 patients was accumulated. Of these patients, 223 patients with unresectable disease were treated with concurrent EBRT and GEM. Histology finding for 108 patients was adenocarcinoma; 3 patients had other histological findings, such as anaplastic carcinoma and undifferentiated carcinoma; and 112 patients had no histological information. These last 115 patients were excluded from this study, and the remaining 108 patients with histological diagnosis of adenocarcinoma were the subjects of the current study. Their tumors were judged to be unresectable by the respective physicians at each institution. Of these 108 patients, there were 3 patients with inoperable cancer, who were not fit for surgery, and the remaining 105 patients had unresectable tumors at presentation.

Patient and treatment characteristics for all 108 patients are shown in Table 1. The median age of patients was 63 years old (range, 40–83 years old), and the Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranged from 0 to 3 (median, 1). We used the tumor staging system devised by the Union Internationale Contre le Cancer (9). The median maximum tumor size was 3.9 cm (range, 1.4–10.0 cm), and the median serum concentration of carbohydrate antigen 19-9 (CA19-9) was 511 U/mL (range, 0–57,300 U/mL). Total doses of EBRT ranged from 3.6 to 60.8 Gy (median, 50.4 Gy), with a single fraction of 1.8 to 2 Gy given 5 days per week in most patients. On the other hand, 11 patients (10.2%) were treated with a single fraction of 2.2 to 2.5 Gy.

Chemotherapy schedules are described in Table 2. During radiotherapy, 8 patients received a dosage of 1,000 mg/m^2 GEM weekly for 3 weeks with a 1-week rest period, depending on their response and toxicity (using the standard dosage of GEM). The remaining 100 patients received GEM at a dosage of 250 to 350 mg/m^2 intravenously weekly during radiotherapy for approximately 6 weeks (low-dose GEM). After radiotherapy, 59 of 108 patients (54.6%) were treated with adjuvant chemotherapy (AC). Fifty-three of 59 patients (89.8%) received GEM maintenance chemotherapy, usually given at 1,000 mg/m^2 weekly for 3 weeks with a 1-week rest period, until disease progression or unacceptable toxicity was reached. Six patients received intravenous bolus infusions of 300 to 500 mg/m^2 5-FU, until disease progression or unacceptable toxicity was reached. For 5 patients, a combination compound of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium (S-1) was administered orally, and S-1 doses ranged from 50 to 80 mg/m^2.

In the current study, there were no definitive treatment policies for pancreatic cancer during the survey period; thus, treatment was determined by the respective physicians at each institution. We assigned 108 patients to two groups (patients treated with AC and those without AC treatment) and determined whether the AC influenced patient characteristics, such as age, tumor size, and clinical stage. There were no significant differences in age, gender, tumor site, tumor size, or clinical T stage and clinical N stage, except for CA19-9 levels, which varied according to the AC used (data not shown). Concerning PS, there were no significant differences according to the AC used, and 56 of 58 patients with

Table 1 Patient and disease characteristics

Characteristic	No. of patients	% of total
Age (median, 63 years old)		
<70	84	77.8
≥70	24	22.2
Gender		
Female	50	46.3
Male	58	53.7
Primary site		
Head	55	50.9
Body	48	44.4
Tail	4	3.7
Unknown	1	0.9
Maximum tumor size (median, 3.9 cm)		
<4.0 cm	48	44.4
≥4.0 cm	54	50.0
Unknown	6	5.6
ECOG performance status scale		
0	28	25.9
1	70	64.8
2	5	4.6
3	1	0.9
Unknown	4	3.7
CA19-9 (U/ml) (median, 248.2 U/ml)		
<1,000	56	51.9
≥1,000	43	39.8
Unknown	9	8.3
Clinical T stage (UICC 2002)		
2	3	2.8
3	15	13.9
4	90	83.3
Clinical N stage (UICC 2002)		
0	57	52.8
1	49	45.4
Unknown	2	1.8
EBRT total radiation dose (Gy) (median, 50.4 Gy)		
<40	6	5.6
40≤ to <50	9	8.3
50≤ to <60	89	86.4
≥60	4	3.7
Dose per fraction (Gy)		
1.8–2	97	89.8
2.2–2.5	11	10.2
Radiation field		
Primary plus LN	65	60.2
Primary only	43	39.8
CT-based treatment planning		
Yes	106	98.1
No	2	1.9
Conformal therapy		
Yes	91	84.3
No	17	15.7
GEM dose during EBRT		
Low dose (250–350 mg/m^2/week)	100	92.6
Standard dose (1,000 mg/m^2/week)*	8	7.4
Adjuvant chemotherapy use		
Yes	59	54.6
No	49	45.4

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CT = computed tomography; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; LN = lymph nodes; UICC = Union Internationale Contre le Cancer.

* Usually administered weekly for 3 weeks with a 1-week rest period.

AC therapy (96.6%) and 42 of 46 patients without AC (91.3%) had PS of 0 to 1 ($p = 0.2543$).

The median follow-up for all 108 patients was 11.0 months (range, 0.4–37.9 months). In the current study, local failure was defined as apparent primary tumor progression detected by computed tomography (CT) scans after CCRT. Assessment of initial response by CCRT was based on CT scans that were obtained within 3 months after CCRT. In the current study, complete response was defined as the complete disappearance of all visible tumor, and partial response (PR) was defined as a reduction of 50% to 99% in the product of the perpendicular diameters of the contrast-enhancing tumor. Progressive disease was defined as an increase of more than 25% in the product of the perpendicular diameters of the contrast-enhancing tumor or any new tumor seen on CT scans, and all other situations were defined as no change (NC). Overall survival (OS), progression-free survival (PFS), and local control (LC) rates were calculated actuarially according to the Kaplan-Meier method (10) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test, Student's *t* test, and the generalized Wilcoxon test (11). Multivariate analysis was performed using the Cox regression model (12). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using SPSS software (version 11.0; SPSS, Inc., Chicago, IL). Acute and late adverse effects were graded in accordance with the National Cancer Institute-Common Terminology Criteria (NCI-CTC) version 3.0.

Results

Data regarding initial responses after CCRT were available for 85 patients (Table 3). Of the 3 patients with inoperable tumors, 1 patient had a response of NC, and there was no information regarding tumor responses for the remaining 2 patients. At the time of this analysis, 95 patients (88.0%) had disease recurrence (local only in 29 patients; regional lymph nodes only in 1 patient; liver only in 24 patients; peritoneum only in 27 patients; other distant metastases, such as at bone or lung, only in 4 patients; and multiple sites in 10 patients). Among the 10 patients with multiple recurrences, 6 patients had simultaneous local recurrences. Therefore, local recurrences occurred in a total of 35 patients (32.4%). The 2-year actuarial LC rate for all 108 patients was 41.9%. Figure 1 shows the LC curves according to the total radiation dose. Patients treated with a total dose of 50 Gy or more

Table 2 Agents and chemotherapy schedules

Drug	No. of patients receiving a drug*	
	During RT	After RT
GEM	108	53†
5-FU	–	6†
S-1	–	5†

Abbreviations: 5-FU = 5-fluorouracil; GEM = gemcitabine; RT = radiotherapy; S-1 = combination of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium.

* A total of 108 patients (100%) received a drug during RT, and 59 patients (54.6%) received a drug after undergoing RT.

† When combination chemotherapy was used, each drug in the combination was counted.

had a significantly more favorable LC rate (2-year LC rate, 42.9%) than patients treated with a total dose of less than 50 Gy (2-year LC rate, 29.6%; $p = 0.0292$). Concerning the regional lymph node recurrence, all 57 patients with clinical stage N0 disease had no regional lymph node recurrence, and only 1 of 49 patients with clinical N1 disease had regional lymph node recurrence.

Eighty-seven of 108 patients (84.5%) died during the period of this analysis. Of these 87 patients, 85 patients died of pancreatic cancer, and the remaining 2 patients died without any sign of clinical recurrence (both of these patients died of intercurrent disease). The 2-year actuarial PFS rate and the median time to progression for all 108 patients were 8.2% and 6.0 months, respectively. Concerning AC use, the 2-year PFS rates for patients treated with AC (10.8%) were significantly higher than those for patients treated without AC (7.8%; $p = 0.0187$). Univariate analysis showed that AC used, clinical T stage, and CA19-9 levels had a significant impact on PFS outcomes, and multivariate analysis showed that AC use and clinical T stage were significant prognostic factors (data not shown).

The 2-year actuarial OS rate and median survival time (MST) in all 108 patients were 23.5% and 11.6 months, respectively. Concerning AC use, 2-year OS rates for patients treated with AC (31.8%) were significantly higher than those for patients treated without AC (12.4%; $p = 0.0022$) (Fig. 2). Univariate analysis showed that AC use, clinical T stage, and CA19-9 levels had a significant impact on OS outcomes (Table 4). However, when we excluded patients with hyperbilirubinemia (more than 2 mg/dl), CA19-9 concentration was not a significant factor for OS, and the 2-year OS rate was 27.4% in patients with CA19-9 concentrations $<1{,}000$ U/ml and 24.8% in patients with CA19-9 concentrations $\geq 1{,}000$ U/ml ($p = 0.7104$). Multivariate analysis showed that the use of AC (relative risk, 2.475; 95% confidence interval [CI], 1.564–3.917; $p < 0.001$) and clinical T stage (relative risk, 0.374; 95% CI, 0.202–0.692; $p = 0.002$) were significant prognostic factors. Other factors, such as CA19-9 level, tumor size, and total radiation dose did not influence OS outcomes.

In the current study, there were significant differences in the frequencies of AC use according to the initial response ($p < 0.0001$) (Table 3), and patients with favorable responses had more frequently received AC than those with unfavorable responses. Therefore, we conducted subgroup analyses of OS according to initial responses. Concerning patients with an NC response, there was a significant survival benefit with AC use. On the other hand, patients with PR and those with progressive disease response had no significant survival benefit with AC use (Table 3).

Concerning adverse acute effects, 46 patients (42.6%) had Grade 3 to 4 leukopenia, 38 patients (35.2%) had Grade 3 to 4 appetite loss, and 16 patients (14.8%) had Grade 3 to 4 vomiting. Late adverse effects of Grade 3 or higher were observed in 1 patient (1.0%; Grade 3 gastrointestinal bleeding). Total radiation dose given to this patient was 50 Gy.

Discussion

The current study indicated that CCRT using GEM yields noticeably favorable LC for unresectable pancreatic cancer, with a 2-year LC rate of 41.9%. Concerning initial responses of the 85 available patients, 27 patients (31.8%) had PR, 50 patients (58.8%) had NC response, and only 8 patients (9.4%) had progressive disease response. Several other reports also have indicated the efficacy of EBRT plus GEM therapy for LC (13, 14). Mattiucci *et al.* (13) treated 40 patients with unresectable pancreatic cancer with CCRT using GEM (1,000 mg/m2), and the 2-year LC rate was 39.6% (13). Yamazaki *et al.* (14) indicated that locoregional progression was observed in only 5 of 13 patients with unresectable tumors treated with EBRT plus GEM (14). These results indicate that CCRT using GEM produces relatively favorable LC for patients with unresectable tumors.

Although the efficacy of CCRT using GEM produces relatively favorable LC, optimal use of EBRT, that is, factors such as total radiation doses and radiation field, has not been clarified. National Comprehensive Cancer Network (NCCN) guidelines have recommended that for primary definitive chemoradiotherapy, total doses of 50 to 60 Gy (1.8–2.0 Gy/day) should be administered (15). Several investigators report using total doses of approximately 50 Gy for these tumors when GEM is combined with radiotherapy (13, 14, 16). In the current study, patients treated with total doses of

Table 3 Comparisons of initial responses and overall survival according to AC use

Initial response	Total no. of patients	No. of patients			2-year OS rate (%)		
		AC (+)	AC (–)	*p* value	AC (+)	AC (–)	*p* value*
PR	26	25	1	<0.0001	25.3	0	0.3560
NC	51	24	27		34.3	12.1	**0.0251**
PD	8	2	6		0	0	0.7423
Unknown	23	8	15		–	–	–
Total	108	59	49		–	–	–

Abbreviations: AC (+) = with adjuvant chemotherapy; AC (–) = without adjuvant chemotherapy; NC = no change; OS = overall survival; PD = progressive disease; PR = partial response.

* *p* value in boldface type indicates significant difference.

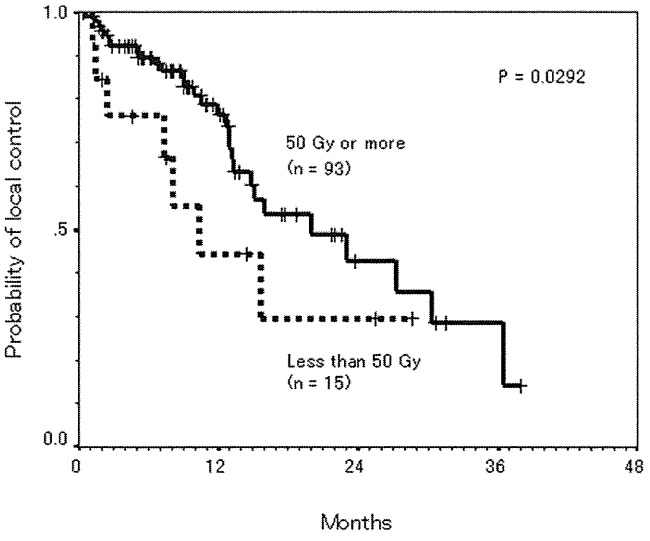

Fig.1. LC curves derived according to the total radiation dose in patients with unresectable pancreatic cancer are shown.

50 Gy or more had a significantly favorable LC rate (2-year LC rate, 42.9%) compared to patients treated with total doses of less than 50 Gy (2-year LC rate, 29.6%). These results suggest that doses of 50 Gy or more are appropriate for these tumors.

Concerning radiation fields, NCCN practice guidelines have also recommended that when 5-FU-based chemoradiotherapy is used, treatment volumes should include the primary tumor location and regional lymph nodes (15). When GEM is added, some authors have used the radiation field encompassing the primary tumor along with regional lymph nodes for treating these tumors (13, 16). Recently, other investigators have tried to irradiate only the primary tumor site in order to reduce radiation volume, especially to the intestine (14, 17). Murphy *et al.* (17) indicated that in conjunction with full-dose GEM, the use of conformal fields encompassing only the gross tumor volume (GTV) does not result in marginal failures. In the current study, regional lymph node recurrence was found in only 1 patient (0.9%), and none of the 57 patients with clinical N0 disease had regional lymph node recurrence. Therefore, when GEM is combined with radiation therapy, the treatment of choice may be to irradiate only the field of the primary tumor, especially for patients with stage N0 tumors. Further studies are required to confirm whether radiation only to the primary tumor field would be sufficient when CCRT with GEM is used.

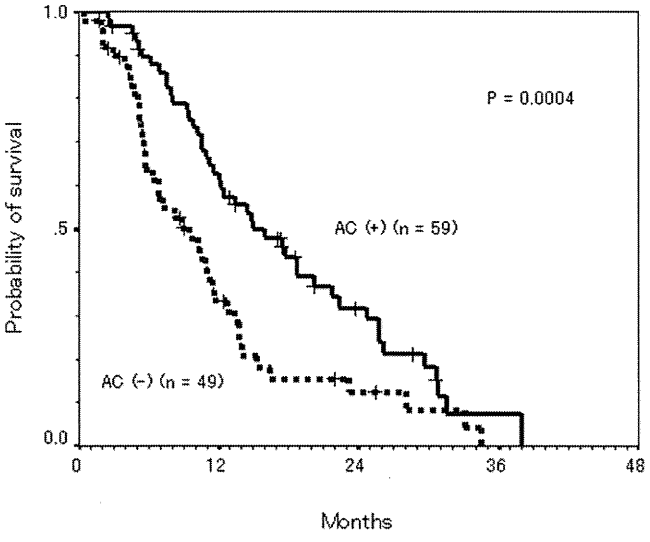

Fig.2. Actuarial OS curves according to administration of AC in patients with unresectable pancreatic cancer are shown.

When GEM is used as a single agent for treating patients with advanced cancer, the standard weekly dosage is approximately 1,000 mg/m^2, and this dosage is regarded as necessary to control occult distant metastases (4). Therefore, considering both the metastasis-prone and the radio-resistant nature of pancreatic cancer, CCRT using full-dose radiotherapy (50 Gy or more) and full-dosage GEM (1,000 mg/m^2 weekly) appears to produce the best outcome. Yamazaki *et al.* (14) indicated that when limited-field 50-Gy radiotherapy was applied, concurrent administration of 1,000 mg/m^2 GEM was safe for these patients. Murphy *et al.* (17) indicated that when conformal fields encompassing only the GTV were applied, CCRT with 1,000 mg/m^2 GEM was safe (17). On the other hand, several reports have pointed out that CCRT with 1,000 mg/m^2 GEM may be too toxic in clinical practice (18, 19). Crane *et al.* (18) indicated that patients receiving GEM-based CCRT developed significantly more severe acute toxicity during treatment than patients receiving 5-FU-based CCRT. Therefore, in order to reduce severe acute toxicity, several researchers conducted studies of CCRT using low-dose GEM (15, 18, 20–22). Shibuya *et al.* (19) conducted a phase II trial of radiotherapy (54 Gy in 28 fractions) with weekly administration of GEM (250 mg/m^2) and reported safe and promising results with a median survival time of 16.6 months and an acceptable level of toxicity (19). Huang *et al.* treated 55 patients with unresectable pancreatic cancer with concurrent 50.4-Gy EBRT and GEM, 400 mg/m^2 weekly, and found that this regimen can be safely administered (20). Further studies are required to investigate the optimal use of GEM for unresectable tumors.

Although CCRT using GEM provides relatively favorable LC rates, the role of this treatment in survival for these patients remains controversial. Several reports have indicated that when CCRT with GEM was administered, the 2-year OS rates and MSTs ranged from 11% to 25% and 10 to 16.6 months, respectively (13–20). In the current study, the 2-year actuarial OS rate and the median MST for all 108 patients were 23.5% and 11.6 months, respectively. These results indicate that despite the use of GEM, treatment outcomes are generally unfavorable for patients with these tumors. Therefore, it is important to investigate possible factors affecting the prognosis for patients treated with CCRT using GEM.

Several previous studies have suggested potential prognostic factors associated with PS and CA19-9 levels when CCRT is combined with GEM (20, 21). Recently, changes in CA19-9 levels after CCRT have emerged as a predictor for OS in patients with unresectable tumors (22). In the current study, we could not analyze changes in CA19-9 levels after CCRT due to limited information; however, it will be worthwhile to investigate more detailed analysis of CA19-9 levels in future studies. Our results indicated that AC use and clinical T stage were independent prognostic factors for OS. Several phase studies have used AC as a part of GEM-based CCRT (14, 20), and NCCN guideline recommend that (GEM-based) AC should be considered for patients with locally advanced disease who are receiving CCRT (15). Our results also indicated that CCRT with GEM-based AC conferred a survival benefit compared to CCRT without AC, and

Table 4 Analysis of prognostic factors for OS in patients with unresectable pancreatic cancer treated with CCRT

Factor	No. of patients	Univariate analysis 2-y OS rate (%)	Univariate analysis p value[†]
Age (years)			
<70	84	22.8	0.9265
≥70	24	27.1	
Gender			
Female	50	28.1	0.7141
Male	58	18.7	
Primary site			
Head	55	30.3	0.8527
Body/tail	52	16.0	
Maximum tumor size			
<4.0 cm	48	31.0	0.6200
≥4.0 cm	54	23.0	
ECOG performance status scale			
0–1	98	21.6	0.7728
2–3	6	33.3	
CA19-9 level (U/ml)			
<1,000	56	24.5	**0.0135**
≥1,000	43	20.8	
Clinical T stage (UICC 2002)			
2–3	18	41.0	**0.0044**
4	90	20.0	
Clinical N stage (UICC 2002)			
0	57	22.9	0.1377
1	49	22.9	
EBRT dose (Gy)			
<50	15	17.8	0.1624
≥50	93	24.6	
Radiation field			
Primary plus LN	65	20.5	0.4224
Primary only	43	27.1	
GEM dose during EBRT			
Low dose (250–350 mg/m^2/week)	100	24.3	0.3199
Standard dose (1,000 mg/m^2/week*)	8	0	
Adjuvant chemotherapy used			
Yes	59	31.8	**0.0004**
No	49	12.4	

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CCRT = concurrent chemoradiotherapy; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; LN = lymph nodes; OS = overall survival; UICC = Union Internationale Contre le Cancer.

* Usually administered weekly for 3 weeks with a 1-week rest period.

† p values in boldface type indicate significant difference.

subgroup analysis indicated that patients with a response of NC had significant clinical benefit with AC use. The possible reason for the clinical benefit of AC may be that AC delays the progression of residual primary tumor and/or development of distant metastasis. Therefore, from our results, AC should be administered after GEM-based CCRT, especially for patients with a response of NC. In the current study, 53 of 59 patients (89.8%) received GEM maintenance chemotherapy, usually given at 1,000 mg/m^2 weekly for 3 weeks with a 1-week rest period, and this regimen may be an attractive regimen for AC!! therapy. Further studies are required to investigate the optimal regimen of AC for these tumors.

Conclusions

In conclusion, our results indicated that CCRT using GEM had a relatively favorable LC rate for unresectable pancreatic adenocarcinoma. Our results also indicated that CCRT in addition to AC conferred survival benefit compared to CCRT without AC. Because CCRT using GEM can achieve relatively favorable LC and the addition of AC increased the OS, CCRT using GEM combined with AC appears to be an attractive strategy for treating patients with unresectable tumors. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

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Multicenter Phase II Study of Gemcitabine and S-1 Combination Therapy (GS Therapy) in Patients With Metastatic Pancreatic Cancer†

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Objective: The aim of this multicenter Phase II study was to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy for metastatic pancreatic cancer.
Methods: Chemotherapy-naïve patients with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. Gemcitabine was administered at a dose of 1000 mg/m^2 over 30 min on days 1 and 8, and oral S-1 at a dose of 40 mg/m^2 twice daily from days 1 to 14, repeated every 3 weeks.
Results: A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4% (95% confidence interval: 30.9–58.6%). The median progression-free survival was 5.9 months (95% confidence interval: 4.1–6.9 months) and the median overall survival was 10.1 months (95% confidence interval: 8.5–10.8 months) with a 1-year survival rate of 33.0%. The major Grade 3–4 toxicities were neutropenia (80%), leucopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥Grade 3.
Conclusions: Gemcitabine and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer. A randomized Phase III study to confirm the efficacy of gemcitabine and S-1 combination therapy is ongoing.

Key words: pancreatic cancer – Phase II – chemotherapy – gemcitabine – S-1

†Part of the content of this report was presented at the ASCO 2007 meeting in the poster presentation (abstract 4550).

INTRODUCTION

Pancreatic cancer is a highly malignant disease and the fifth most common cause of cancer death in Japan. Approximately 80% of patients are ineligible for surgery at diagnosis and more than half of patients have metastatic disease.

Gemcitabine has been the standard chemotherapeutic agent for metastatic pancreatic cancer on the basis of a Phase III study showing clinical and survival benefits over 5-fluorouracil (5-FU) (1). However, the efficacy of gemcitabine monotherapy for advanced pancreatic cancer is limited; most clinical trials have shown response rates of around 10% with a median overall survival of 6–7 months (2–5). Therefore, numerous studies have attempted to increase the efficacy of chemotherapy, but almost all the regimens evaluated in Phase III studies have failed to show survival benefits over gemcitabine. To date, only two randomized trials, gemcitabine plus erlotinib and combination therapy of 5-FU/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) have shown significant prolongation of overall survival (6,7). However, the reported difference in median survival between the gemcitabine plus erlotinib group and the gemcitabine-only group was small (6.24 versus 5.91 months). The results of the FOLFIRINOX trial are more impressive than those of gemcitabine plus erlotinib because FOLFIRINOX led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group. However, the FOLFIRINOX regimen was quite toxic (e.g. 5.4% of patients had Grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger and normal or nearly normal bilirubin levels (8).

S-1, an oral fluoropyrimidine derivative, is now widely used for a variety of malignancies such as gastric cancer (9,10). In Phase II studies of S-1 for metastatic pancreatic cancer, response rates of 21.1–37.5% and median overall survival of 5.6–9.2 months were reported (11,12). Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells (13). On the basis of these findings, we decided to investigate combination therapy with gemcitabine and S-1 therapy (GS therapy) for pancreatic cancer. We initially conducted a Phase I study of GS therapy in patients with advanced pancreatic cancer (14). In that study, gemcitabine was administered as a 30-min intravenous infusion on days 1 and 8 along with oral S-1 twice daily from day 1 through day 14, concluding that a gemcitabine dose of 1000 mg/m^2 and an S-1 dose of 40 mg/m^2 twice daily was recommended in future studies. Since GS therapy showed promising activity, with a 33% response rate and a median survival of 7.6 months, the present multicenter Phase II study was conducted in patients with metastatic pancreatic cancer to evaluate the efficacy and toxicity profile of GS therapy.

PATIENTS AND METHODS

Patient Selection

Patients were included if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma of the pancreas; at least one measurable metastatic lesion; no history of prior chemotherapy or radiotherapy for pancreatic cancer; age 20–74 years; Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ functions (leucocyte count, 4000–12 000/mm^3; neutrophil count, $\geq$2000/mm^3; platelet count, $\geq$100 000/mm^3; hemoglobin level, $\geq$9.0 g/dl; serum creatinine level, $\leq$1.5 mg/dl; 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 present).

The exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; central nervous system metastasis; active concomitant malignancy; severe mental disorder; serious complications such as active gastrointestinal ulcer or severe diabetes mellitus and pregnancy or lactation. The study was approved by the institutional review board of each participating center, and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research (the Ministry of Health, Labour and Welfare, Japan). Written informed consent was obtained from all patients. This study is registered in the UMIN Clinical Trials Registry with the identifier C000000173.

Treatment

This study was an open-label, multicenter, single-arm Phase II study. The dose schedule of gemcitabine and S-1 was planned based on the results of the previous Phase I study (14): gemcitabine at a dose of 1000 mg/m^2 was administered as a 30-min intravenous infusion weekly for 2 weeks followed by 1 week of rest. Oral S-1 was administered at a dose of 40 mg/m^2 twice daily (80 mg/day for body surface area (BSA) $<$1.25 m^2, 100 mg/day for 1.25 $\leq$ BSA $<$ 1.50 m^2 and 120 mg/day for BSA $\geq$1.50 m^2) from days 1 to 14 followed by a 1 week rest period. The treatment was repeated every 3 weeks until disease progression, unacceptable toxicity or patient refusal.

Prophylactic administration of antiemetic agents such as dexamethasone and/or a 5-HT3 receptor antagonist was allowed at the investigator's discretion. If patients showed a leucocyte count of $<$2000/mm^3 or $>$12 000/mm^3, or a platelet count of $<$70 000/mm^3 during the cycle, administration of both gemcitabine and S-1 was suspended. If patients showed a leucocyte count of $<$3000/mm^3 or $>$12 000/mm^3, platelet count of $<$100 000/mm^3, total bilirubin $>$3.0 mg/dl, AST and ALT levels $>$150 U/l, or a creatinine level $>$1.5 mg/dl, initiation of the next cycle was postponed until recovery. When patients experienced (i) Grade 4 leucopenia or neutropenia, (ii) febrile

neutropenia or infection with Grade 3 leucopenia or neutropenia, (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion or (iv) ≥Grade 3 non-hematological toxicity excluding anorexia, nausea, vomiting, constipation, fatigue and hyperglycemia, the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle. The protocol treatment was discontinued if the patients required more than two dose reductions or if the subsequent cycle could not be initiated within 28 days after the final day of the anti-cancer drug administration in the previous cycle.

Evaluation

All the eligible patients who received at least one dose of GS therapy were included in the response and toxicity evaluations. Physical examination, complete blood cell counts and biochemistry tests were assessed at least on days 1 and 8 in each cycle during chemotherapy. Tumor marker carbohydrate antigen (CA) 19-9 was measured every 4–6 weeks. Objective tumor response was evaluated every 4–6 weeks by computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria In Solid Tumors version 1.0. For the purpose of confirmation of objective response, an interval of at least 4 weeks was required for complete response (CR), partial response (PR) and stable disease (SD) in this study. The response duration was defined as the interval from the first documentation of response (PR or CR) to the first documentation of tumor progression. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Progression-free survival (PFS) was calculated from the date of the initiation of treatment until documented disease progression or death due to any cause (whichever occurred first); overall survival was calculated from the date of treatment initiation to the date of death or censored at the last follow-up. An external review committee confirmed objective responses and adverse events.

Statistical analysis

The primary endpoint was the response rate (CR and PR) of GS therapy. Forty-nine patients were required based on the assumption of an expected response rate of 25% and the threshold rate of 10%, with α-error of 2.5% (one-sided) and β-error of 20%. In consideration of ineligible patients or those who dropped out, it was planned that 55 patients would be included in this study. We calculated the response rate with 95% confidence interval (CI) in the patients who met eligibility criteria and received at least one GS therapy. The progression-free and overall survival periods were estimated by the Kaplan–Meier method.

RESULTS

Patients

Fifty-five patients were enrolled from 10 institutions between October 2004 and July 2005. Of these 55 patients, one patient was excluded from analysis because he left the study before administration of GS therapy due to an allergic skin reaction caused by insulin. All of the remaining 54 patients received at least one dose of GS therapy and were included in the evaluation of response and toxicity. Patient characteristics of the 54 patients are listed in Table 1. All patients had metastatic disease and no patient received any prior therapies except surgery for pancreatic cancer. Six patients underwent percutaneous transhepatic or endoscopic biliary drainage for obstructive jaundice prior to the study enrollment.

Treatments

The final data were fixed on 31 March 2007. A total of 425 therapy cycles were administered to the 54 patients,

Table 1. Patient characteristics ($n = 54$)

Characteristics		Number of patients (%)
Median age, years (range)	62 (32–74)	
Sex		
Women		24 (44)
Men		30 (56)
ECOG performance status		
0		38 (70)
1		16 (30)
Body surface area		
Median (range), m^2	1.59 (1.18–1.83)	
History of surgical resection		9 (17)
Metastatic disease		54 (100)
Sites of metastasis		
Liver		50 (93)
Distant lymph nodes		11 (20)
Peritoneum		3 (6)
Lung		2 (4)
Other		2 (4)
Histology		
Adenocarcinoma		53 (98)
Adenosquamous carcinoma		1 (2)
Differentiation		
Well		2 (4)
Moderate		28 (52)
Poor		13 (24)
Unknown		11 (20)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Efficacy results

		Number of patients (%)
Tumor response ($n = 54$)		
Complete response		0 (0)
Partial response		24 (44.4)
Stable disease		26 (48.1)
Progressive disease		2 (3.7)
Cannot be evaluated		2 (3.7)
Response rate (95% CI), %	44.4 (30.9–58.6)	
Tumor control rate (95% CI), %	92.6	
CA 19-9 response ($n = 41$)		
Decreased (≥50%)		35 (85.4)
Decreased (<50%)		3 (7.3)
Increased		3 (7.3)
Progression-free survival ($n = 54$)		
Median (95% CI), months	5.9 (4.1–6.9)	
Overall survival ($n = 54$)		
Median (95% CI), months	10.1 (8.5–10.8)	
1-year survival rate, %	33	

CA 19-9, carbohydrate antigen 19-9.

with a median of 7 cycles each (range, 1–24). GS therapy could generally be administered on an outpatient basis. The gemcitabine on day 8 was administered in 367 (86.4%) of 425 cycles. Dose reduction was required in 30 patients (55.6%), mainly due to leucopenia, neutropenia, rash or gastrointestinal toxicities. At the time of analysis, protocol treatment was discontinued in 52 patients because of disease progression ($n = 30$) or adverse events ($n = 22$). The reasons for discontinuation due to adverse events were the second episode of Grade 4 neutropenia after one dose reduction (11), prolonged myelosuppression (3), anorexia or nausea (4), rash (2), cerebral infarction (1) and cholangitis (1). After discontinuation of GS therapy, 30 patients received gemcitabine-based chemotherapy, 6 patients received other anticancer drugs including irinotecan and the remaining 18 patients received only supportive care.

Efficacy

The efficacy results are shown in Table 2. Of the 54 patients, 2 patients could not be assessed for response since they withdrew their consent due to toxicity before the first response evaluation. Although no CR was observed, a PR was achieved in 24 of 54 patients, resulting in an overall response rate of 44.4% (95% CI: 30.9–58.6%). The median response duration was 5.3 months (range, 2.4–15.6 months). SD was noted in 26 patients (48.1%) and progressive disease (PD) in 2 patients (3.7%). The serum CA 19-9 level was reduced to less than half from baseline values in 35 (85.4%) of the 41 patients whose pretreatment levels were >100 U/ml. The median PFS was 5.9 months (95% CI: 4.1–6.9 months) with a median overall survival of 10.1 months (95% CI: 8.5–10.8 months) and a 1-year survival rate of 33.0% (Fig. 1).

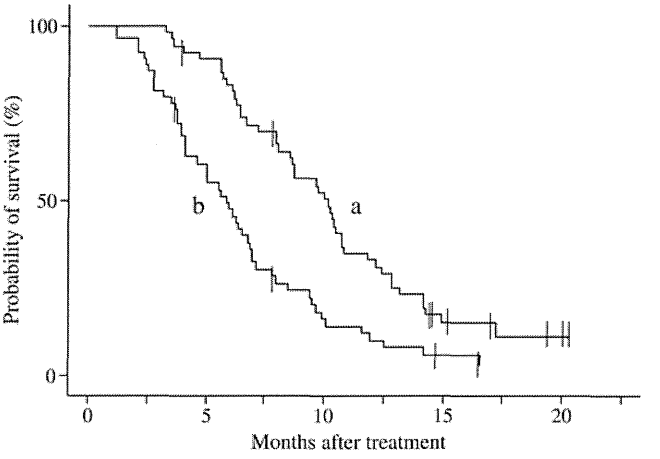

Figure 1. Overall survival curve (a) and progression-free survival (b) for 54 patients.

Toxicity

The major toxicities observed in the 54 patients are listed in Table 3. The most common toxicity was myelosuppression. Grade 3–4 neutropenia and thrombocytopenia occurred in 80 and 22% of the patients, respectively. The neutrophil and platelet count nadirs typically were observed on day 15. Although most of these hematologic toxicities were transient and recovered without serious events, one patient developed Grade 3 febrile neutropenia. No other unexpected severe toxicities were observed during the study and there were no treatment-related deaths. Although gastrointestinal toxicities and skin rash were frequently observed, most of these were manageable with appropriate medical treatment. There were no cumulative toxicities.

DISCUSSION

The major toxicity of GS therapy is myelosuppression, especially neutropenia. Although the incidences of Grade 3–4 neutropenia and thrombocytopenia observed in the current study were high (Table 3), most of these episodes were transient. There was only one episode of neutropenic fever without treatment-related death. Therefore, most patients could be treated on an outpatient basis without receiving granulocyte colony-stimulating factor or a blood transfusion. Although anorexia, nausea, fatigue, rash, pigmentation and aminotransferase elevation were also observed frequently in our study, most of these non-hematological toxicities were manageable with appropriate treatments. Therefore, it is considered that GS therapy in this study is tolerable for patients with metastatic pancreatic cancer.

Table 3. Adverse events ($n = 54$)

	Grade				Grades 1–4	Grades 3–4
	1	2	3	4	%	%
Hematological toxicity						
Leucocytes	3	19	31	1	100	59
Neutrophils	2	9	24	19	100	80
Hemoglobin	11	29	8	0	89	15
Platelets	15	23	12	0	83	22
Non-hematological toxicity						
Bilirubin	15	9	3	0	50	6
AST	23	6	2	0	57	4
ALT	20	11	4	0	65	7
Creatinine	7	0	0	0	13	0
Nausea	19	11	3	—	61	6
Vomiting	11	5	1	0	32	2
Anorexia	18	11	9	0	70	17
Stomatitis	20	10	1	0	57	2
Diarrhea	12	5	0	0	32	0
Constipation	2	0	1	0	6	2
Ileus	—	0	1	0	2	2
Colitis	—	0	1	0	2	2
Fatigue	22	14	3	0	72	6
Fever	15	5	0	0	37	0
Alopecia	13	2	—	—	28	0
Rash	13	17	4	0	63	7
Pigmentation changes	27	7	—	—	63	0
Hand-foot skin reaction	3	0	0	0	6	0
Infection without neutropenia	2	2	2	0	11	4
Febrile neutropenia	—	—	1	0	2	2
CNS cerebrovascular ischemia	—	—	1	1	4	4

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

To date, several Phase II studies testing the gemcitabine plus S-1 combination as first-line therapy for advanced pancreatic cancer have been published (Table 4) (15–18). One study was conducted in Japan and the remaining studies were in Korea. Although various schedules of gemcitabine and S-1 administration were used, the regimens adopted in all studies including this study were similar: gemcitabine at a dose of 1000–1250 mg administered on days 1 and 8 or 8 and 15 and S-1 at a dose of 60–80 mg/m^2/day on days 1–14 of a 21-day cycle. The incidences and severity of toxicities reported in these trials, especially hematological toxicities, have varied widely among the studies. Interestingly, hematological toxicities were more frequently observed in the two Japanese studies, including this study, than the Korean studies. It is well known that the toxicity profile of S-1 differs between Asians and Caucasians (19); Goh and coworkers (20) carried out a study to compare S-1 pharmacokinetics and CYP2A6 activity among Asian and Caucasian patients, and reported that Asian patients had lower 5-FU exposure and lower CYP2A6 activity compared with Caucasian patients. However, the reasons for the discrepancies between the Japanese and Korean studies remain unclear.

In this trial, GS therapy produced a promising efficacy with a response rate of 44.4%. The efficacy of GS therapy reported in the recent studies as well as this study has been consistent (Table 4), with response rates of 27.3–38%, median time to tumor progression of 4.6–5.43 months and median overall survival of 7.89–12.5 months. Recently, the results of a randomized Phase II study comparing GS therapy with gemcitabine alone were reported (21). In that study, 106 patients were randomly assigned at a 1:1 ratio to either the GS group or the gemcitabine-alone group. Patients assigned to GS therapy received gemcitabine at a dose of 1000 mg/m^2 on days 1 and 15 and S-1 at a dose of 40 mg/m^2 twice daily on days 1–14, every 4 weeks. The objective response rate was 18.9% in the GS group and 9.4% in the gemcitabine group. Patients in the GS group demonstrated significantly longer PFS than those in the gemcitabine group [median PFS, 5.4 versus 3.6 months; hazard ratio = 0.64 (95% CI: 0.42–0.97); $P = 0.036$], while overall survival did not differ significantly between the two groups [median

Table 4. Phase II studies of GS therapy for advanced pancreatic cancer

Author	Gemcitabine (mg/m^2)	S-1 (mg/m^2/day)	Cycle (day)	No. of patients	Metastatic disease (%)	RR (%)	Median TTP/PFS (months)	Median OS (months)	Grade 3/4 neutropenia (%)	Grade 3/4 thrombocytopenia (%)
Nakamura *et al.* (15)	1000 (days 8, 15)	60 (days 1–14)	21	33	100	48	5.4	12.5	55	15
Lee *et al.* (16)	1250 (days 1, 8)	80 (days 1–14)	21	32	90.6	44	4.92	7.89	28.1	15.6
Kim *et al.* (17)	1000 (days 8, 15)	60 (days 1–14)	21	22	86.3	27.3	4.6	8.5	18.2	4.5
Oh *et al.* (18)	1000 (days 1, 8)	80 (days 1–14)	21	38	84	29	5.43	8.4	39.5	2.6
Current study	1000 (days 1, 8)	80 (days 1–14)	21	55	100	44.4	5.9	10.1	80	22

RR, response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival.

overall survival, 14.1 versus 8.7 months; hazard ratio = 0.69 (95% CI: 0.43–1.08); $P = 0.105$].

Since it is speculated that combination chemotherapy with S-1 and gemcitabine might be superior to monotherapy with gemcitabine from the results of the recent trials, a Phase III trial was planned to confirm the efficacy of GS therapy (ClinicalTrials.gov, NCT00498225). The Phase III study known as 'GEST' is a randomized controlled study involving three arms: gemcitabine monotherapy as a control arm, S-1 monotherapy and GS therapy. The trial was designed to evaluate overall survival as the primary endpoint, non-inferiority of S-1 to gemcitabine and superiority of GS therapy over gemcitabine. The enrollment of 750 patients was planned and has already been completed and the final analysis of the results will be reported in the near future.

In conclusion, the current Phase II study demonstrated encouraging antitumor activity following GS therapy with good overall survival in patients with metastatic pancreatic cancer. The clinical benefits of GS therapy are now investigated in the GEST trial.

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Conflict of interest statement

None declared.

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Appendix

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Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer

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Erlotinib combined with gemcitabine has not been evaluated in Japanese patients with unresectable pancreatic cancer. This two-step phase II study assessed the safety and pharmacokinetics of erlotinib 100 mg/day (oral) plus gemcitabine 1000 mg/m^2 (i.v. days 1, 8, 15) in a 28-day cycle in the first step, and efficacy and safety in the second step. The primary end-point was safety. One hundred and seven patients were enrolled (first step, n = 6; second step, n = 101). The most common adverse event was RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) in 93.4% of patients. One treatment-related death occurred. While interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%), all patients recovered or improved. The median overall survival, the 1-year survival rate and median progression-free survival were 9.23 months, 33.0% and 3.48 months, respectively. The overall response and disease control rates were 20.3% and 50.0%, respectively. In Japanese patients with unresectable pancreatic cancer, erlotinib plus gemcitabine had acceptable toxicity and efficacy that was not inferior to that seen in Western patients. (*Cancer Sci* 2011; 102: 425–431)

Approximately 232 000 individuals are diagnosed with pancreatic cancer worldwide each year, with an annual death rate estimated at 227 000.[1] In Japan, approximately 22 000 new cases were reported in 2005.[2] Furthermore, data from 2007 show that around 24 000 individuals in Japan died from pancreatic cancer, making this tumor type the fifth leading cause of cancer-related death.[3] The majority of pancreatic cancer cases are diagnosed at an unresectable stage when prognosis is extremely poor.

Current treatment for advanced pancreatic cancer is based on systemic chemotherapy with gemcitabine. Single-agent gemcitabine has been shown to extend median overall survival (OS) to 5.65 months in chemonaïve patients compared with 4.41 months in patients who received fluorouracil.[4] Addition of other cytotoxic agents to gemcitabine has not demonstrated survival benefits over gemcitabine alone.[5–13] The potential of combining gemcitabine with biological agents in patients with advanced pancreatic cancer has also been evaluated in several phase III studies, but these trials failed to show a survival benefit.[14–19]

Epidermal growth factor receptor (EGFR)-mediated signaling is associated with various cellular processes, and the dysregulation of these processes is common in tumorigenesis.[20,21] Furthermore, EGFR is overexpressed in many tumors and its overexpression is often associated with poor prognosis.[22–26] EGFR tyrosine-kinase inhibitors (TKI, such as erlotinib) are used in the treatment of various types of solid tumors.

Erlotinib has demonstrated antitumor activity in pancreatic cell lines[27] and was subsequently assessed as a potential therapeutic agent in pancreatic cancer. In the PA.3 study (n = 569), the risk of death with erlotinib plus gemcitabine was reduced by 18% versus gemcitabine alone (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69–0.99; P = 0.038 after adjustment for stratification factors), with a median OS of 6.24 months *vs* 5.91 months, respectively. Erlotinib plus gemcitabine combination therapy provided significant improvements in the 1-year survival rate (23% *vs* 17%; P = 0.023) and progression-free survival (PFS; HR 0.77; 95% CI, 0.64–0.92; P = 0.004).[28] As a result, this combination was approved for use in pancreatic cancer in many countries.

In Japanese patients with non-small-cell lung cancer (NSCLC), a phase II study has specifically shown that erlotinib monotherapy is well tolerated and has promising antitumor activity.[29] However, there are no data on the use of erlotinib combined with gemcitabine in Japanese patients with pancreatic cancer. This phase II study evaluated the safety and efficacy of erlotinib in combination with gemcitabine in Japanese patients with unresectable locally advanced or metastatic pancreatic cancer.

Methods

Patients. Patients aged 20–80 years with histological/cytological evidence of unresectable locally advanced or metastatic adenocarcinoma/adenosquamous carcinoma of the pancreas were eligible for inclusion in the present study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, adequate hematological, renal and hepatic function and a life expectancy of at least 2 months. No more than one prior regimen for pancreatic cancer was permitted. Patients who had received prior gemcitabine and/or a TKI were excluded from participation, as were those who had previously been exposed to a human epidermal growth factor receptor 2 (HER2) or EGFR inhibitor. Other key

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Clinical trial registry: JAPIC Clinical Trials Information (see links below). http://rctportal.niph.go.jp/examDetail.php?center=3&center_seq=698 http://www.clinicaltrials.jp/user/cteDetail.jsp?clinicalTrialId=839&language=ja. Trial registration number: JapicCTI-060337.

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exclusion criteria were: symptomatic cerebral metastases; a concurrent lung disorder (such as idiopathic pulmonary fibrosis, interstitial lung disease [ILD] or pneumoconiosis); concurrent or previous drug-induced pneumonia; or a history of radiation to the chest.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients, and the protocol was approved by ethics committees at all participating institutions.

Study design and treatment. This was a phase II, multicentre, open-label, two-step study. In the first step, six patients were enrolled into the study and treated with oral erlotinib 100 mg/day on days 3–28, plus i.v. gemcitabine 1000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle. The starting doses of erlotinib and gemcitabine were chosen in reference to the PA.3 study. Dose-limiting toxicities (DLT) were assessed in these study participants using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE, National Cancer Institute, Bethesda, MD, USA). Dose-limiting toxicities were defined in conformity to the P1b study as follows:[30] (i) grade 4 decrease (i.e. to <500/mm^3) in neutrophil count >5 days; (ii) grade ≥3 decrease (i.e. to <1000/mm^3) in neutrophil count with associated fever (≥38.5°C); (iii) grade 4 decrease in platelet count (i.e. to <25 000/mm^3); (iv) any grade ILD; (v) grade 4 elevation of alanine transaminase (ALT)/aspartate transaminase (AST) levels, or grade 3 elevation of ALT/AST levels >7 days; (vi) grade ≥3 non-hematological toxicity (excluding rash, hyperglycemia, γ-GTP and events that were judged to be transient/had no effect on study continuation); and (vii) dose-reduction/interruption required due to persistent adverse events (AE), which meant that the second cycle could not be started.

If treatment-related DLT occurred in no more than two of the six patients, transition to the second step of the study was permissible with approval of the Data Safety and Monitoring Committee (DSMC). If DLT occurred in three or more patients, transition to the second step was limited to those cases that were judged to be safe for this study after the DSMC had evaluated the safety data of the patients with a DLT. In the second step, it was planned that 94 patients would be treated with the same dose as the first step. Treatment was continued until disease progression, death, unacceptable toxicity or patient/investigator request.

The primary end-point of the study was safety, with secondary end-points including OS, 1-year survival rate, PFS, overall response rate (ORR), disease control rate (DCR = complete response [CR] + partial response [PR] + stable disease), pharmacokinetics (PK) and correlation of *EGFR* mutation status with outcomes.

Toxicity evaluation. Adverse events were monitored and graded using NCI-CTCAE v3.0. Clinical and laboratory assessments were conducted throughout the study. Adverse events prespecified in the study to be monitored carefully were rash, diarrhea, vomiting, liver dysfunction and ILD-like events. Chest X-ray examination to assess pulmonary toxicity was conducted weekly until week 4 and every 2 weeks thereafter. In addition, chest computed tomography (CT) scan was performed every 4 weeks. The DSMC reviewed the images and clinical data associated with all potential ILD-like events. All ILD-like events were reported to be serious AE (SAE), regardless of the grade.

Efficacy evaluation. The tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) in patients who had at least one measurable target lesion. Tumors were measured using computed tomography (CT) at baseline and on day 22 of every two cycles thereafter. Median PFS, ORR and DCR were estimated by the extramural review. The relationship between efficacy and the severity of RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) was also examined.

Pharmacokinetic evaluation. Pharmacokinetic evaluation of erlotinib and its O-desmethylated metabolite (OSI-420) was performed in the six patients enrolled in the first step of the study. Venous blood samples were taken prior to erlotinib dosing on day 3 and day 8 of cycle 1 at 0.5, 1, 2, 4, 6, 8 and 24 h after erlotinib administration. Samples were also taken prior to gemcitabine infusion on days 1 and 8 at 0.5, 0.75, 1, 1.5, 2.5 and 4.5 h after dosing.

The plasma concentrations of erlotinib, OSI-420 and gemcitabine were measured by liquid chromatography, tandem mass spectrometry (LC-MS-MS). The LC-MS-MS analytical methods have been described previously.[31,32] Derived PK parameters included the maximum plasma drug concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration-time curve to the last plasma sample (AUC_{last}), terminal half-life ($t_{½}$) and oral clearance (Cl/F).

Biomarker analysis. *EGFR* mutations were assessed in patients with available tumor tissue specimens, which were formalin fixed and paraffin embedded. Samples were analyzed at a central laboratory where DNA was extracted and exons 18–21 sequenced using a nested PCR.

Statistical analysis. Progression-free survival and OS were estimated using the Kaplan–Meier method in all patients who received at least one dose of the study treatment, with 95% CI for the median duration calculated using Greenwood's formula. The Clopper–Pearson method was used to calculate the 95% CI around the ORR, DCR and AE rate. Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model. Baseline characteristics investigated for this analysis included gender, age, lung metastasis, emphysema and various baseline laboratory values. The target enrollment was 100 patients, as this was required to evaluate the safety of erlotinib.

Results

Patient characteristics. Between December 2006 and October 2007, a total of 107 patients were enrolled (first step, n = 6; second step, n = 101) from 12 institutions (Fig. 1). One patient who enrolled into the second step did not receive treatment due to deterioration in PS prior to the start of treatment. A total of 106 patients were evaluable for safety (safety population, full analysis set).

The patient demographics and baseline characteristics are shown in Table 1. The median age was 62 years (range, 36–78) and 52.8% of patients were male. Almost all patients were chemonaïve (95.3%). The majority (75.5%) of patients had an ECOG PS of 0 and most (83.0%) had metastatic disease. Over half (63.2%) of the patients had a history of current or past smoking.

Toxicity and dose modifications. The median duration of erlotinib exposure was 102.5 days and its median dose intensity was 100.0 mg/day, with the majority of patients (78.3%) receiving more than 90% of the relative dose intensity. The median duration of gemcitabine treatment was 4.0 cycles and its median dose intensity was 688.0 mg/m^2 per week, with approximately half of the patients (51.4%) receiving more than 90% of the relative dose intensity.

As only one patient had a DLT (grade 3 diarrhea) in the first step, the second step of the study was initiated. One hundred and six patients received at least one dose of erlotinib; these patients were assessable for toxicity. Treatment-related AE and treatment-related changes in laboratory values are summarized in Table 2; most of these were mild to moderate in severity. The most frequently reported AE was RASH, which occurred in

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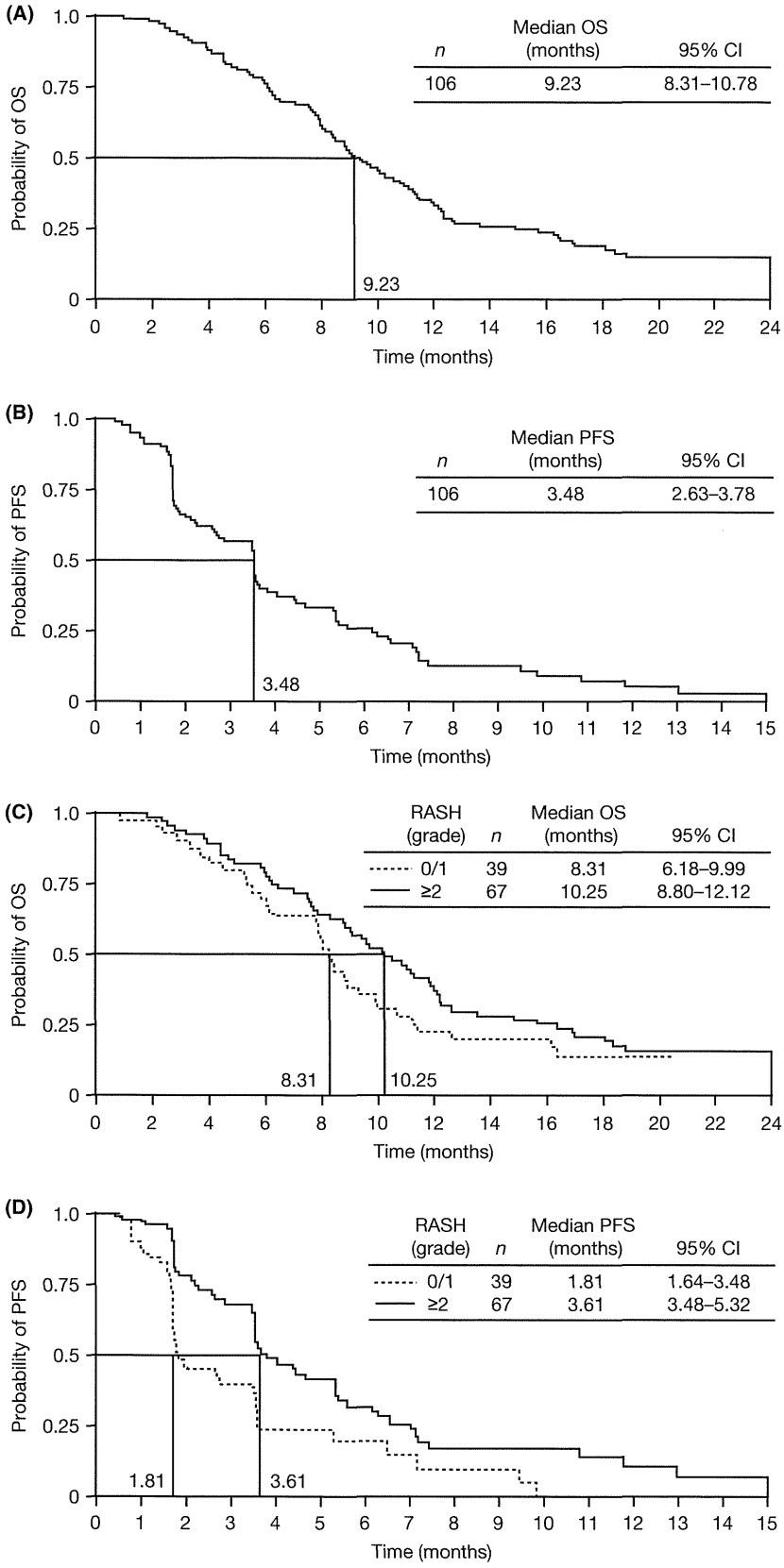

Fig. 1. Kaplan–Meier estimates of (A) overall survival (OS) and (B) progression-free survival (PFS) in the study population (n = 106); (C) OS and (D) PFS according to the severity of RASH (grade ≤1 [n = 39] *vs* grade ≥2 [n = 67]). RASH is a composite of the terms: rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash. CI, confidence interval.

Table 1. Baseline characteristics and demographics (n = 106)

Characteristic	
Median age (range) (years)	62 (36–78)
Gender, *n* (%)	
Male	56 (52.8)
Female	50 (47.2)
Median bodyweight (range) (kg)	52.3 (33.1–95.0)
Smoking history,† *n* (%)	
Never smoker	39 (36.8)
Past smoker	37 (34.9)
Current smoker	30 (28.3)
ECOG PS, *n* (%)	
0	80 (75.5)
1	26 (24.5)
2	0 (0)
Disease status, *n* (%)	
Metastatic	88 (83.0)
Locally advanced	18 (17.0)
Primary tumor identified, *n* (%)	92 (86.8)
Primary sites, *n* (%)	
Head	46 (43.4)
Body and tail	23 (21.7)
Body	22 (20.8)
Tail	10 (9.4)
Other	5 (4.7)‡
Biliary drainage, *n* (%)	19 (17.9)
Sites of distant metastases, *n* (%)	
Liver	56 (52.8)
Distant lymph nodes	39 (36.8)
Lung	17 (16.0)
Other	26 (24.5)
Prior lines of therapy, *n* (%)	
None	101 (95.3)
One regimen	5 (4.7)§
Median CA19–9 (range) (U/mL)	
Median	776 (0–435 000)
Median CEA (range) (ng/mL)	
Median	4.8 (0.6–1100.1)

†Never smoker, never/hardly smoked; past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). ‡Whole of pancreas (n = 1); head and body (n = 3); other (n = 1). §Tegafur, gimeracil, oteracil potassium (S-1) (n = 3); 5-fluorouracil plus leucovorin (n = 2). CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Co-Operative Group.

93.4% of the patients; most cases were mild to moderate in severity (87.7%, grade ≤2; 5.7%, grade ≥3). Other common non-hematological AE included anorexia, pruritus, fatigue, nausea and diarrhea. Most patients experienced some degree of hematological toxicity, with grade 3 or 4 neutropenia (neutrophil decreased), leucopenia (white blood cell count decreased) and anemia (hemoglobin decreased) occurring in 34.9%, 29.2% and 14.2% of patients, respectively. Only one treatment-related death occurred (due to gastrointestinal hemorrhage), which was probably due to arterial bleeding caused by the invasion of the primary tumor into the gastrointestinal tract. Although the likelihood of this event being treatment-related was deemed remote, a causal relationship could not be completely excluded because the event occurred during the study treatment administration period.

Treatment-related SAE were reported in 26 (24.5%) patients. These included nine ILD-like events (8.5%), the majority of which (n = 7) were grade 1–2 in severity. Importantly, all of these nine patients recovered or improved, and four of these patients did so without any treatment for ILD-like events. Other

Table 2. Treatment-related adverse events occurring in >30% of patients treated with erlotinib and gemcitabine (n = 106)

	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Non-hematological			
Rash	78 (73.6)	3 (2.8)	0 (0)
Anorexia	75 (70.8)	15 (14.2)	0 (0)
Pruritus	57 (53.8)	1 (0.9)	0 (0)
Fatigue	56 (52.8)	3 (2.8)	0 (0)
Nausea	56 (52.8)	6 (5.7)	0 (0)
Diarrhea	52 (49.1)	2 (1.9)	0 (0)
Dry skin	49 (46.2)	0 (0)	0 (0)
Stomatitis	38 (35.8)	0 (0)	0 (0)
Pyrexia	32 (30.2)	0 (0)	0 (0)
Hematological			
White blood cell count decreased	85 (80.2)	31 (29.2)	0 (0)
Platelet count decreased	77 (72.6)	9 (8.5)	0 (0)
Hemoglobin decreased	76 (71.7)	13 (12.3)	2 (1.9)
Hematocrit decreased	73 (68.9)	8 (7.5)	0 (0)
Neutrophil decreased	73 (68.9)	32 (30.2)	5 (4.7)
Red blood cell count decreased	72 (67.9)	8 (7.5)	0 (0)
ALT increased	59 (55.7)	10 (9.4)	0 (0)
AST increased	57 (53.8)	4 (3.8)	1 (0.9)
Weight decreased	53 (50.0)	3 (2.8)	0 (0)
Lymphocyte count decreased	46 (43.4)	14 (13.2)	0 (0)
Blood albumin decreased	35 (33.0)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	35 (33.0)	12 (11.3)	1 (0.9)

ALT, alanine amino transferase; AST, aspartate amino transferase.

treatment-related SAE were anorexia (3.8%), vomiting, pyrexia and abnormal hepatic function (1.9% each). The baseline characteristics, treatment and outcomes of patients who developed treatment-related ILD-like events during the study are detailed in Table 3. The onset times of ILD-like events ranged from 7 to 187 days after the start of treatment. In these patients, a relatively long survival was observed (from 119 to 568+ days), and five patients received post-study therapy. All of these nine patients were past or current smokers, and six had emphysema at baseline (not detected prior to treatment, but diagnosed at the extramural review by a radiologist in the DSMC). Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model and emphysema at baseline was indicated as a risk factor for onset of ILD-like events (odds ratio [95% CI], 12.13 [1.01–145.7]; P = 0.0491).

Adverse events led to erlotinib discontinuation in 30 patients (28.3%) and gemcitabine discontinuation in 27 patients (25.5%). The main reasons for treatment discontinuation were ILD (n = 6) and anorexia (n = 3); no patient discontinued treatment due to RASH or diarrhea. Due to the onset of AE, a total of 65 patients (61.3%) required one or more interruptions of erlotinib (36 patients [34.0%] for longer than seven consecutive days and 17 patients [16.0%] for longer than 14 consecutive days) and 56 patients (52.8%) had one or more skip of gemcitabine. Modifications in the erlotinib or gemcitabine dosage were required in 17 (16.0%) and 11 (10.4%) patients, respectively, due to AE.

Efficacy. The median OS was 9.23 months (95% CI, 8.31–10.78; Fig. 1A) and the 1-year survival rate was 33% (95% CI, 24–42). Median PFS was 3.48 months (95% CI, 2.63–3.78; Fig. 1B). Among the patients evaluable for tumor response (n = 64), the ORR was 20.3% (13/64; 95% CI, 11.3–32.2) and the DCR was 50.0% (95% CI, 37.2–62.8; CR, n = 0; PR, n = 13; stable disease, n = 19).

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Table 3. Characteristics, treatment and outcomes of patients with treatment-related ILD-like events (n = 9)

Event	Gender	Age (years)	Smoking status†	Days on treatment	ILD maximum grade	Suspicious findings of ILD	Steroids	Oxygen	ILD outcome	Presence of emphysema (assessed by radiologist)	Survival outcome (days)	Post-therapy (chemotherapy)
Lymphoid ILD	M	62	Past	82	1	Pyrexia	None	No	Improved	Yes	362	Yes
ILD	M	42	Current	50	3	Pyrexia	Pulse	Yes	Recovered	Yes	517	Yes
Organising pneumonia	M	60	Past	183	2	Respiratory symptoms	None	No	Improved	Yes	568+	Yes
ILD	F	62	Past	113	2	Cough	Oral	No	Recovered	Yes	376	No
ILD	F	74	Past	111	3	Cough, dyspnea	Pulse	Yes	Improved	None	183	No
ILD	M	60	Current	25	1	Pyrexia	Pulse	No	Recovered	None	119	Yes
ILD	M	77	Past	7	1	X-ray	None	No	Recovered	Yes	255	No
ILD	M	55	Past	187	1	CT	None	No	Recovered	Yes	415	No
ILD	F	60	Current	76	2	Cough	Oral	No	Recovered	None	346	Yes

†Past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). CT, computed tomography; F, female; ILD, interstitial lung disease; M, male.

The median OS was longer in patients who experienced RASH of grade ≥2 (n = 67) than in those with RASH of grade ≤1 (n = 39) (10.25 months [95% CI, 8.80–12.12] *vs* 8.31 months [95% CI, 6.18–9.99], respectively; Fig. 1C) and the 1-year survival rate was higher (39% [95% CI, 27–50] *vs* 23% [95% CI, 10–36], respectively). Similarly, the median PFS was longer in patients with RASH of grade ≥2 versus those with RASH grade ≤1 (3.61 months [95% CI, 3.48–5.32] *vs* 1.81 months [95% CI, 1.64–3.48]; Fig. 1D). While there was no notable difference in ORR between patients with RASH grade ≥2 and those with grade ≤1 (21.1% [95% CI, 9.6–37.3] *vs* 19.2% [95% CI, 6.6–39.4]), the DCR was higher in those with more severe RASH (60.5% [95% CI, 43.4–76.0] *vs* 34.6% [95% CI, 17.2–55.7]).

Pharmacokinetics. Plasma sampling for PK analyses was performed in all six patients enrolled in the first step. On day 8, the values of C_{max} were 1760 ± 456.9 ng/mL (mean ± SD) for erlotinib, 169.7 ± 64.5 ng/mL for OSI-420 and 22 700 ± 3272.9 ng/mL for gemcitabine. The AUC_{last} was 29 001 ± 6560 h ng/mL, 2748 ± 788 h ng/mL and 10 717 ± 1458 h ng/mL (mean ± SD), respectively. The mean t_{max} was 8.0 h (range, 2.0–23.9 h), 9.0 h (2.0–23.9 h) and 0.51 h (0.45–0.57 h), respectively. Also on day 8, the mean plasma $t_{1/2}$ was 54.92 h (range, 9.25–144.61 h), 32.79 h (10.36–60.46 h), and 0.63 h (0.31–1.14 h), respectively. The Cl/F of erlotinib and gemcitabine showed interindividual variability; the Cl/F on day 8 was 3972.6 ± 772.1 mL/h (mean ± SD; coefficient of variation 19.4%) and 146 580.4 ± 31 101.3 mL/h (21.2%), respectively.

Biomarker analysis. Of the 106 patients enrolled, *EGFR* mutation status was evaluated in 47 patients (44.3%), all of whom had wild-type *EGFR*. The mutation status of the remaining patients was classified as unknown because samples were not available (30.2%), not examined (9.4%) or the results following sequencing were inconclusive (16.0%).

Discussion

This study was designed to initially assess the safety of erlotinib with gemcitabine for Japanese patients with pancreatic cancer, in whom there had been no prior exposure to either drug. As no significant safety concerns were raised in the first step of the study, enrollment of a further 101 patients was performed. Although the incidence of AE in this study was higher than in the PA.3 study, the incidence of grade 3–4 AE was similar.[28] Despite these results, no new AE specific to Japanese patients were observed. As expected, RASH and gastrointestinal events were among the most common AE in this study, and most of these cases were mild to moderate in severity.

Interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%) in the current study, while its incidence was reported to be 2.4% in patients treated in the erlotinib plus gemcitabine arm of the PA.3 study.[28] In addition, in Japanese patients with advanced pancreatic cancer, ILD-like events were reported in two (6.1%) of 33 patients treated with gemcitabine plus S-1, and were reported in three (1.1%) of 264 patients with gemcitabine monotherapy, respectively.[33,34] Likewise, the higher incidence of ILD-like events were documented using S-1 or erlotinib in combination with gemcitabine compared with gemcitabine as monotherapy in patients with pancreatic and biliary tract cancer.[35] On another front, outside of Japan, a high incidence of ILD-like events was reported in gemcitabine and paclitaxel combination therapy in patients with NSCLC.[36] From the above information, considering the higher incidence of ILD when gemcitabine is used in combination, an additive effect from such combinations cannot be ruled out.

In NSCLC, Japanese patients have an increased risk of developing ILD-like events when treated with EGFR TKI.[29,37–39] Fatal cases of ILD-like events have been reported following EGFR TKI administration for the treatment of NSCLC.[37–41] Importantly, however, no patients died due to an ILD-like event in this study. Seven patients experienced ILD-like events of grade 1–2 in severity. This may be due to active management of ILD-like cases during the study period. This management included regular and immediate chest X-rays, in addition to diagnosis with CT scans after any early signs and symptoms were observed (e.g. pyrexia, cough or dyspnea), timely discontinuation of the antitumor drugs (as a precautionary measure in case these drugs were associated with the symptoms) and appropriate treatment for the events (including oral/pulse steroids). By appropriately treating the early symptoms of ILD-like events, patients could restart antitumor therapy (chemotherapy: treatment change). In this study, the onset time for ILD-like events varied markedly between patients (7–187 days). It is therefore necessary to monitor the patients throughout the treatment period.

All of the patients who developed ILD in this study were current or past smokers, and smoking status has been shown to be a risk factor for ILD in the NSCLC population.[38] Results from the multivariate analyses in this study suggest that emphysema is also a risk factor for developing ILD; six of the nine

patients with ILD-like events were diagnosed with emphysema at baseline. Although the number of reports of an ILD-like event may have been artificially elevated due to underlying patient baseline characteristics and the active management of ILD-like events, these results demonstrate the need to consider the risk of ILD-like events in Japanese patients treated with TKI. In particular, it is important that chest CT scans are closely checked for the presence of emphysema or comorbid ILD and that pulmonary status is assessed prior to treatment administration.

This study corroborates the results of the combination of gemcitabine and erlotinib shown in the PA.3 study. The median OS in this study of 9.23 months was longer than those reported in trials with gemcitabine alone. In this study, patients who experienced skin toxicity of grade ≥2 had better outcomes than those with less severe toxicity or the overall study population. Retrospective analyses of data from the PA.3 and AViTA studies have found a significant association between the development of skin toxicity and efficacy in patients with pancreatic cancer treated with erlotinib-based therapy, although the precise mechanisms for the association between skin toxicity and effectiveness are unknown.[28,41,42]

Although the presence of mutations in the tyrosine-kinase region of the *EGFR* gene appears to predict a better response to erlotinib in NSCLC,[43,44] this has not yet been evaluated in pancreatic cancer. *EGFR* mutations are very rare in patients with pancreatic cancer;[45–47] indeed in the present study, no *EGFR* mutations were detected. Further work is required to determine whether *EGFR* mutations can be used as predictive markers for improved survival in Japanese patients receiving erlotinib and gemcitabine as treatment for advanced pancreatic cancer.

In conclusion, the present study shows that erlotinib in combination with gemcitabine is generally well tolerated in Japanese patients with advanced pancreatic cancer. This combination is associated with efficacy and survival outcomes, and the results of this study are consistent with the findings of the global PA.3 study.

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