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様式第19

学会等発表実績

委託業務題目	切除不能膵癌に対する標準治療の確立に関する研究
分担研究者名	伊藤芳紀
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1. 学会等における口頭・ポスター発表

発表した成果		発表者氏名	発表した場所(学会等名)	発表した時期	国内・外の別
発表題目	口頭・ポスター発表等の別				
膵癌診療ガイドライン2013年版における放射線療法分野の問題点と今後の課題	口頭	伊藤芳紀、澁谷景子、中村聡明、大栗隆行、永倉久泰、中村晶、高橋昌太郎	第45回日本膵臓学会大会	2014年7月11－12日	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文(発表題目)	発表者氏名	発表した場所(学会誌・雑誌等名)	発表した時期	国内・外の別
EBM-based Clinical Guidelines for Pancreatic Cancer (2013) issued by the Japan Pancreas Society: a synopsis.	Yamaguchi K, Okusaka T, Shimizu K, Furuse J, Ito Y, Hanada K, Shimosegawa T; Committee for revision of clinical guidelines for pancreatic cancer of Japan Pancreas Society.	Jpn J Clin Oncol.	2014 ;44(10):883-8	国内

様式第19

学会等発表実績

委託業務題目	切除不能膵癌に対する標準治療の確立に関する研究
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1．学会等における口頭・ポスター発表

発表した成果		発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
発表題目	口頭・ポスター発表等の別				
膵癌の化学放射線療法	シンポジウム	中村聡明	2014日本消化器病学会	2014/4/23-26	国内
膵癌癌	教育講演	中村聡明	2014日本放射線腫瘍学会夏季セミナー	2014/8/31-9/1	国内
Radiotherapy of pancreatic cancer	Guest lecture	Nakamura S	2014インド放射線腫瘍学会(AROI)	2014/11/7-9	国外

2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
該当なし				

Ⅳ.　研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Retrospective analysis of fixed dose rate infusion of gemcitabine and S-1 combination therapy (FGS) as salvage chemotherapy in patients with gemcitabine-refractory advanced pancreatic cancer: inflammation-based prognostic score predicts survival

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Abstract
Purpose The purpose of this study was to assess the efficacy and safety of fixed dose rate infusion of gemcitabine and S-1 combination therapy (FGS) in patients with gemcitabine (GEM)-refractory pancreatic cancer (PC) and to explore independent variables associated with survival.
Methods We retrospectively reviewed consecutive patients with GEM-refractory PC who received FGS at our institution from March 2009 to December 2013. GEM was administered by fixed dose rate intravenous infusion of 1,200 mg/m^2 as a 120-min infusion on day 1, and S-1 was administered orally twice a day at a dose of 40 mg/m^2 on days 1–7. Cycles were repeated every 14 days.
Results Sixty-one patients with GEM-refractory PC received FGS. Sixteen patients received FGS as third-line treatment. Twenty-nine patients (48 %) had a history of S-1 administration. The objective response rate was 13 %, and the disease control rate was 49 %. The median progression-free survival time was 2.7 months, and the median overall survival time was 6.0 months. Major Grade 3 or 4 adverse events included neutropenia (15 %), diarrhea (3 %), anorexia (2 %), and fatigue (2 %). A high inflammation-based prognostic score (modified Glasgow prognostic score (mGPS), which incorporates C-reactive protein and albumin), a performance status >0, and serum carbohydrate antigen 19–9 level >2,000 IU/ml were independently associated with a poor outcome.
Conclusions FGS might be effective and well tolerated as salvage chemotherapy in a practical setting. The inflammation-based prognostic score is a simple and reliable indicator of survival in the setting of salvage chemotherapy.

Keywords Pancreatic cancer · Chemotherapy · Gemcitabine refractory · Fixed dose rate infusion · S-1 · Inflammation-based prognostic score · Glasgow prognostic score

Introduction

Gemcitabine (GEM) monotherapy has been applied for advanced pancreatic cancer (PC) as a standard treatment since a randomized controlled trial demonstrated improved overall survival (OS) compared with that with fluorouracil [1]. Although various GEM-based combination regimens have been evaluated, only nab-paclitaxel or erlotinib added to GEM showed a survival benefit over GEM alone in a phase III study [2–4]. Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a GEM-free combination regimen, demonstrated a clear survival benefit compared with GEM for patients with metastatic PC [5]. Therefore, these combination therapies have been considered to be standard first-line therapies.

However, after disease progression during first-line chemotherapy, the options for further anticancer treatment are limited. In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. A phase II study of S-1 first-line monotherapy led to a median progression-free survival (PFS) time of 2.0 months and a median OS time of 4.5 months in GEM-refractory metastatic PC [6]. In GEM-refractory metastatic PC, a recent phase I/II study

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of fixed dose infusion (FDR) GEM and S-1 combination therapy (FGS) yielded results that demonstrated activity including a response rate of 18 %, a median PFS time of 2.8 months, and a median OS time of 7.0 months, with a favorable toxicity profile [7]. A randomized phase II study comparing GEM administration via 30-min infusion and FDR infusion showed that FDR-GEM was associated with higher intracellular drug concentrations and efficacy [8]. A phase III study E6201 designed to test two promising approaches, FDR-GEM and GEM and oxaliplatin combination therapy (GEMOX), against standard GEM showed that OS time for FDR-GEM was longer than that for standard GEM ($p = 0.04$), but the difference was not statistically significant with respect to the parameters of the study ($p < 0.025$) [9]. The results of a phase I/II study of FGS for GEM-refractory PC suggested that even after the failure of standard GEM, the increased intracellular concentration of GEM as a result of FDR infusion and/or the synergistic effect of GEM and S-1 might play an important role in the antitumor effect of FGS for advanced GEM-refractory PC.

No standard salvage chemotherapy has been established for patients with advanced PC after the failure of GEM-based treatment. It is important to clarify the prognostic factors for patients with GEM-refractory advanced PC as well as to evaluate the efficacy and safety of salvage chemotherapy. With respect to measurement of the systemic inflammatory response, the combination of C-reactive protein and albumin (the original Glasgow prognostic score and the modified Glasgow prognostic score (mGPS)) has been shown to have prognostic value in a variety of common solid tumors [10, 11]. To our knowledge, there has been no report on the relationship between the modified Glasgow prognostic score and outcome in salvage chemotherapy for advanced PC.

As noted above, FGS was reported to provide promising antitumor activity and tolerable toxicity in patients with GEM-refractory PC. However, the previous study of FGS was limited in patient number, and the efficacy and safety of FGS for patients with GEM-refractory advanced PC are not well known. The aim of the present study was to retrospectively evaluate the efficacy and safety of FGS as salvage chemotherapy for advanced GEM-refractory PC in a clinical setting and to establish a method of selecting patients who will benefit from salvage chemotherapy.

Materials and methods

The subjects were consecutive patients with advanced GEM-refractory PC who received FGS between March 2009 and December 2013 as second-line or third-line treatment at Kyorin University Hospital. We retrospectively reviewed their medical records. All patients had a pathological and clinical diagnosis of PC. Informed consent was obtained from each patient, and this retrospective study was approved by the independent ethics committee of Kyorin University School of Medicine.

Eligibility

The patient selection criteria for this study were as follows: both a pathological and clinical diagnosis of PC; disease progression under GEM-based chemotherapy; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; good bone marrow function (white blood cell count $\geq$3,000/mm^3, platelet count $\geq$75,000/mm^3, and hemoglobin $\geq$8.0 g/dl); renal function (serum creatinine $\leq$1.5 mg/dl); and liver function (total bilirubin $\leq$2.0 mg/dl and transaminase levels $\leq$5 times the upper limit of the respective normal ranges). Patients who had obstructive jaundice were eligible, but only after their serum transaminase levels had decreased to within five times the upper normal limit after biliary drainage. Exclusion criteria were as follows: severe complications, such as active infection, uncontrolled diabetes, massive pleural effusion or ascites, active concomitant malignancy, or severe drug hypersensitivity.

Treatment

GEM was administered every 2 weeks by FDR intravenous infusion of 1,200 mg/m^2/120 min on day 1. S-1 was administered orally twice daily on day 1 to day 7, followed by a 1-week rest. The initial dose was determined according to the body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA < 1.50 m^2, 100 mg/day; and BSA $\geq$ 1.50 m^2, 120 mg/day. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred.

Evaluation

Tumor response was assessed approximately every 2 months by contrast-enhanced computed tomography according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Laboratory variables were initially recorded as continuous variables, and later dichotomized according to the median and reference value of each variable. mGPS was constructed, using C-reactive protein and albumin, as follows: Patients with both elevated C-reactive protein ($\geq$1.0 mg/dl) and low albumin (<3.5 g/dl) were allocated a score of 2; patients in whom only C-reactive protein was elevated ($\geq$1.0 mg/dl) were allocated a score of 1, and those with normal C-reactive protein were allocated a score of 0 [11].

Table 1 Patient characteristics

	Patients ($n = 61$)	Percent (%)
Age (years)		
Median	63	
Range	37–83	
Gender		
Male	40	(66)
Female	21	(34)
ECOG performance status		
0	22	(36)
1	36	(59)
2	3	(5)
Primary tumor		
Head	29	(48)
Body/tail	32	(52)
Extent of disease		
Locally advanced	1	(2)
Metastatic	48	(79)
Recurrence after surgery	12	(20)
Metastatic site		
Liver	38	(62)
Lung	17	(28)
Peritoneum	36	(59)
Lymph node	45	(74)
Ascites	22	(36)
Prior treatment		
First Line		
GEM	37	(61)
GEM+S-1	19	(31)
GEM+erlotinib	1	(2)
GEM+ganitumab	2	(3)
GEM+nab-paclitaxel	1	(2)
S1	1	(2)
Second Line		
Yes	17	(28)
S-1	9	(15)
GEM+S-1	2	(3)
GEM	1	(2)
Clinical trial drug	3	(5)
Others	2	(3)
No	44	(72)
History of S-1 administration		
Yes	29	(48)
No	32	(52)
TTF of prior treatment (months)		
Median	6.3	
Range	0.47–32.43	
CEA (ng/ml)		
Median	8.6	
Range	0.9–1,412	
CA19-9 (IU/ml)		
Median	1,805	
Range	0.1–120,000	
ALP (IU/l)		
Median	301	
Range	147–1,429	
Alb (g/dl)		
Median	3.7	
Range	2.3–4.6	
CRP (mg/dl)		
Median	0.3	
Range	0.0–7.1	

ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; TTF, time to treatment failure; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ALP, alkaline phosphatase; Alb, albumin; CRP, C-reactive protein

Statistical analysis

PFS was counted from the date of treatment initiation to the date of documentation of disease progression or death, and OS was counted from the date of treatment initiation to the date of death or the last follow-up. OS and PFS were calculated using the Kaplan–Meier method. Subgroup analyses were evaluated with the log-rank test, and prognostic factors were identified by univariate analysis. Multivariate analysis was carried out using stepwise Cox proportional hazards regression modeling to identify independent prognostic factors. For the analysis of factors predictive for response to FGS, the univariate relationship between each clinical variable and the achievement of partial response was evaluated using Pearson's Chi-square test or Fisher's exact probability test. These variables were also evaluated by a multivariate logistic regression model using backward stepwise selection. The variables with p values <0.1 were selected for multivariate analysis. P values <0.05 were considered statistically significant. The SPSS statistical software program (version 20.0; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Between March 2009 and December 2013, 61 patients with GEM-refractory PC received FGS. The patient characteristics of the subjects are shown in Table 1. Of the 61 patients, the median age was 63 years, 40 (66 %) were male, 58 (95 %) had an ECOG PS of 0–1, and 60 (98 %) had metastatic disease. Disease progression had been confirmed before FGS in all patients. All patients had received prior GEM-based

therapy. Before FGS, 44 (72 %) received one regimen, and 17 (28 %) received two regimens. As for prior treatment regimens, 29 (48 %) had received S-1 as monotherapy or GEM plus S-1 combination therapy. Median time to treatment failure of prior treatment was 6.3 months (range 0.5–32.4).

A total of 542 courses were administered, with a median of five courses (range 1–62). Dose reduction in GEM and S-1 because of adverse events was conducted in 11 (18.0 %) and 12 (19.7 %) patients, respectively. A rest period of more than 14 days during treatment was required in 22 (36.1 %) patients. The relative dose intensity for GEM and S-1 was 92.6 and 92.3 %, respectively. FGS was discontinued in 56 (91.8 %) patients because of disease progression and in five (8.2 %) patients because of adverse events (Grade 3 cholangitis in two patients, grade 3 interstitial lung disease in one patient, grade 3 stroke in one patient, and grade 3 sick sinus syndrome in one patient). All the patients had died at the time of analysis.

After FGS treatment failure, 17 patients (27.9 %) received chemotherapy: paclitaxel in five patients, clinical trial drugs in four patients, GEM monotherapy in four patients, and others in four patients.

Toxicity

The toxic effects are summarized in Table 2. Hematologic and non-hematologic toxicity were generally mild, with grade 3 neutropenia observed in nine patients (14.8 %), grade 3 diarrhea in two patients (3.3 %), grade 3 anorexia in only one patient (1.6 %), and grade 3 fatigue in only one patient (1.6 %). Grade 3 stroke, which was irreversible, occurred in one patient (1.6 %). Other than this case, all of the adverse events were reversible. There were no treatment-related deaths.

Efficacy

Eight (13.1 %) patients showed a partial response and 22 (36.1 %) showed stable disease, resulting in an overall objective response rate of 13.1 % and a disease control rate of 49.2 %. The median OS time was 6.0 months (95 % CI 3.6–8.4), and the median PFS time was 2.7 months (95 % CI 1.9–3.5) (Fig. 1). The median OS time after the start of first-line therapy was 15.4 months.

Prognostic factors

The median survival time and p values for univariate analysis are shown in Table 3. Among these variables, ECOG performance status (PS) >0, the presence of ascites, serum carcinoembryonic antigen (CEA) level >10 ng/ml, serum carbohydrate antigen 19-9(CA19-9) level >2,000 IU/ml, serum alkaline phosphatase level (ALP) >500 IU/ml, serum albumin level (ALB) <3.5 g/dl, serum C-reactive protein (CRP) level $\geq$1.0 g/dl, and a high mGPS were significantly associated with poor survival. A previous history of S-1 administration was not a prognostic factor. The results of the Cox proportional hazards model are shown in Table 4. High mGPS, ECOG PS >0, and CA19-9 level >2,000 IU/ml were independently associated with a poor outcome.

Table 2 Toxicity according to CTCAE v 4.0

	Grade							
	1		2		3		4	
	n		*n*		*n*		*n*	
Hematologic								
Anemia	41	(67 %)	20	(33 %)	0	(0 %)	0	(0 %)
Leukopenia	12	(20 %)	11	(18 %)	7	(11 %)	0	(0 %)
Neutropenia	10	(16 %)	9	(15 %)	9	(15 %)	1	(2 %)
Thrombocytopenia	23	(38 %)	0	(0 %)	0	(0 %)	0	(0 %)
Non-hematologic						(0 %)		(0 %)
Anorexia	32	(52 %)	14	(23 %)	1	(2 %)	0	(0 %)
Nausea	21	(34 %)	11	(18 %)	0	(0 %)	0	(0 %)
Diarrhea	19	(31 %)	5	(8 %)	2	(3 %)	0	(0 %)
Oral mucositis	12	(20 %)	5	(8 %)	0	(0 %)	0	(0 %)
Fatigue	38	(62 %)	14	(23 %)	1	(2 %)	0	(0 %)
Dysgeusia	22	(36 %)	4	(7 %)	0	(0 %)	0	(0 %)
Skin hyperpigmentation	24	(39 %)	0	(0 %)	0	(0 %)	0	(0 %)
Vomiting	7	(11 %)	1	(2 %)	0	(0 %)	0	(0 %)
Constipation	11	(18 %)	9	(15 %)	0	(0 %)	0	(0 %)
Rash	3	(5 %)	1	(2 %)	0	(0 %)	0	(0 %)

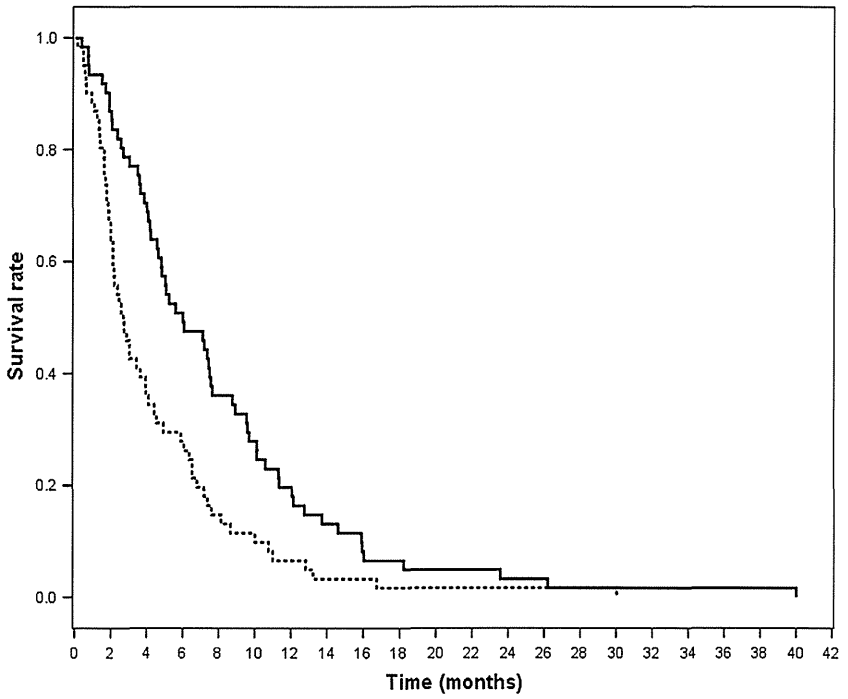

Fig. 1 Kaplan–Meier curves for overall survival (*black line*) and progression-free survival (*dotted line*). Median progression-free survival and overall survival were 2.7 months (95 % CI 1.9–3.5) and 6.0 months (95 % CI 3.6–8.4), respectively

Predictive factors

The relationships between clinical factors and the attainment of partial response to FGS were evaluated. ECOG PS >0 ($p = 0.103$), site of primary lesion($p = 0.588$), number of prior chemotherapy regimens ($p = 0.607$), history of S-1 administration ($p = 0.162$), time to treatment failure of prior treatment ($p = 0.548$), the presence of liver metastasis ($p = 0.346$), the presence of lung metastasis ($p = 0.281$), the presence of ascites ($p = 0.608$), CEA level >10 ng/ml ($p = 0.452$), CA19-9 level >2,000 IU/ml ($p = 0.588$), ALP > 500 IU/ml ($p = 0.128$), ALB < 3.5 g/dl ($p = 0.136$), CRP level ≥1.0 g/dl ($p = 0.281$), and a high mGPS ($p = 0.153$) were not significantly associated with response to FGS. There were no variables with p values <0.1 selected for multivariate analysis.

Discussion

This retrospective study of FGS in patients with GEM-refractory PC demonstrated an ORR of 13 %, DCR of 49 %, and median PFS and OS of 2.7 and 6.0 months, respectively. FGS showed efficacy in both S-1-naïve and non-naïve patients in this study. We explored the independent variables associated with survival in a salvage chemotherapy setting for advanced PC. This study demonstrated that the inflammation-based prognostic score (mGPS) was independently associated with survival in patients with GEM-refractory advanced PC receiving salvage chemotherapy.

In regard to treatment for GEM-refractory PC, the results of a randomized trial comparing best supportive care (BSC) versus oxaliplatin, fluorouracil, and folinic acid (OFF) indicated the benefit of second-line chemotherapy as compared to BSC alone for patients with GEM-refractory advanced pancreatic cancer. Median second-line survival time was 4.8 months for OFF treatment and 2.3 months for BSC alone [12]. However, since the patient number was small ($n = 46$), OFF has not been recognized as standard salvage chemotherapy in patients with advanced pancreatic cancer. Thus, no standard salvage chemotherapy has been established. Several clinical trials (mainly phase II) of oral fluoropyrimidine monotherapy such as S-1 have been conducted in patients with advanced PC after failure of first-line GEM or a GEM-based combination regimen [6, 13–16]. Median PFS time and median OS time of oral fluoropyrimidine monotherapy were 2.1–4.1 and 4.5–7.6 months (Table 5), which are almost the same as the results of a previous prospective study of FGS [7]. As FOLFIRINOX regimen demonstrated survival benefit over GEM in first-line setting, it could be promising salvage chemotherapy for GEM-refractory patients. Although there is no prospective study using FOLFIRINOX in second-line setting. A retrospective analysis of 27 patients with GEM-refractory PC showed median time to progression of 5.4 months, and median OS was 8.5 months [17]. Another retrospective from Korea assessed 18 patients with GEM-refractory PC noted progression-free survival of 2.8 months and overall survival of 8.4 months [18]. These results suggest the modest clinical activity regarding efficacy with the

Table 3 Univariate analysis of prognostic factors for FGS-treated patients

	n	Median survival (months)	*p* value
ECOG performance status			
0	22	9.6	0.006
1, 2	39	4.2	
Primary tumor			
Head	29	7.4	0.562
Body/tail	32	5.1	
Prior chemotherapy			
First Line	44	6.1	0.911
Second Line	17	5.2	
History of S-1 administration (including GS therapy)			
Yes	29	5.1	0.842
No	32	7.1	
TTF of prior treatment (months)			
≦6	28	5.0	0.506
>6	33	7.4	
Liver metastasis			
Present	38	4.6	0.095
Absent	23	9.6	
Lung metastasis			
Present	17	5.1	0.490
Absent	44	7.1	
Ascites			
Present	22	3.9	0.021
Absent	39	7.5	
CEA (ng/ml)			
≦10	33	9.6	<0.001
>10	28	4.6	
CA19-9 (IU/ml)			
≦2,000	32	7.1	0.028
>2,000	29	4.8	
ALP (IU/l)			
≦500	48	7.4	<0.001
>500	13	2.7	
Alb (g/dl)			
<3.5	22	3.6	<0.001
≧3.5	39	7.6	
CRP (mg/dl)			
<1.0	44	7.6	<0.001
≧1.0	17	2.4	
mGPS			
Low (0, 1)	49	7.5	<0.001
High (2)	12	2.0	

ECOG, Eastern Cooperative Oncology Group; GS, gemcitabine and S-1 combination therapy; TTF, time to treatment failure; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ALP, alkaline phosphatase; Alb, albumin; CRP, C-reactive protein; mGPS, modified Glasgow prognostic scale

Table 4 Multivariate analysis of prognostic factors for FGS-treated patients

Variable	Odds ratio	95 % confidence interval	*p* value
High mGPS (2)	6.605	2.965–14.709	<0.001
CA19-9 > 2,000	2.573	1.448–4.573	0.001
ECOG performance status >0	2.192	1.192–4.031	0.012

mGPS, modified Glasgow prognostic scale; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group

FOLFIRINOX regimen as a second-line treatment. However, FOLFIRINOX is a potentially highly toxic combination of drugs with serious side effects, and only patients with good performance status are candidates for the regimen even in the first-line setting. Significant toxicity is a concern with FOLFIRINOX in any setting. Prospective studies are needed to better define risks and to determine FOLFIRINOX in the salvage setting.

Whether gemcitabine as FDR infusion is active even after progression during treatment with standard 30-min administration of GEM was the critical clinical question examined in this study. Differentiation between the relative roles of GEM and S-1 in overcoming tumor resistance is difficult. This retrospective study included patients with a history of S-1 administration. Subgroup analysis showed that a history of S-1 administration was not a significant prognostic factor ($p = 0.842$). This might suggest that FDR infusion of gemcitabine is efficacious ever after failure of standard GEM-based regimens.

Regarding toxicity, grade 3–4 adverse events were not frequent. One death was observed after grade 3 stroke, in a patient with other risk factors, such as age of 82 years and poor performance status. Other than this event, most episodes were reversible, and treatment was generally well tolerated in this study. The median relative dose intensity of GEM and S-1 was 92.6 and 92.3 %, respectively, indicating that treatment was carried out as scheduled in most patients. The safety profile in this study suggests that FGS can be safely administered to patients with PC even in a salvage setting, at least in selected populations. Since the FGS regimen was applied in a practical setting in this study, physical examination and laboratory tests usually were not conducted on day 8. The biweekly schedule allows enough time for recovery from myelosuppression and non-hematologic toxicity before the following cycle, enabling patients to receive treatment as scheduled.

Subgroup analysis of this study showed that high mGPS, high CA19-9 level, and poor PS were independently associated with a poor outcome. Previous reports indicated that

Table 5 Comparison between current study and previous studies on oral fluoropyrimidine-based therapy as salvage chemotherapy for advanced pancreatic cancer

Study	Phase	Regimen	*n*	ORR (%)	Median PFS (months)	Median OS (months)
Morizane et al. [6]	II	S-1	40	15	2.0	4.5
Sudo et al. [13]	II	S-1	21	9.5	4.1	6.3
Todaka et al. [14]	Retrospective	S-1	52	4	2.1	5.8
Boeck et al. [15]	II	Capecitabine	39	0	2.3	7.6
Morizane et al. [7]	II	FGS	40	18	2.8	7.0
Takahara et al. [16]	Retrospective	SOX	30	10	3.4	5.0
Current study	Retrospective	FGS	61	13.1	2.7	6.0

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; FGS, fixed dose rate infusion gemcitabine and S-1 combination therapy; SOX, S-1 and oxaliplatin combination therapy

PS, CRP, ALB, and inflammation-based prognostic score were important prognostic factors in a first-line setting [19–22]. mGPS was reported to be identified as an independent predictor of survival in patients undergoing potentially curative pancreatic resection [23]. It is now widely accepted that inflammation-based prognostic score is a reliable indicator of survival for several malignant tumors [10, 11]. Our results suggested that it is also an important prognostic factor in the setting of salvage chemotherapy for advance pancreatic cancer.

It is important to point out the limitations of this retrospective study. Patients who received FGS may have been more fit, better able to tolerate it and therefore more likely to derive benefit from it. In addition, the gap between the median OS time and the median PFS time in the present study was relatively large. In this study, 27.9 % of patients received chemotherapy after failure of FGS. Post-treatment, including paclitaxel and clinical trial drugs may prolong the survival of selected patients. Although the reason for this gap is unknown, bias arising from the selection of patients with a good general condition may explain these findings. On the other hand, this retrospective study included patients after failure of second-line chemotherapy as well as those after failure of first-line chemotherapy. It thus seems that the patient backgrounds were rather poor when compared to those in recent phase II trials [6, 7, 13, 15].

In conclusion, FGS as salvage chemotherapy in patients with GEM-refractory advanced PC might be effective and well tolerated in a practical setting. Furthermore, the FGS regimen might possibly show some benefit in patients even after both GEM and S-1 failure. These results suggest that it would be of value to further investigate FGS in a clinical trial in patients with GEM-refractory pancreatic cancer. mGPS is simple and useful as a novel predictor of survival for patients with GEM-refractory advanced PC. mGPS is helpful for planning salvage treatment for these patients.

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Efficacy and safety of axitinib in combination with gemcitabine in advanced pancreatic cancer: subgroup analyses by region, including Japan, from the global randomized Phase III trial

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Abstract

Objective: Axitinib is a potent and selective inhibitor of vascular endothelial growth factor receptors 1–3. This analysis compared efficacy and safety of axitinib plus gemcitabine in patients with advanced pancreatic cancer from Japan, North America and the European Union, enrolled in a randomized Phase III study.

Methods: Patients ($n = 632$), stratified by disease extent, were randomly assigned (1:1) to receive axitinib/gemcitabine or placebo/gemcitabine. Axitinib was administered at a starting dose of 5 mg orally twice daily and gemcitabine at 1000 mg/m^2 once weekly for 3 weeks in 4 week cycles. Primary endpoint was overall survival.

Results: Among Japanese patients, median overall survival was not estimable (95% confidence interval, 7.4 months—not estimable) with axitinib/gemcitabine ($n = 58$) and 9.9 months (95% confidence interval, 7.4–10.5) with placebo/gemcitabine ($n = 56$) (hazard ratio 1.093 [95% confidence interval, 0.525–2.274]). Median survival follow-up (range) was 5.1 months (0.02–12.3) with axitinib/gemcitabine vs. 5.4 months (1.8–10.5) with placebo/gemcitabine. Similarly, no difference was detected in overall survival between axitinib/gemcitabine and placebo/gemcitabine in patients from North America or the European Union. Common adverse events with axitinib/gemcitabine in Japanese patients were fatigue, anorexia, dysphonia, nausea and decreased platelet count. Axitinib safety profile was generally similar in patients from the three regions, although there were differences in incidence of some adverse events. An exploratory analysis did not show any correlation between axitinib/gemcitabine-related hypertension and overall survival.

Conclusions: Axitinib/gemcitabine, while tolerated, did not provide survival benefit over gemcitabine alone in patients with advanced pancreatic cancer from Japan or other regions.

Key words: axitinib, gemcitabine, Japanese, pancreatic cancer

Introduction

Pancreatic cancer was diagnosed in an estimated 337 872 patients and claimed ~330 372 deaths worldwide in 2012 (1). The estimated incidences and deaths, respectively, were 42 885 and 41 509 in the USA, 79 331 and 78 651 in the European Union and 32 899 and 31 046 in Japan (1). Currently, surgical resection is the only potentially curative treatment of pancreatic cancer, but patients are often diagnosed with advanced unresectable disease (2). For advanced pancreatic cancer, combination chemotherapy with FOLFIRINOX (5-fluorouracil/leucovorin, oxaliplatin and irinotecan) or gemcitabine with nab-paclitaxel or erlotinib (an inhibitor of epidermal growth factor receptor), as well as gemcitabine monotherapy, are recommended by the National Comprehensive Cancer Network (2). Pancreatic cancer is associated with the poorest 5-year survival rate (6%) of any cancer in the USA (3). Therefore, new treatment options are urgently needed to improve survival of patients with advanced pancreatic cancer.

Vascular endothelial growth factor (VEGF) is highly expressed in pancreatic cancer, with the level of expression correlated with microvascular density (4–6) and possibly with poor prognosis (5,6). Axitinib is a potent and selective inhibitor of VEGF receptors 1, 2 and 3 (7), approved for second-line treatment of advanced renal cell carcinoma. Based on promising activity against advanced pancreatic cancer reported in an open-label randomized Phase II study (8), a randomized Phase III study was conducted globally to evaluate the efficacy and safety of axitinib in combination with gemcitabine (9). At the pre-planned interim analysis, median overall survival (OS), the primary endpoint of the study, was 8.5 months in the axitinib/gemcitabine arm ($n = 314$) compared with 8.3 months in the placebo/gemcitabine arm ($n = 316$) (hazard ratio [HR] 1.014; 95% confidence interval [CI], 0.786–1.309; $P = 0.5436$, stratified one-sided log-rank test), and the independent Data Monitoring Committee (DMC) concluded that the futility boundary had been crossed (9). Thus, the study failed to demonstrate survival benefit of adding axitinib to gemcitabine in the treatment of advanced pancreatic cancer in the overall population.

To the best of our knowledge, there has been no report describing potential geographic differences in efficacy and safety outcomes in patients with advanced pancreatic cancer treated with anticancer drugs, including antiangiogenic agents. Therefore, we have undertaken in-depth analyses of the data from this Phase III study to evaluate the efficacy and safety of axitinib/gemcitabine in Japanese patients and compare the results with those from North America and the European Union in order to assess potential geographic differences in patient outcomes. In addition, based on a *post hoc* exploratory analysis of data from the Phase II study of axitinib/gemcitabine in advanced pancreatic cancer, which indicated a longer median OS in patients who experienced diastolic blood pressure (BP) ≥90 mm Hg during treatment compared with those who did not (8), the exploratory analysis was expanded using the data from this Phase III study to further assess potential correlations between the axitinib efficacy outcome and hypertension in these patients.

Methods

Study design

This was a randomized, double-blind Phase III study conducted in 24 countries, including Japan. The details of the study design and treatment have been published previously (9). In brief, eligible patients were stratified by extent of the disease (metastatic vs. locally advanced pancreatic cancer), and randomly assigned (1:1) to receive axitinib/gemcitabine or placebo/gemcitabine. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), objective response rate (ORR) and safety. For Japanese patients enrolled in the study, an additional review of the first 16 patients was conducted by the DMC to evaluate the safety of axitinib/gemcitabine, and subsequent enrollment and initiation of treatment was based on the feedback from the DMC.

The study protocol, amendments and informed consent documentation were reviewed and approved by the institutional review boards and independent ethics committees at each center. The study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines as well as applicable local regulatory requirements. All patients provided written informed consent prior to study entry. This study is registered with ClinicalTrials.gov (identifier NCT00471146).

Patients

As previously described in detail (9), eligible patients were aged 18 years or older (≥20 years old in Japan) with histologically or cytologically confirmed metastatic or locally advanced unresectable pancreatic adenocarcinoma; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; adequate bone marrow, hepatic, renal and coagulation function; and without uncontrolled hypertension, i.e. baseline BP readings must be ≤140/90 mm Hg. Use of antihypertensive medications was permitted. Exclusion criteria included prior systemic chemotherapy; prior therapy with gemcitabine, axitinib or VEGF inhibitors; or active seizure or brain metastasis.

Study treatment

Patients received gemcitabine (1000 mg/m^2) as a 30 min intravenous infusion once weekly for 3 weeks followed by 1 week off. Gemcitabine dose could be reduced to 750, 550 or 425 mg/m^2 to manage toxicities. Axitinib or placebo was administered at a starting dose of 5 mg twice daily (BID) orally with food. Axitinib or placebo dose could be increased stepwise to 7 mg BID, and then to the maximum 10 mg BID, in patients who had no drug-related, Grade ≥3 adverse event (AE) per Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for consecutive 2-week periods, and had BP ≤150/90 mm Hg without any antihypertensive medication. Axitinib or placebo dose could be reduced to 3 mg BID, and then to 2 mg BID, if necessary, to manage treatment-related toxicity. Patients were treated in 4-week cycles until disease progression, unmanageable AEs or withdrawal of consent.

Assessments

As reported previously (9), tumor assessments were conducted at screening and repeated every 8 weeks until 28 days after the last dose and whenever disease progression was suspected. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Safety was monitored throughout the study and AEs were graded per CTCAE version 3.0. BP was measured in-clinic at screening and once every week. In addition, all patients were provided with a BP-monitoring device and instructed to measure BP twice daily at home and to contact their physician if BP was >150/100 mm Hg or symptoms related to elevated BP developed. Plasma level of thyroid-stimulating hormone and free thyroxine was monitored during treatment period, and hypothyroidism was treated with standard medication. Urinalysis was performed at screening and once every cycle.

Statistical analyses

Statistical analyses were previously described in detail (9). For time-to-event endpoints (OS, PFS), median and two-sided 95% CIs were estimated using the Kaplan–Meier method in the two treatment arms in each region (Japan, North America and the European Union). The OS and PFS between the two treatment arms within each region were compared using a log-rank test (one-sided), stratified by extent of the disease. The ORR and corresponding exact two-sided 95% CI were summarized in the two treatment arms in each region, and Cochran–Mantel–Haenszel test (two-sided), stratified by the stratification factor, was used for comparison between the two treatment arms. To explore potential correlation between OS and hypertension, univariate Cox proportional regression was performed using maximum diastolic BP during Cycle 1 as a categorical variable. Patients were divided into two groups; one group with patients who experienced maximum diastolic BP ≥90 mm Hg during Cycle 1 and the other group with patients who did not.

Results

Patient baseline characteristics

Of 632 randomized patients with advanced pancreatic cancer ($n = 316$ in each arm), two patients in the axitinib/gemcitabine arm did not have randomization information in the clinical database at the time of the analysis, and were excluded from the analyses. Randomized patients were from Japan ($n = 114$), North America ($n = 158$), the European Union ($n = 264$), Asia other than Japan ($n = 55$) and other countries/regions (Argentina, Australia and South Africa; $n = 39$). By country, Japan had the second highest number of patients closely following the USA ($n = 119$). Due to small number of patients, Asia other than Japan, Argentina, Australia and South Africa were not included in the current analysis.

Median age and the proportion of male and female patients were comparable among Japanese, North American and European Union

Table 1. Patient demographics and baseline characteristics

	Overall study population		Japan		North America		European Union	
	Axitinib/Gem ($n = 314$)	Placebo/Gem ($n = 316$)	Axitinib/Gem ($n = 58$)	Placebo/Gem ($n = 56$)	Axitinib/Gem ($n = 77$)	Placebo/Gem ($n = 81$)	Axitinib/Gem ($n = 132$)	Placebo/Gem ($n = 132$)
Age, years								
Median	61	62	60	61	62	65	60	62
Range	34–84	35–89	43–77	39–77	39–84	37–89	34–82	35–81
Sex, %								
Male	60.8	59.5	69.0	62.5	54.5	60.5	55.3	56.1
Female	39.2	40.5	31.0	37.5	45.5	39.5	44.7	43.9
Race, %								
White	67.2	69.6	0	0	85.7	91.4	97.7	97.0
Black	2.5	2.2	0	0	9.1	6.2	0	0.8
Asian	28.3	26.6	100	100	2.6	0	0.8	0
Other	1.9	1.6	0	0	2.6	2.5	1.5	2.3
ECOG PS[a], %								
0	46.8	50.0	77.6	76.8	37.7	38.3	44.7	50.8
1	51.6	48.7	22.4	23.2	62.3	61.7	51.5	47.7
Disease stage[b], %								
Locally advanced	24.2	23.7	31.0	33.9	19.5	19.8	25.0	25.0
Metastatic	75.8	76.3	69.0	66.1	80.5	80.2	75.0	75.0
Prior surgery[a,c], %								
Yes	11.8	10.8	3.4	10.7	5.2	6.2	17.4	14.4
No	86.3	86.4	93.1	76.8	93.5	93.8	80.3	84.8
Prior adjuvant therapy, %								
Yes	3.8	3.5	1.7	5.4	0	2.5	5.3	3.8
No	96.2	96.5	98.3	94.6	100	97.5	94.7	96.2
Prior radiotherapy[a], %								
Yes	3.2	4.1	0	0	1.3	7.4	3.0	5.3
No	95.5	94.3	98.3	98.2	97.4	92.6	95.5	91.7

Gem, gemcitabine; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]The remaining percent due to missing and/or unknown.

[b]At randomization.

[c]Resected or partially resected.

Table 2. *Exposure to study drugs*[a]

	Overall study population		Japan		North America		European Union	
	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem
Gemcitabine	*n* = 305	*n* = 308	*n* = 57	*n* = 56	*n* = 75	*n* = 81	*n* = 127	*n* = 126
No. cycles started[b,c]								
Median	3	3	5	4	2	3	3	4
Range	1–13	1–12	1–10	1–10	1–9	1–12	1–13	1–10
Days on treatment[c,d]								
Median	71	73	119	99	43	71	71	85
Range	1–336	1–358	1–267	1–267	1–232	1–334	1–336	1–358
Dose interruption, *n* (%)	194 (63.6)	165 (53.6)	33 (57.9)	29 (51.8)	54 (72.0)	44 (54.3)	73 (57.5)	62 (49.2)
Dose reduction, *n* (%)	125 (41.0)	100 (32.5)	37 (64.9)	27 (48.2)	23 (30.7)	26 (32.1)	42 (33.1)	34 (27.0)
Relative dose intensity[c,e], %								
Median	77.4	79.4	70.1	72.8	70.8	78.8	81.7	83.0
Range	27.7–106.4	19.6–106.3	32.1–104.5	33.3–101.3	27.7–101.4	19.6–104.5	32.5–106.4	32.7–106.3
Axitinib or placebo	*n* = 298	*n* = 301	*n* = 57	*n* = 56	*n* = 75	*n* = 81	*n* = 127	*n* = 126
Days on treatment[d,f]								
Median	84	85	95	88	63	84	84	111
Range	1–335	2–361	24–280	5–280	2–251	2–361	1–335	4–281
Days on drug[f,g]								
Median	84	84	91	88	59.5	84	84	91
Range	1–336	2–334	24–280	5–280	2–251	2–334	1–336	4–288
Dose interruption, *n* (%)	223 (74.8)	183 (60.8)	50 (87.7)	36 (64.3)	59 (78.7)	60 (74.1)	82 (64.6)	61 (48.4)
Dose reduction, *n* (%)	74 (24.8)	30 (10.0)	18 (31.6)	4 (7.1)	12 (16.0)	8 (9.9)	33 (26.0)	12 (9.5)
Dose increase, *n* (%)	95 (31.9)	131 (43.5)	7 (12.3)	32 (57.1)	16 (21.3)	29 (35.8)	51 (40.2)	57 (45.2)
Relative dose intensity[e,f], %								
Median	100.0	100.0	100.0	117.1	100.0	100.0	100.0	100.0
Range	36.3–186.7	50.0–190.2	40.0–184.4	55.6–190.2	48.2–179.6	54.4–168.0	38.4–186.7	62.6–188.1

Gem, gemcitabine

[a]Based on patients who received study treatment.

[b]If patients took at least some gemcitabine, they were considered to have started a cycle.

[c]*n* = 304 and 302 for Axitinib/Gem and Placebo/Gem, respectively, in the overall study population; *n* = 74 and 79 for Axitinib/Gem and Placebo/Gem, respectively, in North America; and *n* = 123 for Placebo/Gem in the European Union.

[d]Time period starting from date of the first dose to date of the last dose or data cutoff.

[e](Actual total dose/intended total dose) × 100.

[f]*n* = 55 and 53 for Axitinib/Gem and Placebo/Gem, respectively, in Japan; *n* = 72 and 79 for Axitinib/Gem and Placebo/Gem, respectively, in North America; and *n* = 125 and 124 for Axitinib/Gem and Placebo/Gem, respectively, in the European Union.

[g]Total number of days on which axitinib or placebo was actually administered.

patients (Table 1). However, a higher percentage of Japanese patients had ECOG PS 0 and locally advanced disease compared with those in the other two regions.

Treatments and patient disposition

The exposure to study drugs in each region as well as in the overall population is summarized in Table 2. Median treatment duration for gemcitabine in the axitinib/gemcitabine- and placebo/gemcitabine-treated patients was generally similar between Japan and the European Union. In North America, however, patients in the axitinib/gemcitabine arm received fewer days of gemcitabine treatment compared with those in the placebo/gemcitabine arm (43 vs. 71 days, respectively), and had more gemcitabine dose interruptions (72.0 vs. 54.3%, respectively). For axitinib treatment, median duration was longest for patients in Japan, followed by those in the European Union and then North America (95 vs. 84 vs. 63 days, respectively). However, axitinib dose interruptions and dose reductions, respectively, were more frequent among Japanese patients (87.7 and 31.6%) compared with those in North America (78.7 and 16.0%) or the European Union (64.6 and 26.0%).

At the time of final analysis (data cutoff date: 23 January 2009), 24 and 27% of Japanese patients in the axitinib/gemcitabine and placebo/gemcitabine arms, respectively, discontinued study treatment, whereas a higher percentage of patients in North America (74 and 67%) and in the European Union (50 and 56%) discontinued treatment. The main reason for discontinuation in each arm was disease progression.

The most common systemic treatment administered to Japanese patients following the study treatment was S-1, whereas gemcitabine, 5-FU and oxaliplatin were the common follow-up treatments received by patients in North America and the European Union (Supplementary Material 1).

Efficacy

The OS in the overall study population and individual region by study treatment arm is presented in Table 3. In the overall study population, there was no statistically significant difference in OS between the axitinib/gemcitabine and placebo/gemcitabine arms (HR 1.014; $P = 0.5436$; Fig. 1A), as previously reported (9).

Since the study was terminated, which was recommended by the independent DMC due to the futility at the interim analysis, median survival follow-up period among all Japanese patients was short as well as those in other regions. The HR for OS between the axitinib/gemcitabine vs. placebo/gemcitabine arms in all Japanese

Table 3. Summary of overall survival in the overall study population and by disease extent and region

	Overall study population		Japan		North America		European Union	
	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem
Overall								
No. of patients	314	316	58	56	77	81	132	132
No. of events (%)	118 (37.6)	120 (38.0)	15 (25.9)	15 (26.8)	45 (58.4)	44 (54.3)	41 (31.1)	41 (31.1)
Follow-up period								
Median, months	4.4	4.8	5.1	5.4	4.3	5.1	4.1	4.7
(range)	(0.02–12.8)	(0.02–11.9)	(0.02–12.3)	(1.8–10.5)	(0.2–12.1)	(0.4–11.9)	(0.02–12.8)	(0.02–10.6)
Median OS, months	8.5	8.3	NE	9.9	5.6	6.6	10.1	8.7
(95% CI)	(6.9–9.5)	(6.9–10.3)	(7.4–NE)	(7.4–10.5)	(4.6–8.5)	(5.3–10.3)	(6.9–NE)	(7.1–NE)
Hazard ratio[a,b] (95% CI)	1.014 (0.786–1.309)		1.093 (0.525–2.274)		1.288 (0.849–1.954)		1.018 (0.659–1.571)	
P value[c]	0.5436		0.5937		0.8845		0.5309	
Locally advanced disease								
No. of patients	76	75	18	19	15	16	33	33
No. of events (%)	21 (27.6)	13 (17.3)	3 (16.7)	3 (15.8)	8 (53.3)	5 (31.3)	7 (21.2)	4 (12.1)
Follow-up period								
Median, months	5.1	6.0	6.0	6.8	3.0	5.5	4.2	6.0
(range)	(0.02–10.6)	(0.4–11.9)	(0.02–10.3)	(2.9–10.5)	(1.3–10.0)	(1.4–11.9)	(0.02–10.6)	(0.4–10.6)
Median OS, months	9.5	10.6	NE	9.9	6.3	NE	10.1	10.4
(95% CI)	(7.4–NE)	(9.9–NE)	(8.0–NE)	(9.9–10.5)	(3.0–9.5)	(5.0–NE)	(7.3–NE)	(10.4–NE)
Hazard ratio[a] (95% CI)	2.079 (1.031–4.189)		1.939 (0.319–11.787)		2.273 (0.741–6.974)		2.351 (0.684–8.086)	
P value[d]	0.9818		0.7678		0.9330		0.9187	
Metastatic disease								
No. of patients	238	241	40	37	62	65	99	99
No. of events (%)	97 (40.8)	107 (44.4)	12 (30.0)	12 (32.4)	37 (59.7)	39 (60.0)	34 (34.3)	37 (37.4)
Follow-up period								
Median, months	4.3	4.4	4.9	4.8	4.4	5.1	4.0	4.3
(range)	(0.2–12.8)	(0.02–11.7)	(1.1–12.3)	(1.8–10.4)	(0.2–12.1)	(0.4–11.7)	(0.5–12.8)	(0.02–9.8)
Median OS, months	7.0	6.9	NE	NE	5.5	6.2	7.5	8.2
(95% CI)	(5.8–9.3)	(6.2–8.0)	(6.9–NE)	(6.4–NE)	(4.3–8.5)	(5.2–8.0)	(6.1–NE)	(6.4–NE)
Hazard ratio[a] (95% CI)	0.904 (0.686–1.190)		0.972 (0.435–2.170)		1.170 (0.746–1.837)		0.897 (0.563–1.430)	
P value[d]	0.2345		0.4721		0.2456		0.3230	

Gem, gemcitabine; OS, overall survival; CI, confidence interval; NE, not estimable.

[a]Axitinib/gemcitabine vs. placebo/gemcitabine; assuming proportional hazards model, a hazard ratio <1 indicates a reduction in hazard rate in favor of axitinib/gemcitabine and a hazard ratio >1 indicates a reduction in favor of placebo/gemcitabine.

[b]Hazard ratio stratified by extent of the disease (locally advanced vs. metastatic pancreatic cancer).

[c]From a one-sided log-rank test of treatment stratified by extent of the disease (locally advanced vs. metastatic pancreatic cancer).

[d]From a one-sided, unstratified log-rank test.

patients was 1.093 (95% CI, 0.525–2.274; $P = 0.5937$; Fig. 1B). In Japanese patients with locally advanced disease, HR for OS was 1.939 (95% CI, 0.319–11.787; $P = 0.7678$), whereas in those with metastatic disease, it was 0.972 (95% CI, 0.435–2.170; $P = 0.4721$) (Table 3). Similarly, median OS did not differ between the two treatment arms in patients from North America or the European Union (Fig. 1C and D).

The PFS in each treatment arm is summarized in Table 4. In the overall study population, PFS was also similar between the axitinib/gemcitabine and placebo/gemcitabine arms (HR 1.006; 95% CI, 0.779–1.298; $P = 0.5203$; Supplementary Material 2A) (9). Among all Japanese patients, there was no difference in median PFS between the two treatment arms (HR 0.905; 95% CI, 0.416–1.968; $P = 0.5995$; Supplementary Material 2B). There was no difference in PFS between the two treatment arms in patients from North America or the European Union as well (Supplementary Material 2C and D).

The ORR in the overall population was numerically higher with axitinib/gemcitabine than placebo/gemcitabine (4.9 vs. 1.6%, respectively; $P = 0.038$). The ORR for the axitinib/gemcitabine and placebo/gemcitabine arms, respectively, was 6.7% (95% CI, 0.8–22.1) and 0% (95% CI, 0–9.7) ($P = 0.145$) in Japanese patients, 3.1% (95% CI, 0.4–10.8) and 2.6% (95% CI, 0.3–9.2) ($P = 0.885$) in patients in North America, and 4.6% (95% CI, 1.5–10.5) and 1.0% (95% CI, 0–5.3) ($P = 0.117$) in patients in the European Union.

Safety

All-causality AEs reported by >20% of patients in each arm in the overall study population and in individual regions are summarized in Table 5. Among Japanese patients, fatigue, anorexia, dysphonia, nausea and decreased platelet count were common AEs in patients treated with axitinib/gemcitabine, whereas anorexia and decreased neutrophil count were common with placebo/gemcitabine treatment. Grade ≥3 AEs reported by ≥10% of Japanese patients included decreased neutrophil count, anorexia, decreased platelet count and hypertension with axitinib/gemcitabine, decreased neutrophil count and decreased platelet count with placebo/gemcitabine. The profile of common AEs was generally similar between Japanese patients and the overall study population, North American or the European Union patients, although there were some differences in incidence rates for some AEs.

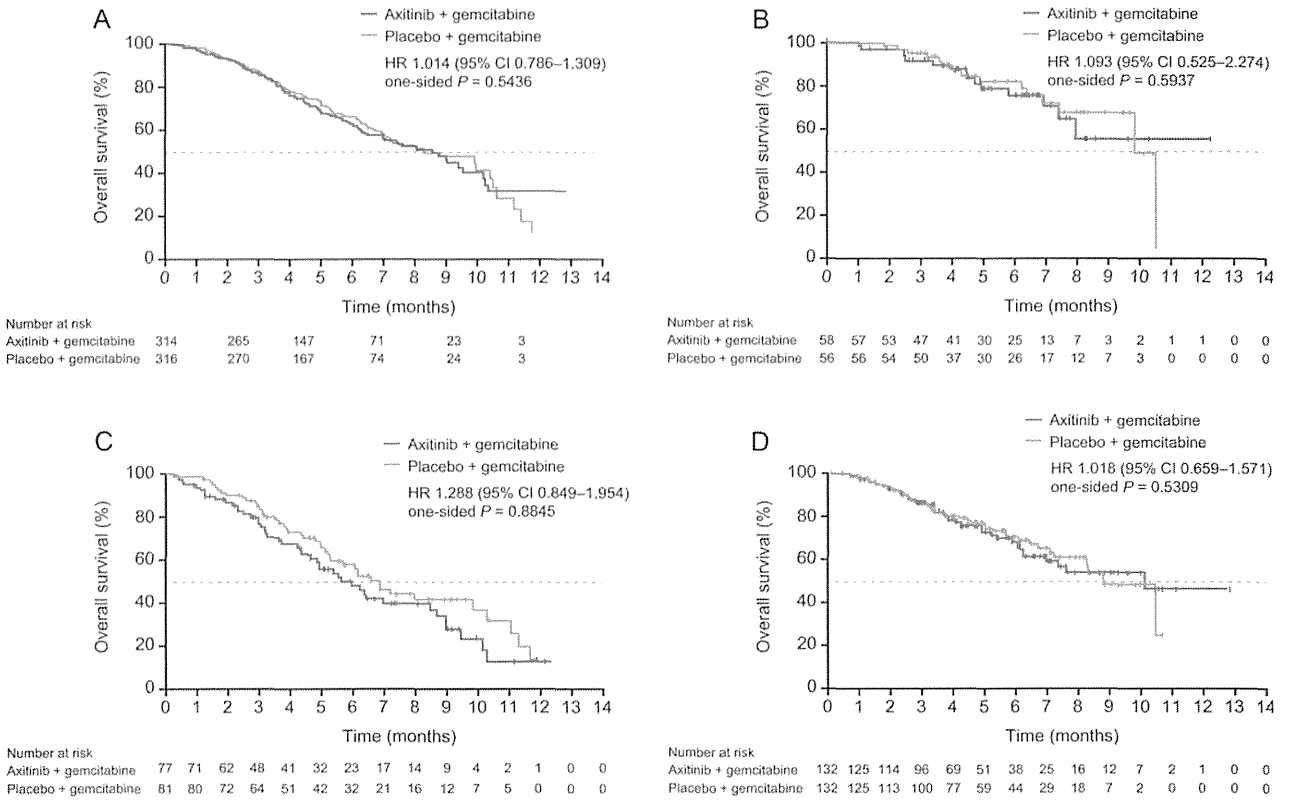

Figure 1. *Kaplan–Meier estimates for overall survival for axitinib/gemcitabine vs. placebo/gemcitabine in the overall study population* (**A**)*, and in patients in Japan* (**B**), North America (**C**) and the European Union (**D**). Panel A reprinted from The Lancet Oncology, 12 (3), Kindler HL, et al. (9). Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised Phase 3 study, 256–62, Copyright 2011, with permission from Elsevier.

Table 4. Summary of progression-free survival in the overall study population and by disease extent and region

	Overall study population		Japan		North America		European Union	
	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem	Axitinib/ Gem	Placebo/ Gem
Overall								
No. of patients	314	316	58	56	77	81	132	132
No. of events (%)	116 (36.9)	125 (39.6)	12 (20.7)	16 (28.6)	39 (50.6)	38 (46.9)	44 (33.3)	47 (35.6)
Median, months	4.4	4.4	5.8	5.8	4.1	3.7	5.7	4.9
(95% CI)	(4.0–5.6)	(3.7–5.2)	(4.8–7.2)	(4.0–10.5)	(2.9–5.3)	(3.4–5.7)	(3.7–7.5)	(3.8–7.0)
Hazard ratio[a,b] (95% CI)	1.006 (0.779–1.298)		0.905 (0.416–1.968)		1.290 (0.814–2.045)		0.908 (0.594–1.390)	
P value[c]	0.5203		0.5995		0.8635		0.6707	
Locally advanced disease								
No. of patients	76	75	18	19	15	16	33	33
No. of events (%)	22 (28.9)	17 (22.7)	4 (22.2)	2 (10.5)	7 (46.7)	4 (25.0)	7 (21.2)	9 (27.3)
Median, months	5.9	9.1	5.8	10.5	7.2	9.0	7.3	10.4
(95% CI)	(4.2–7.3)	(5.8–10.6)	(5.6–NE)	(5.8–10.5)	(1.7–9.5)	(2.0–9.0)	(4.2–9.5)	(4.1–10.4)
Hazard ratio[a] (95% CI)	1.888 (0.978–3.645)		4.775 (0.531–42.915)		1.477 (0.413–5.287)		1.384 (0.500–3.832)	
P value[d]	0.9732		0.9382		0.7273		0.7379	
Metastatic disease								
No. of patients	238	241	40	37	62	65	99	99
No. of events (%)	94 (39.5)	108 (44.8)	8 (20.0)	14 (37.8)	32 (51.6)	34 (52.3)	37 (37.4)	38 (38.4)
Median, months	4.2	3.8	7.2	4.1	4.1	3.7	3.9	4.1
(95% CI)	(3.7–5.4)	(3.6–4.5)	(4.8–7.2)	(3.5–7.4)	(2.4–5.3)	(3.2–5.4)	(3.5–7.5)	(3.5–5.9)
Hazard ratio[a] (95% CI)	0.897 (0.679–1.184)		0.629 (0.259–1.527)		1.264 (0.770–2.073)		0.834 (0.523–1.329)	
P value[d]	0.2214		0.1506		0.1718		0.2206	

Gem, gemcitabine; CI, confidence interval; NE, not estimable

[a]Axitinib/gemcitabine vs. placebo/gemcitabine; assuming proportional hazards model, a hazard ratio <1 indicates a reduction in hazard rate in favor of axitinib/gemcitabine and a hazard ratio >1 indicates a reduction in favor of placebo/gemcitabine.

[b]Hazard ratio stratified by extent of the disease (locally advanced vs. metastatic pancreatic cancer).

[c]From a one-sided log-rank test of treatment stratified by extent of the disease (locally advanced vs. metastatic pancreatic cancer).

[d]From a one-sided, unstratified log-rank test.