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FOLFIRINOX for locally advanced pancreatic cancer: Results and prognostic factors of subset analysis from a nation-wide multicenter observational study in Japan

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ABSTRACT

Background: FOLFIRINOX (oxaliplatin, irinotecan, 5-fluorouracil, leucovorin) treatment significantly improved overall survival in the recent phase III study and became a standard therapy for metastatic pancreatic cancer. However, treatment for locally advanced pancreatic cancer is still controversial. We conducted subset analyses from a nation-wide multicenter observational study in Japan to evaluate the tolerability and efficacy of FOLFIRINOX in patients with locally advanced pancreatic cancer and to investigate independent prognostic factors with pre-treatment variables.

Methods: The study included 66 patients with unresectable locally advanced pancreatic cancer from 27 institutions in Japan who received FOLFIRINOX as first-line treatment between December 20, 2013 and December 19, 2014 and surveyed until December 2015.

Results: The median age was 63 with the Eastern Cooperative Oncology Group performance status of 0 or 1. Major Grade 3 or 4 adverse events included neutropenia (64%), leukopenia (33%), febrile neutropenia (15%), and diarrhea (15%). Severe adverse event occurred in 14 patients (11%) without fatal event. The median overall survival and progression-free survival times were 18.5 and 7.6 months, respectively. The objective response rate 15.2% and the disease control rate was 81.9%. A high modified Glasgow prognostic score (mGPS, ≥1) (95%CI 1.96–12.5) and female (95%CI 0.20–0.97) were identified as independent poor prognostic factors.

Conclusions: First-line FOLFIRINOX treatment for locally advanced pancreatic cancer seems to be effective with acceptable toxicities. A high mGPS may be associated with poor survival in patients with locally advanced pancreatic cancer who receive FOLFIRINOX. This study was registered at the UMIN Clinical Trials Registry (UMIN000014658).

Introduction

Pancreatic cancer remains one of the most lethal malignancies,

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with a 5-year survival rate of less than 10% in all patients. And pancreatic cancer is the fourth leading cause of cancer death in Japan and its incidence has been increasing. At the time of diagnosis, about 30% of patients have locally advanced pancreatic cancer, which is considered surgically unresectable due to local involvement of adjacent vessels.

In the recent phase III study conducted by Conroy et al. (PRODIGE4/ACCORD11), FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil [5-FU], leucovorin) significantly improved overall survival (OS), progression-free survival (PFS), and quality of life compared with gemcitabine alone in patients with metastatic pancreatic cancer [1]. The median OS and PFS times were 11.1 and 6.4 months in the FOLFIRINOX group compared to 6.8 and 3.3 months in the gemcitabine group, respectively. Currently, FOLFIRINOX has become one of the standard treatments for patients with metastatic pancreatic cancer. Although systemic chemotherapy is the main treatment for patients with both locally advanced and metastatic pancreatic cancer, no randomized controlled study has been conducted of FOLFIRINOX in patients with locally advanced pancreatic cancer. A recent phase II study and many observational studies indicate that FOLFIRINOX has a survival benefit in locally advanced pancreatic cancer when compared with historical controls [2–7]. However, the sample sizes of most studies have been too small to draw definitive conclusions as to the efficacy and safety of FOLFIRINOX for patients with locally advanced pancreatic cancer. In particular, there has been no report of FOLFIRINOX in Japanese patients with locally advanced pancreatic cancer.

The optimal treatment regimen for locally advanced pancreatic cancer is still controversial and current guidelines are not consistent including various regimens of chemotherapy, chemoradiotherapy, and induction chemotherapy. Although many treatment options are provided for locally advanced pancreatic cancer, evidence and guidance are limited as to the best treatment for individual cases. Our group previously reported the results of a nationwide multicenter observational study of FOLFIRINOX chemotherapy in 399 patients with unresectable or recurrent pancreatic cancer in Japan [8]. The median overall survival times and progression-free survival times were 10.8, and 4.5 months, respectively. The study concluded that FOLFIRINOX was efficient with acceptable safety in Japanese patients.

In this study, we conducted subgroup analyses to evaluate the tolerability and efficacy of FOLFIRINOX in patients with locally advanced pancreatic cancer as first-line treatment and to investigate independent prognostic factors with pretreatment variables in Japanese patients.

Methods

Patients

Data for this subgroup analysis were derived from the nationwide multicenter observational study of FOLFIRINOX chemotherapy in 399 patients with unresectable or recurrent pancreatic cancer from 27 institutions in Japan [8]. Sixty-six patients with unresectable locally advanced pancreatic cancer who received FOLFIRINOX as first-line treatment between December 20, 2013 and December 19, 2014 were included in this study (Fig. 1). Locally advanced pancreatic cancer was defined by the National Comprehensive Cancer Network guidelines criteria [9]. More specifically, all patients who presented with encasement (>180° contact) of the celiac artery or superior mesenteric artery, unreconstructable portal or superior mesenteric vein, or tumor involvement of the first jejunal artery were staged as locally advanced pancreatic cancer and were included in the study. Patient registration began in November 2014 and was completed in May 2015. Patients were

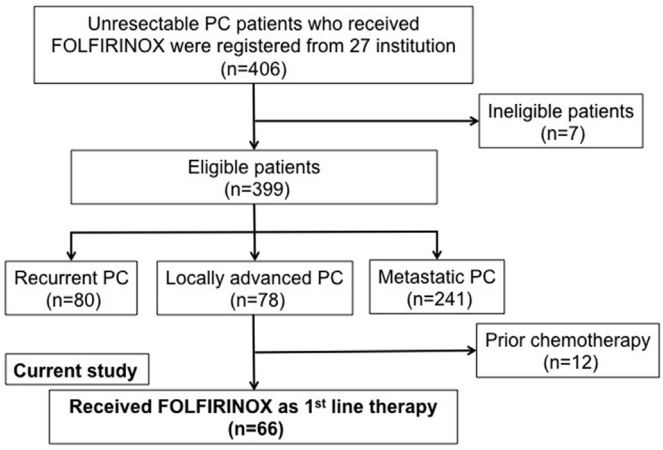

Fig. 1. Patients flow diagram.

followed up until December 2015. Patients in the second and third cohorts provided written informed consent for this study. Patients in the first cohort did not provide informed consent. However, investigators at each participating institution informed patients of their right to opt out of the study via public announcements. This study was approved by the ethical committee of each participating institution and was conducted in accordance with the Ethical Guidelines for Epidemiological Research posted on the University Hospital Medical Information Network (UMIN000014658).

Treatment

The FOLFIRINOX regimen used in our study was the same as that used in the PRODIGE/ACCORD11 study [1]: 85 mg/m^2 oxaliplatin (divided), 200 mg/m^2 levoforinate calcium (*l*-LV) (divided), 180 mg/m^2 irinotecan (divided), and 400 mg/m^2 5-FU (bolus), followed by continuous intravenous infusion of 2400 mg/m^2 5-FU for 46 h. The treatment was repeated every 2 weeks. The bolus infusion of 5-FU was sometimes omitted in the first cycle and the initial dose of each drug was sometimes reduced at the physician's discretion based on the patient's condition.

Assessment

The patient's characteristics and uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) genetic status before the treatment were evaluated. Adverse events, laboratory data, drug doses (oxaliplatin, irinotecan, and 5-FU), and reasons for dose-reduction at the first treatment cycle, and reasons for discontinuation, were recorded for 6 months after treatment was started or until the treatment was discontinued, whichever came first. All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Serious adverse events (SAEs) were defined as events that were required hospitalization or an extension of hospitalization, life-threatening, or resulted in death. Responses were evaluated via computed tomography or magnetic resonance imaging every 2 or 3 months at the physician's discretion (not specified in the protocol) and categorized in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1 [10]. Prognostic factors for OS and PFS were determined using pretreatment variables. Modified Glasgow prognostic score (mGPS) was defined as follows [11]; patients with both an elevated C-reactive protein (CRP) (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a score of 2; patients with only one of these biochemical abnormalities were given a score of 1; and patients with

neither of these abnormalities were given a score of 0.

Statistics

Data were collected and managed by the Shizuoka Industrial Foundation Pharma Valley Center. Median OS and PFS times and corresponding 95% confidence intervals (CIs) were estimated by using the Kaplan-Meier method. OS was defined as the time from day 1 of therapy cycle 1 to death from any cause. PFS was defined as the time from day 1 of therapy cycle 1 to disease progression or death from any cause. Data for OS and PFS were censored if the patient was alive at the end of the study period and if the disease did not progress during the study period, respectively. The median time to treatment failure, defined as the time from day 1 of therapy cycle 1 to discontinuation of all 3 cytotoxic agents as decided by the investigators, was estimated by using the Kaplan-Meier method. Survival times and frequencies of SAEs were analyzed up until the cutoff time of December 2015. Prognostic factors were identified by univariate and multivariate analyses. Multivariate analysis was carried out using stepwise Cox proportional hazards regression modeling to identify independent prognostic factors. P value < 0.05 were considered statistically significant. All statistical analyses were performed with the use of R, version 3.4.3 (R Foundation for Statistical Computing).

Results

Patients

The patient characteristics are shown in Table 1. The median age was 63 years (range, 39–75). The Eastern Cooperative Oncology Group performance status were 0 in 45 patients (68%) and 1 in 21 (32%). Pathological examination before treatment was conducted in 57 patients (87%). Of these, 56 patients (98%) were diagnosed as ductal adenocarcinoma and one patient was unknown. Of the 65 patients (98%) examined for *UGT1A1* polymorphism, 24 (37%) were heterozygous for *UGT1A1*6* or *UGT1A1*28*, and 2 (3%) were heterozygous for both *UGT1A1*6* and *UGT1A1*28* or homozygous for *UGT1A1*6* or *UGT1A1*28*.

Table 1
Patients characteristics.

	Patients (n = 66)	Percent (%)
Age (years)		
Median	63	
Range	39–75	
Gender		
Male	44	67
Female	22	33
ECOG PS		
0	45	68
1	21	32
2	0	0
Tumor location		
Head	37	56
Body/tail	29	44
Biliary drainage		
Yes	24	36
Metal stent	17	26
Plastic stent	5	8
PTBD	2	3
No	42	64
CEA (ng/mL)		
Median	3.2	
Range	0.8–62.8	
CA19-9 (IU/mL)		
Median	247	
Range	0.4–15,929	
Alb (g/dL)		
Median	3.9	
Range	2.3–4.7	
CRP (mg/dL)		
Median	0.185	
Range	0.00–7.49	
Total bilirubin (mg/dL)		
Median	0.6	
Range	0.2–2.6	

ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; PTBD; Percutaneous transhepatic biliary drainage; CA19-9, carbohydrate antigen 19-9; Alb, albumin; CRP, C-reactive protein.

Treatment exposure

Drug doses were reduced in 39 patients (59%) in the first treatment cycle. Doses of irinotecan, oxaliplatin, and continuously infused 5-FU were reduced in 39 (59%), 1 (2%), and 0 (0%) patients, respectively, and the 5-FU bolus was omitted in 28 patients (42%). The reasons for initial dose reduction were as follows: poor performance status or inadequate physical condition in 3 patients (8%); *UGT1A1*6* and *UGT1A1*28* heterozygosity, *UGT1A1*6* or *UGT1A1*28* homozygosity in 3 (8%); and unspecified in 33 patients (85%).

The median time to treatment failure was 4.7 months (range, 0.2–13.6), and the median number of treatment cycles was 8 (range, 1–14 or more). Treatment was discontinued in 56 patients owing to tumor progression in 33 patients (59%), toxicity in 12 (21%), or tumor shrinkage in 7 (13%). Four patients (7%) requested and consented to treatment withdrawal for reasons unrelated to adverse events.

Toxicity

The toxic effects are summarized in Table 2. Grade 3 or 4 adverse events occurred in 47 patients (71%). Major Grade 3 or 4 adverse events included neutropenia in 42 patients (64%), leukopenia in 22 (33%), febrile neutropenia in 10 (15%), diarrhea in 10 (15%), anorexia in 5 (8%), and peripheral sensory neuropathy in 1 (2%).

SAEs occurred 18 times in 14 patients (21%). SAEs consisted of cholangitis in 6 patients (9%), neutropenia in 5 (8%), febrile neutropenia in 3 (5%), and others in 6 (9%). Notably, cholangitis occurred 7 times in 6 patients. Five of 6 patients were placed biliary drainage. The occurrence rate of cholangitis in patients with biliary drainage was 21% (5/24). All patients required hospitalization or extension of hospitalization. However, neither life threatening nor fatal adverse events occurred.

Efficacy

All Patients had measurable lesions. Ten patients (15.2%) showed a partial response and 44 patients (66.7%) showed stable disease, resulting in an overall objective response rate of 15.2% and a disease control rate of 81.9%. The median follow up time was 12.7 months with a range of 1.8 months and 21.1 months. The median OS time was 18.5 months (95%CI, 13.1-not achieved) with 1-year OS rate of 69.3% (95%CI, 58.7–81.8). The median PFS time was 7.6 months (95%CI, 5.3–9.9) with 1-year PFS rate of 23.1% (95%CI, 14.8–36.0) (Fig. 2).

Prognostic factor

Table 3 summarizes the univariate analyses of pretreatment prognostic factors for PFS and OS. Performance status and mGPS were significantly associated with PFS. mGPS was significantly associated with OS. The results of multivariate analyses of pretreatment prognostic factors for PFS and OS are shown in Table 4. High mGPS was identified as an independent poor prognostic factor for PFS. Female and high mGPS were identified as independent

Table 2
Toxicity according to CTCAE version 4.0

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	(%)	n	(%)	n	(%)	n	(%)
Hematologic								
Anemia	35	(53%)	24	(36%)	4	(6%)	0	(0%)
Leukopenia	11	(17%)	24	(36%)	19	(29%)	3	(5%)
Neutropenia	0	(0%)	14	(21%)	25	(38%)	17	(26%)
Thrombocytopenia	35	(53%)	10	(15%)	3	(5%)	0	(0%)
Non-hematologic								
Febrile neutropenia	0	(0%)	0	(0%)	7	(11%)	3	(5%)
Fever	17	(26%)	4	(6%)	0	(0%)	0	(0%)
Nausea	20	(30%)	21	(32%)	3	(5%)	0	(0%)
Vomiting	9	(14%)	7	(11%)	0	(0%)	0	(0%)
Diarrhea	20	(30%)	11	(17%)	10	(15%)	0	(0%)
Fatigue	26	(39%)	17	(26%)	0	(0%)	0	(0%)
Anorexia	25	(38%)	25	(38%)	5	(8%)	0	(0%)
Peripheral sensory neuropathy	31	(47%)	9	(14%)	1	(2%)	0	(0%)
Oral mucositis	18	(27%)	1	(2%)	0	(0%)	0	(0%)
Hand-foot syndrome	2	(3%)	1	(2%)	0	(0%)	0	(0%)
Increased AST	33	(50%)	12	(18%)	3	(5%)	1	(2%)
Increased ALT	42	(64%)	6	(9%)	5	(8%)	2	(3%)
Increased bilirubin	4	(6%)	4	(6%)	2	(3%)	0	(0%)
Increased creatinine	6	(9%)	0	(0%)	0	(0%)	0	(0%)
Decreased albumin	39	(59%)	21	(32%)	2	(3%)	0	(0%)

CTCAE, Common Terminology Criteria for Adverse Events; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

poor prognostic factors for OS.

Discussion

This subset analyses of the nationwide multicenter observational study showed that first-line FOLFIRINOX treatment is effective for locally advanced pancreatic cancer with acceptable toxicities in Japanese clinical practice. The median OS and PFS times were 18.5 and 7.6 months, respectively. The response rate and disease control rate were 15.2% and 81.9%, respectively. The OS time was longer in patients with locally advanced pancreatic cancer who received gemcitabine-based induction chemotherapy for 4 months with or without subsequent radiotherapy in the LAP07 randomized clinical trial (the median OS time of 12.8 months) [12]. In phase II of the study of gemcitabine mono-therapy (JCOG0506) in Japanese patients with locally advanced pancreatic cancer, the median OS time was 15.0 months and the response rate was 6% [13] Moreover, in the subset analyses of a large scale randomized phase III GEST trial, the median OS times in patients with locally advanced pancreatic cancer who received gemcitabine mono-therapy (n = 66), S-1 mono-therapy (n = 68), and gemcitabine plus S-1 (n = 68) were 12.7, 13.8, and 15.9 months, respectively [14,15]. Therefore, FOLFIRINOX may be more effective as a first-line chemotherapy treatment than other regimens for locally advanced pancreatic cancer. In a recent meta-analysis, Suker et al. reported a median OS time of 24.2 months ranged from 10.0 months to 32.7 months after FOLFIRINOX treatment in patients with locally advanced pancreatic cancer [16].

Recently, prolonged survival in patients with locally advanced pancreatic cancer who undergo radical resection following preoperative chemo(radio)therapy, called for “conversion surgery”, has been reported in many studies [3–5,17]. Use of FOLFIRINOX for locally advanced pancreatic cancer is of particular interest given its high response rate of 32% in metastatic disease [1]. Recent retrospective studies on conversion surgery following to FOLFIRINOX have been published with favorable results. FOLFIRINOX improves R0 resection rates to up to 80% in conversion surgery [3,5]. In our study, 7 patients (13%) underwent radiotherapy, chemoradiotherapy, or surgical resection with a curative intent because of tumor shrinkage. Unfortunately, further data was not available in our study. Marthey L et al. reported a multicenter prospective observational study of FOLFIRINOX for locally advanced pancreatic cancer (n = 77) [3]. They reported a median OS time was 21.1 months with an objective response rate of 28%. It is noted that 75% of the patients received a consolidation therapy (70% had radiotherapy and 36% underwent a surgical resection). Sadot E et al. reported similar results in a single-institution retrospective study of FOLFIRINOX for locally advanced pancreatic cancer (n = 101) [4]. They reported a median OS time was 25.0 months with an objective response rate of 29%. Sixty-three patients (63%) had proceeded to chemoradiotherapy and 31 patients (31%) underwent surgical resection. The OS time was shorter and the objective response rate was lower in our study compared with these studies. The unfavorable results in our study may be associated without subsequent radiotherapy or chemoradiotherpy. Radiotherapy or chemoradiotherapy followed by FOLFIRINOX might increase the objective response rate, surgical resection rate, and improve OS time. Patient selection biases and lower doses of FOLFIRINOX in our study may be other potential reasons. As the patients at each participating hospital were registered consecutively, more aggressive or advanced diseases might be registered in our study. Moreover, FOLFIRINOX doses were reduced in 39 patients in the first instance at the individual physician's decision. In other words, as our study represents actual clinical practice, the results were unfavorable when compared to those of other clinical studies.

In our study, the incidence of grade 3 or 4 adverse events included neutropenia (64%), leucopenia (34%), diarrhea (15%), and febrile neutropenia (16%), respectively. SAEs occurred in 14 patients (21%), but there was no fatal event. The toxicity in the study was acceptable. However, it is noted that 59% of the patients received modified regimens the first time and 85% of these patients had no specific reason for dose reduction. It is probably due to the previous Japanese phase II study of FOLFIRINOX for patients with metastatic pancreatic cancer [18]. Although the efficacy was comparable, the incidence of grade 3 or 4 toxicities was much higher in the Japanese study than in the French study [1,18]. The toxicities were reported as follows; neutropenia (77.8% vs 45.7%), febrile neutropenia (22.2% vs 5.4%), thrombocyteopenia (11.1% vs 9.1%), and anemia (11.1% vs 7.8%). Furthermore, dose reductions and treatment delays were required in 32 patients (88.9%) in the Japanese study. After the

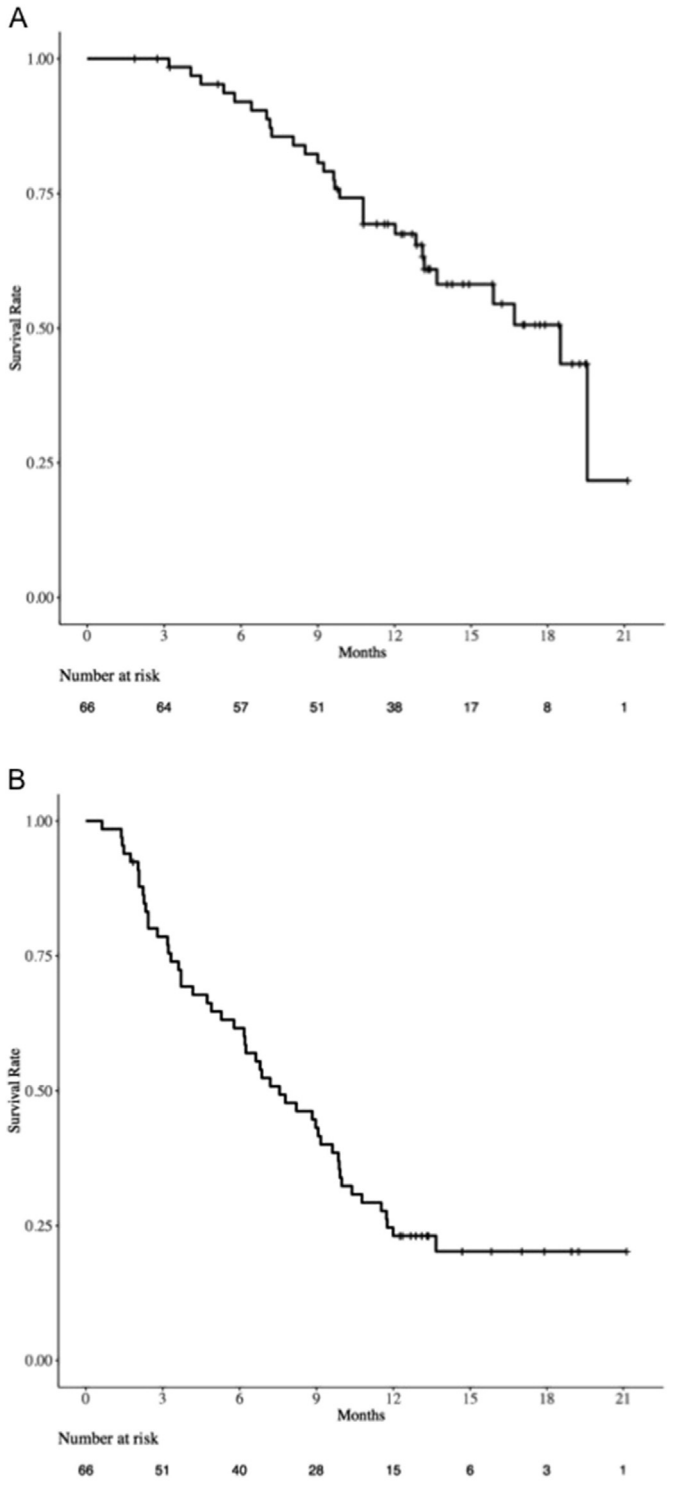

Fig. 2. Kaplan-Meier plot of overall survival (A) and progression-free survival (B). The median overall survival and progression-free survival times were 18.5 (95%CI, 13.1-not achieved) and 7.6 months (95%CI, 5.3–9.9), respectively.

phase II study, FOLFIRINOX was approved for unresectable and recurrent pancreatic cancer in Japan in December 2013. Because of the high rates of toxicities and the limited number of the patients (n = 36) of the phase II study, the observational multicenter study examined the efficacy and safety of FOLFIRINOX in Japanese patients with unresectable or recurrent pancreatic cancer had been

Table 3
Univariate analyses of pretreatment variables for PFS and OS.

	n	PFS		OS	
		MST (days)	P value	MST (days)	P value
Sex					
Male	44	269	0.482	563	0.105
Female	22	199		508	
Age					
<65	39	230	0.528	595	0.259
≥65	27	237		483	
Tumor location					
Head	37	207	0.573	563	0.542
Body/tail	29	237		595	
Biliary drainage					
Yes	24	271	0.199	–	0.315
No	42	207		483	
PS					
0	45	276	0.032	563	0.110
1	21	161		416	
WBC (/μ L)					
<5600	30	284	0.452	595	0.195
≥5600	36	189		401	
Hb (g/dL)					
<12.65	33	237	0.832	508	0.655
≥12.65	33	230		563	
CA19-9 (IU/mL)					
<250	33	250	0.388	–	0.608
≥250	33	189		508	
mGPS					
0	55	276	<0.01	563	<0.001
1 or 2	11	74		259	

PFS, progression-free survival; OS, overall survival; MST, median survival time; WBC, white blood cell; CA19-9, carbohydrate antigen 19-9; mGPS, modified Glasgow Prognostic Score.

conducted [8]. Each participating institution consecutively registered all patients with unresectable and recurrent pancreatic cancer who received FOLFIRINOX therapy one year after the approval (between December 20, 2013 and December 19, 2014). Our study is subgroup analyses of the observational multicenter study to evaluate the tolerability and efficacy of FOLFIRINOX in patients with locally advanced pancreatic cancer as first-line treatment in Japanese patients.

Recently, Ozaka et al. conducted a multicenter phase II study of modified FOLFIRINOX for chemotherapy naïve patients with metastatic pancreatic cancer in Japan [19]. The modified regimen consisted of 85 mg/m^2 oxaliplatin, 150 mg/m^2 irinotecan, 2400 mg/m^2 continuously infused 5-FU, 200 mg/m^2 l-LV, and no bolus 5-FU. The response and disease control rates were 37.7% and 78.3%, respectively. The incidence of grade 3 or higher neutropenia was 47.8%, and all the other adverse events proportion were less than those in the previous Japanese full-dose phase II study. They concluded that modified FOLFIRINOX improved safety profiles while maintaining the efficacy.

The ability to predict patients at risk of poor survival before treatment would be valuable for determining the best candidates for FOLFIRINOX use. Our study showed that mGPS was a potent predictive factor for both PFS and OS. The impact of systemic inflammation as measured by the mGPS, a score based on the combination of circulating CRP and albumin levels is independently associated with short- and long-term results in various types of cancer [20–22]. It has been reported that mGPS was prognostic factors in patients undergoing surgical resection for pancreatic cancer [11,23]. In the National Comprehensive Cancer Network, American Society for Clinical Oncology Guideline, FOLFIRINOX is recommend for pancreatic cancer patients with either 0 or 1 ECOG PS and favorable comorbidity profile in order to offer appropriate treatment with a safe toxicity profile [24]. We suggest that it should

Table 4
Multivariate analyses by Cox proportional hazard model for PFS and OS.

	Hazard ratio	95% CI	P value
PFS			
Tumor location	1.67	0.88–3.17	0.118
Biliary drainage	0.55	0.28–1.07	0.079
mGPS	3.06	1.49–6.30	0.002
OS			
Sex	0.44	0.20–0.97	0.041
mGPS	4.93	1.96–12.5	<0.001

PFS, progression-free survival; OS, overall survival; CI, confidence interval; mGPS, modified Glasgow Prognostic Score.

be carefully considered FOLFIRINOX use in patients with high mGPS because of poor prognostic factor in our study.

This study had some limitations because of multicenter observational study regarding to patient selection, dose reduction, and management of adverse events, etc. However, this is the first study to evaluate the tolerability and efficacy of FOLFIRINOX in Japanese patients with locally advanced pancreatic cancer as first-line treatment and to represent current actual clinical practice in Japan. We believe that the results may be helpful in clinical practice and be of use as a reference for future clinical trials.

In conclusion, first-line FOLFIRINOX treatment for locally advanced pancreatic cancer seems to be effective. The regimen had acceptable toxicities owing to careful management in Japanese patients. A high mGPS may be associated with poor survival in patients with locally advanced pancreatic cancer who receive FOLFIRINOX.

Declaration of interest

KK, NM, HU, SK, AT, and AF received grants and KO received personal fees from the Shizuoka Industrial Foundation Pharma Valley Center during the course of the study. NM reports personal fees from Taiho Pharmaceutical Co., Ltd., Novartis Co., Ltd., Ono Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Pfizer Co., Ltd., Kyowa-Hakko Kirin Co., Ltd., and Teijin Phama Co., Ltd., as well as grants from Taiho Pharmaceutical Co., Ltd., Merck Serono, AstraZeneca, Zeria Pharmaceutical Co., Ltd., Nano Carrier Co., Ltd., Eisai, and MSD K.K., Novartis, Pfizer Inc., Dainippon Sumitomo Pharma Co., Ltd., ASLAN Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd., for purposes unrelated to the submitted work. MO received lecture fees from Taiho Pharmaceutical Co., Ltd. HU received lecture fees from Taiho Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., and Chugai Pharmaceutical Co., Ltd. SK received lecture fees from AstraZeneca, Boston Scientific, Nippon Kayaku, Kyowa Hakko Kirin, Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Bayer. MK is employed by the Shizuoka Industrial Foundation Pharma Valley Center. AT received lecture fees from Yakult Honsha Co., Ltd., Daiichi Sankyo Co., Ltd., and Ono Pharmaceutical Co., Ltd.

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