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Gemcitabine Plus Nanoparticle Albumin–bound Paclitaxel *Versus* FOLFIRINOX for Recurrent Pancreatic Cancer After Resection

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Key Words: FOLFIRINOX (FFX), gemcitabine plus nanoparticle albumin–bound paclitaxel (GnP), recurrent pancreatic cancer after resection.

Abstract. *Background/Aim: The aim of the study was to evaluate gemcitabine plus nanoparticle albumin-bound paclitaxel (GnP) and FOLFIRINOX for recurrent pancreatic cancer (rPC) after resection. Patients and Methods: Forty-four patients with rPC and 211 with de novo metastatic pancreatic cancer (mPC) who received GnP or FOLFIRINOX as first-line chemotherapy were retrospectively analyzed. Results: On crude analysis, the median overall survival (OS) was significantly*

longer in the rPC group than in the mPC group (14.0 vs. 10.6 months, respectively; p=0.02). However, the difference was not significant on adjusted analysis using the Cox proportional hazards model (adjusted p=0.90). Patients receiving FOLFIRINOX (n=10) and GnP (n=34) in the rPC group had comparable OS (medians, 12.2 vs. 14.4 months, respectively; p=0.82) even after adjusting for covariates using the Cox model (adjusted p=0.18). Conclusion: The outcomes of patients in the rPC and mPC groups were comparable following chemotherapy. Both FOLFIRINOX and GnP may be reasonable options for treating rPC.

The prognosis of patients with pancreatic cancer remains poor; the 5-year survival rate in Japan is less than 8%, which is the lowest among all carcinomas (1). One of the reasons that this disease is associated with a poor prognosis is that approximately 80% of patients are already unresectable at the time of diagnosis (2, 3). Although surgery may provide the greatest chance for cure, almost all patients who receive no adjuvant chemotherapy relapse within 2 years, leading to a 5-year survival rate of approximately 10% (4-6). In previous studies, patients who underwent 6 months of fluorouracil plus leucovorin (4) or gemcitabine (GEM) (5, 6) had a survival advantage over those who were merely observed after surgery; as such, adjuvant chemotherapy is the standard of care in patients who undergo pancreatic cancer resection (7, 8). Recently, patients who received S-1, GEM plus capecitabine, and modified FOLFIRINOX (FFX) experienced significantly longer survival than those who received GEM alone in an adjuvant setting (9-11). However, the recurrence rates for patients receiving GEM, S-1, and modified FFX as postoperative adjuvant chemotherapy agents were reportedly 83.4% in 5 years, 66% in 5 years, and 51.4% in 3 years, respectively (6, 9, 11).

On the other hand, FOLFIRINOX (FFX) and GEM plus nanoparticle albumin-bound (nab) paclitaxel (GnP) are recommended as standard treatment for patients with metastatic pancreatic cancer. However, the efficacy of these regimens for patients with recurrent pancreatic cancer (rPC) are not fully known, because only a small number of patients had rPC in the pivotal phase III studies (12, 13). In patients who undergo pancreatic cancer resection, postoperative adjuvant chemotherapy is commonly performed using a fluorouracil- or GEM-based regimen based on evidence from the abovementioned studies. This raises the question of whether the effectiveness of FFX and GnP in patients with rPC may be comparable to that in patients with *de novo* metastatic pancreatic cancer (mPC). Moreover, it is unknown whether the type of relapse (*i.e.*, sensitive or refractory, which are categories used for patients with recurrent lung and ovarian cancers) can be consequential for the choice of treatment for patients with rPC. Therefore, we conducted this study to investigate these clinical questions using real-world data from a multicenter retrospective study.

Patients and Methods

Study design. We previously reported a multicenter retrospective study of FFX *vs*. GnP administered to patients with unresectable pancreatic cancer as the NAPOLEON study, which was conducted in 14 institutions in the Kyushu region of Japan (14). As a post-hoc subgroup analysis of the NAPOLEON study, we assessed the efficacy of GnP or FFX treatment in patients with rPC in comparison with mPC. The FFX group comprised patients who received both the original and modified regimens. The original FFX regimen corresponded to a 2 h intravenous (*i.v.*) infusion of oxaliplatin (85 mg/m^2), 2 h *i.v.* infusion of l-leucovorin (200 mg/m^2), 90 min *i.v.* infusion of irinotecan (180 mg/m^2), a bolus of 5-fluorouracil (5-FU; 400 mg/m^2), and continuous *i.v.* infusion of 5-FU for 46 h (2,400 mg/m^2) every 2 weeks (12). Modified FFX corresponded to a 2 h *i.v.* infusion of oxaliplatin (85 mg/m^2), 2 h *i.v.* infusion of l-leucovorin (200 mg/m^2), 90 min *i.v.* infusion of irinotecan (150 mg/m^2), and continuous *i.v.* infusion of 5-FU at 46 h (2,400 mg/m^2) every 2 weeks (15). On the other hand, GnP treatment involved a 30 min *i.v.* infusion of nab-paclitaxel (125 mg/m^2) followed by a 30 min *i.v.* infusion of GEM (1,000 mg/m^2) on days 1, 8, and 15 of a 4-week cycle (13). First, we evaluated rPC *vs*. mPC. rPC was defined as pancreatic cancer that relapsed after curative resection, whereas mPC was defined as so-called '*de novo*' pancreatic cancer with metastatic lesions. Second, we evaluated FFX *vs*. GnP in the patients with rPC. Finally, we evaluated the type of relapse in the patients with rPC as a subanalysis. Patients with rPC were classified as having sensitive or refractory relapse during the period after adjuvant chemotherapy. Sensitive relapse was defined as recurrence ≥6 months after adjuvant chemotherapy, whereas refractory relapse was defined as that which occurred within 6 months after adjuvant chemotherapy. This study was approved by the institutional review board or ethics committee of each participating institution prior to the study, and conducted in accordance with the Declaration of Helsinki.

Outcome measures. The primary outcome measure was overall survival (OS), whereas secondary outcome measures were progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and treatment-related adverse events (AEs). OS and PFS were evaluated using the Kaplan–Meier method and compared between 2 groups using the log-rank test; the risk factors for OS and PFS were evaluated using the Cox proportional hazards model. First, OS and PFS were compared between patients with mPC and rPC; next, patients who underwent FFX *versus* GnP were compared in terms of OS, PFS, ORR, DCR, and AEs. Finally, OS and PFS in patients of the rPC group with sensitive *versus* refractory relapse were compared. Radiological data including computed tomography and magnetic resonance imaging were reviewed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (16). An objective response was defined as a complete or partial response, and disease control was defined as a complete or partial response with stable disease as the best response. AEs were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. The following variables were recorded before initiating GnP or FFX: age, sex, history of malignancy, Eastern Cooperative Oncology Group performance status (ECOG PS) score, body mass index, previous therapy (tumor resection, radiation, and/or biliary drainage), tumor location in the pancreas, histology, site of metastasis (liver, peritoneum, and/or

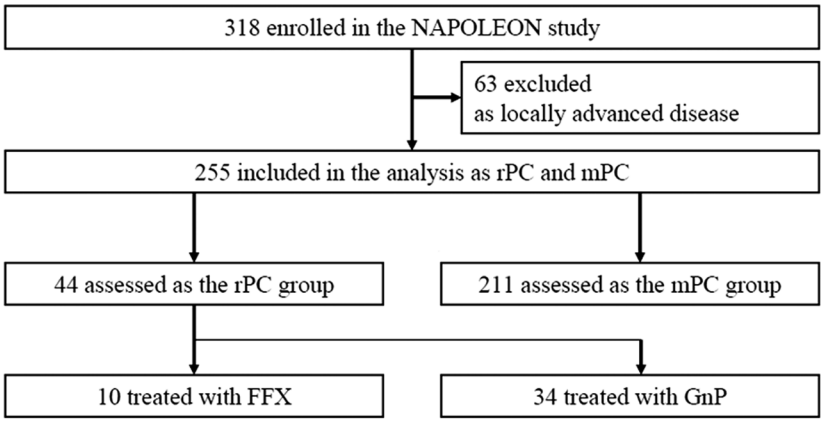

Figure 1. *A flow diagram of this study. rPC: Recurrent pancreatic cancer; mPC: metastatic pancreatic cancer; FFX: FOLFIRINOX; GnP: gemcitabine plus nanoparticle albumin-bound paclitaxel.*

lung), number of metastatic sites, maximum tumor size, and presence of ascites. Moreover, the levels of albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) were noted, as was the neutrophil-to-lymphocyte ratio (NLR). In patients with rPC, the type of relapse was also considered.

Statistical analyses. The responses of patients in the FFX and GnP groups were compared using the Mann–Whitney *U*-test for continuous data and the Cochran-Mantel-Haenszel χ^2 test for categorical data. OS was defined as the interval between the start of first-line chemotherapy and death from any cause or else was censored at the final follow-up examination. PFS was defined as the interval between the start of first-line chemotherapy and confirmation of tumor growth or death from any cause, whichever occurred earlier, or was censored at the time of the final follow-up examination. Relapse-free survival (RFS) was defined as the interval between tumor resection and confirmation of recurrence. The Kaplan–Meier method was used to estimate OS, PFS, and RFS, which were compared using log-rank tests. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95 percent confidence intervals (95% CIs). In all analyses, a *p*-value of <0.05 was considered statistically significant. The covariates for calculating the adjusted HR were chosen by clinicians according to the international consensus statement for unresectable pancreatic cancer (17). All statistical analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Recurrent pancreatic cancer (rPC) vs. de novo metastatic pancreatic cancer (mPC). Forty-four and 211 patients with rPC and mPC, respectively, were included in this analysis (Figure 1); their characteristics are shown in Table I. The median body mass index, previous biliary drainage episodes, liver metastasis rate, maximum tumor diameter, rate of ≥2 metastatic organs, serum CRP levels, serum CEA levels, NLR, and rate of FFX administration as first-line chemotherapy were significantly higher in the mPC group than in the rPC group. Meanwhile, previous radiotherapy episodes and the rate of adenocarcinoma were significantly higher in the rPC group than in the mPC group.

The median follow-up duration was 10.7 months (95% CI=9.8-11.5 months). Thirty-one patients in the rPC group (70%) and 166 in the mPC group (79%) had died by the end of the study. The OS among patients with rPC was longer than that among patients with mPC (median: 14.0 *vs*. 10.6 months; HR=0.62; 95% CI=0.42-0.92; p=0.02) (Figure 2A). Moreover, the median PFS in the rPC group (8.1 months) was significantly longer than that in the mPC group (5.7 months) (HR=0.54; 95% CI=0.37-0.77; p<0.01). On univariate analysis, ECOG PS score ≥1; liver metastasis; having ≥2 sites of metastases; having abnormal levels of albumin, LDH, CRP, CEA, and CA19-9; and a high NLR were significantly correlated with a shorter OS. Moreover, liver metastasis as well as abnormal levels of albumin, LDH, CRP, CEA, and CA19-9 were significantly associated with shorter PFS. After adjusting for these variables that were deemed to be clinically significant factors according to the Cox proportional hazards model, rPC and mPC were found not to be independent predictors of OS (adjusted HR=1.03; 95% CI=0.67-1.58; p=0.90) and PFS (adjusted HR=0.80; 95% CI=0.54-1.20, p=0.29). The adjusted median OS was 12.1 months in the rPC group and 10.9 months in the mPC group (Figure 2B), while the corresponding adjusted median PFS was 7.3 and 5.7 months, respectively.

FOLFIRINOX (FFX) vs. gemcitabine plus nanoparticle albumin-bound paclitaxe (GnP) treatment in patients with rPC. Among the 44 patients with rPC, 10 received FFX and 34 received GnP; their characteristics are shown in Table I.

Table I. *Baseline characteristics of included patients.*

Characteristics	mPC	rPC		
	Overall n=211	Overall n=44	First-line regimen	
			FFX n=10	GnP n=34
Age, years (range)	64 (35-86)	67 (29-79)	61 (49-67)†	69 (29-79)†
Age ≥65 years, n (%)	102 (48)	28 (64)	4 (40)	24 (71)
Male, n(%)	128 (61)	30 (68)	8 (80)	22 (65)
ECOG PS=0, n (%)	133 (63)	28 (64)	10 (100)†	18 (53)†
PS≥1	78 (37)	16 (36)	0†	16 (47)†
Body mass index (range)	21.5 (11.4-33.3)*	20.7 (15.6-25.3)*	21.2 (17.0-25.2)	20.3 (15.6-25.3)
Body mass index <22, n (%)	117 (55)*	36 (82)*	6 (60)	30 (88)
Previous therapy, n (%)				
Radiotherapy	2 (1)*	4 (9)*	0	4 (12)
Biliary drainage	63 (30)*	2 (5)*	0	2 (6)
Pancreatic tumor location, n (%)				
Head	99 (47)	24 (55)	6 (60)	18 (53)
Body or tail	112 (53)	20 (55)	4 (40)	16 (18)
Adenocarcinoma, n (%)	170 (81)*	42 (95)*	10 (100)	32 (94)
Site of metastatic disease, n (%)				
Liver	139 (66)*	15 (34)*	5 (50)	10 (29)
Peritoneum	47 (22)	15 (34)	1 (10)	14 (41)
Lung	36 (17)	3 (7)	0	3 (9)
No. of metastatic sites ≥2, n (%)	88 (42)*	9 (20)*	1 (10)	8 (24)
Maximum tumor size, mm (range)	35 (1-98)*	20 (1-48)*	20 (10-43)	20 (1-48)
Maximum tumor size ≥20 mm, n (%)	190 (90)*	20 (45)*	5 (50)	15 (44)
Ascites, n (%)	49 (23)	7 (16)	0	7 (21)
Albumin level, g/dl (range)	3.8 (2.2-4.8)	3.9 (2.5-4.6)	4.0 (3.7-4.6)	3.8 (2.5-4.6)
Albumin level <4.0 g/dl, n (%)	125 (59)	25 (57)	6 (60)	19 (56)
Albumin level, missing, n (%)	13 (6)	1 (2)	0	1 (3)
LDH level, U/l (range)	178 (74-1320)	181 (131-305)	187 (153-234)	178 (131-305)
LDH level ≥240 U/l, n (%)	40 (19)	3 (7)	0	3 (9)
LDH level, missing, n (%)	5 (2)	0	0	0
CRP level, mg/dl (range)	0.43 (0.01-17.00)*	0.14 (0.01-7.24)*	0.13 (0.04-0.93)	0.19 (0.01-7.24)
CRP level ≥0.03 mg/dl, n (%)	117 (55)*	11 (25)*	1 (10)	10 (29)
CRP level, missing, n (%)	6 (3)	3 (7)	0	3 (9)
CEA level, ng//ml (range)	6.6 (0.4-626.6)*	3.4 (1.0-36.1)*	4.6 (1.0-28.0)	3.4 (1.1-36.1)
CEA level ≥5.0 ng/ml, n (%)	108 (51)*	14 (32)*	5 (50)	9 (26)
CEA level, missing, n (%)	24 (11)	2 (5)	0	2 (6)
CA19-9 level, U/ml (range)	1085 (1-6554100)	365 (2-24974)	683 (2-10229)	365 (4-24974)
CA19-9 level ≥37 U/ml, n (%)	154 (73)	30 (68)	6 (60)	24 (71)
CA19-9 level, missing, n (%)	18 (9)	3 (7)	1 (10)	2 (6)
NLR (range)	2.32 (0.09-21.96)*	1.67 (0.36-9.65)*	1.64 (0.63-3.66)	1.67 (0.36-9.65)
NLR ≥5.00, n (%)	35 (17)	3 (7)	0	3 (9)
NLR, missing, n (%)	11 (5)	1 (2)	0	1 (3)
First-line chemotherapy				
FFX or mFFX	92 (44)*	10 (23)*	10 (100)	–
GnP	119 (56)*	34 (77)*	–	34 (100)

*$p<0.05$ for rPC *vs.* mPC. †$p<0.05$ for FFX *vs.* GnP as the first-line chemotherapy in rPC. mPC: Metastatic pancreatic cancer; rPC: recurrent pancreatic cancer; FFX: FOLFIRINOX; mFFX: modified FOLFIRINOX; GnP: gemcitabine plus nanoparticle albumin-bound paclitaxel; ECOG PS: Eastern Cooperative Oncology Group performance status (score); LDH: lactate dehydrogenase; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; NLR: neutrophil-to-lymphocyte ratio.

Patients in the GnP group were significantly older than those in the FFX group and had a higher rate of a family history of cancer. Meanwhile, the number of patients with ECOG PS scores of 0 was significantly higher in the FFX group than in the GnP group. S-1 and GEM were used as adjuvant therapy in 9 (90%) and 1 (10%) patient(s), respectively, in the FFX group and in 27 (79%) and 2 (6%) patients, respectively, in the GnP group. Five patients (15%) did not undergo any

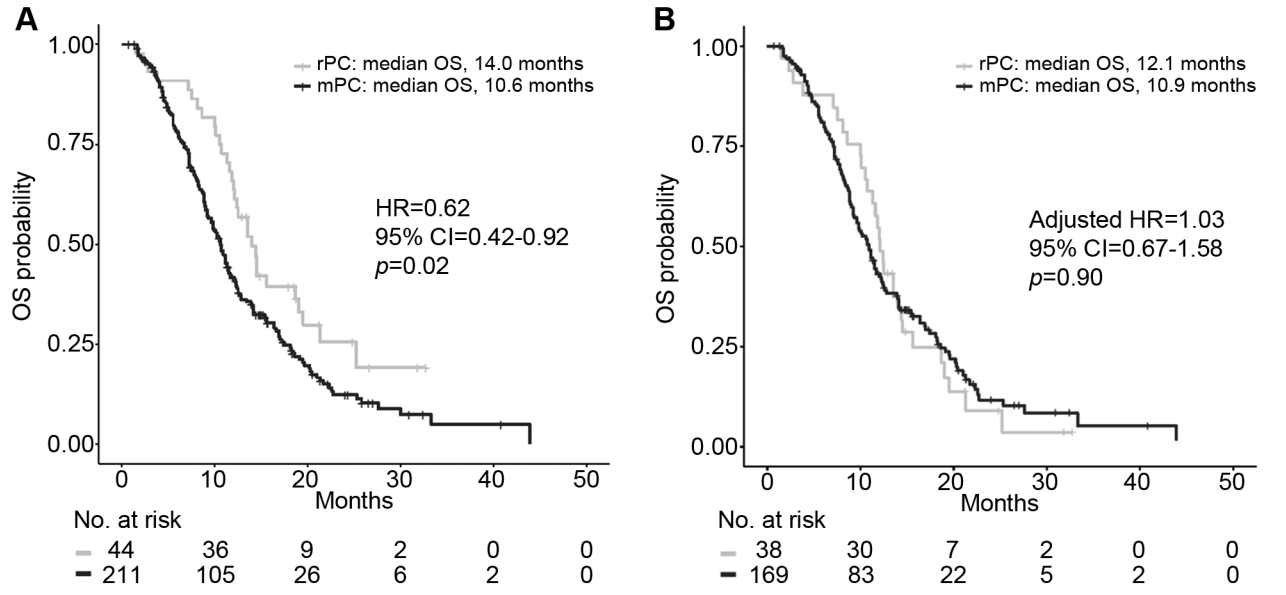

Figure 2. *Kaplan–Meier curves for crude OS (A) and adjusted OS (B). Panel (B) shows curves adjusted for variables found significant on univariate analysis (p<0.05) stratified by rPC or mPC status. OS: Overall survival; rPC: recurrent pancreatic cancer; mPC: metastatic pancreatic cancer; HR: hazard ratio; CI, confidence interval.*

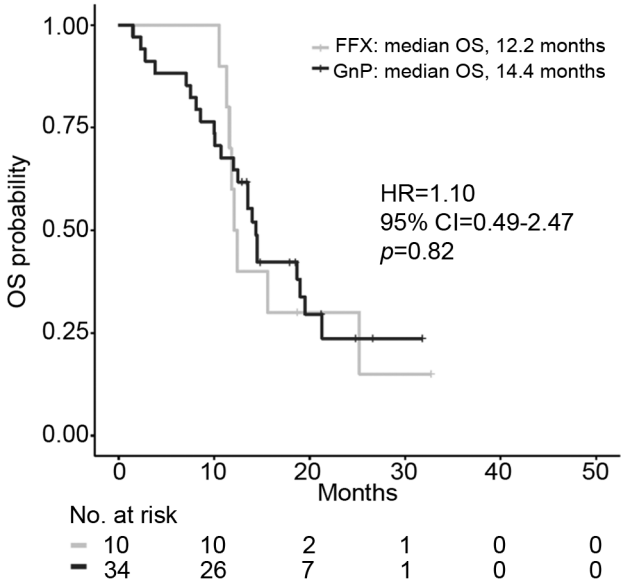

Figure 3. *Kaplan–Meier curves for crude overall survival. OS: Overall survival; FFX: FOLFIRINOX; GnP: gemcitabine plus nanoparticle albumin-bound paclitaxel; HR: hazard ratio; CI: confidence interval.*

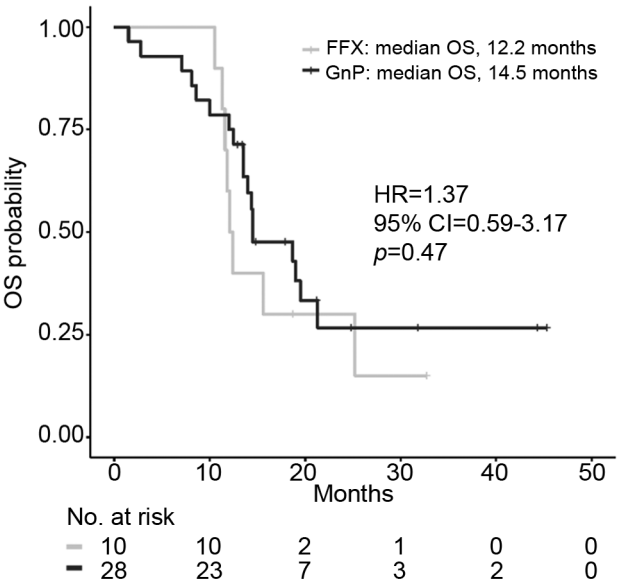

Figure 4. *Log-rank tests for overall survival. Panel shows crude estimated curves in the fundamental dataset. OS: Overall survival; FFX: FOLFIRINOX; GnP: gemcitabine plus nanoparticle albumin-bound paclitaxel; HR: hazard ratio; CI: confidence interval.*

adjuvant therapy. The adjuvant chemotherapy period for patients with rPC was 5.3 months overall and 5.1 months with S-1 alone. There were no significant differences between the FFX and GnP groups in terms of the postoperative chemotherapy period (overall chemotherapy, 6.2 *vs*. 5.2 months; S-1 alone, 5.7 *vs*. 5.1 months). Among patients with FFX, the median relative dose intensity (RDI) of oxaliplatin, irinotecan, 5-FU bolus, and continuous 5-FU infusion were

Table II. *Grade 3 or worse adverse events that occurred in ≥5% of patients.*

	Any grade			Grade 3 or 4		
	rPC n=44	mPC n=211	*p*-Value	rPC n=44	mPC n=211	*p*-Value
Leukopenia	34 (77)	136 (64)	0.02	15 (34)	68 (33)	0.81
Neutropenia	40 (91)	155 (73)	0.02	28 (64)	119 (56)	0.38
Anemia	33 (75)	133 (63)	0.19	5 (11)	32 (15)	0.51
Thrombocytopenia	26 (59)	103 (49)	0.66	6 (14)	21 (10)	0.47
Febrile neutropenia	–	–	–	4 (9)	24 (11)	0.78
Anorexia	16 (36)	122 (58)	0.04	1 (2)	25 (12)	0.06
Diarrhea	15 (34)	61 (29)	0.77	3 (7)	10 (5)	0.57
Constipation	14 (32)	66 (31)	0.62	–	–	–
Nausea	10 (23)	69 (33)	0.10	0	13 (6)	0.09
Vomitting	10 (23)	38 (18)	0.71	–	–	–
Fatigue	28 (64)	117 (55)	0.60	2 (5)	5 (2)	0.42
Peripheral sensory neuropathy	28 (64)	115 (55)	0.31	7 (16)	17 (8)	0.10
Peripheral motor neuropathy	4 (9)	14 (7)	0.15	–	–	–
AST/ALT increased	13 (30)	70 (33)	0.70	4 (9)	12 (6)	0.40
Alopecia	21 (48)	77 (36)	0.21	–	–	–
Eruption	6 (14)	29 (14)	0.53	0	4 (2)	0.36
Pruritus	1 (2)	1 (<1)	0.77	0	0	–
Oral mucositis	8 (18)	28 (13)	0.07	0	2 (1)	0.81
Pneumonia	2 (5)	7 (3)	0.09	–	–	–
Dysgeusia	6 (14)	21 (10)	0.10	–	–	–
Biliary tract infection	–	–	–	1 (2)	11 (5)	0.66
Other infection	2 (5)	3 (1)	0.20	2 (5)	2 (1)	0.14
Pain	2 (5)	7 (3)	0.69	–	–	–

rPC: Recurrent pancreatic cancer; mPC: metastatic pancreatic cancer; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine.

75.1%, 86.0%, 11.9%, and 98.0%, respectively. Among patients with GnP, the median RDI of GEM and nab-PTX were 66.5% and 54.6%, respectively. The ORRs in the FFX and GnP groups were 30% and 24%, respectively, (p=0.68), while the DCRs were 60% and 68%, respectively (p=0.65).

Eight patients in the FFX group (80%) and 23 in the GnP group (68%) ultimately died; the median OS in these groups were 12.2 months and 14.4 months, respectively, with no clinically important difference (HR=1.10; 95% CI=0.49-2.47; p=0.82) (Figure 3). On univariate analysis, serum CA19-9 levels and type of relapse were significantly correlated with OS, and therefore considered clinically consequential. After adjusting for these variables using the Cox proportional hazards model, the OS was similar between the 2 groups (median, 12.1 and 14.4 months in the FFX and GnP groups, respectively; adjusted HR=1.84; 95% CI=0.76-4.41; p=0.18) (data not shown). The median PFS was 7.9 months in the FFX group and 8.1 months in the GnP group; the difference was not clinically important (HR=1.17; 95% CI=0.55-2.50; p=0.69). The median RFS was 10.7 months for all patients with rPC, 9.1 months for those who received FFX, and 12.4 months for those who received GnP; there was no clinically important difference between the FFX and GnP groups (HR=1.71; 95% CI=0.82-3.58; p=0.16) (data not shown).

AEs. Patients in the rPC group had significantly higher incidence of any grade leukopenia, neutropenia, and hand-foot syndrome than did those in the mPC group, whereas the incidence of anorexia was significantly higher in the latter. However, the rates of grade 3 or higher AEs did not differ between the 2 groups. When comparing patients with rPC who were treated with FFX to those treated with GnP, the incidence of any grade leukopenia, anemia, and alopecia was significantly higher in the latter group. There were no statistically significant differences in the rate of grade 3 or higher AEs between the FFX and GnP groups. Grade 3 or higher AEs that affected >5% of patients in each group are summarized in Table II.

Sensitive vs. refractory relapse in patients with recurrent pancreatic cancer (rPC) as a subanalysis. Thirty-eight and 6 patients with rPC experienced sensitive and refractory relapse, respectively. All patients in the refractory relapse group received GnP as first-line chemotherapy, whereas 10 and 28 patients received FFX and GnP, respectively, in the sensitive relapse group (Table III). The median OS in the sensitive and refractory relapse groups were 14.5 and 8.8 months, respectively; the difference was significant (HR=3.38; 95% CI=1.25-9.14; p=0.02) (data not shown). In the sensitive

Table III. *Type of relapse in patients with rPC.*

Type of relapse in rPC (n=44)	Refractory relapse n=6	Sensitive relapse n=38
Age, years (range)	67 (63-71)	67 (29-79)
Age ≥65 years, n (%)	5 (83)	23 (61)
Male, n (%)	5 (83)	25 (66)
ECOG PS =0, n (%)	4 (67)	24 (63)
ECOG PS ≥1	2 (33)	14 (37)
Body mass index (range)	21.0 (15.6-21.8)	20.3 (15.9-25.3)
Body mass index <22, n (%)	6 (100)	30 (79)
Previous therapy		
Radiotherapy, n (%)	1 (17)	3 (8)
Biliary drainage, n (%)	0	2 (5)
Pancreatic tumor location		
Head, n (%)	1 (17)	23 (61)
Body or tail, n (%)	5 (83)	15 (39)
Adenocarcinoma, n (%)	6 (100)	36 (95)
Site of metastatic disease		
Liver, n (%)	2 (33)	13 (34)
Peritoneum, n (%)	5 (83)‡	10 (26)‡
Lung, n (%)	0	3 (8)
Number of metastatic sites ≥2, n (%)	2 (33)	7 (18)
Maximum tumor size, mm (range)	12 (1-30)	20 (1-48)
Maximum tumor size ≥20 mm, n (%)	2 (33)	18 (47)
Ascites, n (%)	0	6 (16)
Albumin level, g/dl (range)	3.7 (3.5-4.2)	3.9 (2.5-4.6)
Albumin level <4.0 g/dl, n (%)	3 (50)	22 (58)
Albumin level, missing, n (%)	1 (17)	0
LDH level, U/l (range)	184 (131-231)	181 (135-305)
LDH level ≥240 U/l, n (%)	0	3 (8)
CRP level, mg/dl (range)	0.36 (0.03-2.02)	0.14 (0.01-7.24)
CRP level ≥0.03 mg/dl, n (%)	3 (50)	8 (21)
CRP level, missing, n (%)	0	3 (8)
CEA level, ng//ml (range)	2.7 (1.7-4.6)	3.6 (1.0-36.1)
CEA level ≥5.0 ng/ml, n (%)	0	14 (37)
CEA level, missing, n (%)	0	2 (5)
CA19-9 level, U/ml (range)	1183 (70-5690)	365 (2-24974)
CA19-9 level ≥37 U/ml, n (%)	6 (100)	24 (63)
CA19-9 level, missing, n (%)	0	3 (8)
NLR (range)	2.00 (0.59-7.57)	1.67 (0.36-9.65)
NLR ≥5.00, n (%)	2 (33)‡	1 (3)‡
NLR, missing, n (%)	0	1 (3)
First-line chemotherapy		
FFX or mFFX	0	10 (26)
GnP	6 (100)	28 (74)

‡$p<0.05$ for refractory relapse vs. sensitive relapse in rPC. mPC: Metastatic pancreatic cancer; rPC: recurrent pancreatic cancer; FFX: FOLFIRINOX; mFFX: modified FOLFIRINOX; GnP: gemcitabine plus nanoparticle albumin-bound paclitaxel; ECOG PS: Eastern Cooperative Oncology Group performance status (score); LDH: lactate dehydrogenase; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; NLR: neutrophil-to-lymphocyte ratio.

relapse group, the median OS was 12.2 months for patients who received FFX and 14.5 months for those who received GnP (HR=1.37; 95% CI=0.59-3.17; p=0.47) (Figure 4).

Discussion

Chemotherapy regimens for pancreatic cancer are continuously improving. Many studies of chemotherapeutic regimens have been published, such as those investigating preoperative neoadjuvant chemotherapy (18-22), postoperative adjuvant chemotherapy for resectable pancreatic cancer (4-6, 9-11, 23), and palliative chemotherapy for mPC (12-15). The treatment choices for patients with rPC could be considered the same as those for patients with mPC. However, there is little reliable evidence regarding palliative chemotherapy for patients with rPC who underwent adjuvant chemotherapy per the standard

of care after surgery, as such patients were not included in the phase III trials of FFX and GnP that led to their establishment as standard regimens for mPC (12, 13). First, we investigated whether patients with rPC and mPC can be considered comparable populations, and initially found that OS and PFS in the rPC group were more favorable than those in the mPC group on crude analysis. Based on these results, it was assumed that the 2 populations should be considered distinct. However, the statistically significant differences between them disappeared after adjusting for certain factors using the Cox regression model. Therefore, FFX and GnP can indeed be considered as first-line treatment options for both patients with rPC and those with mPC.

Next, we examined whether FFX or GnP is a more effective chemotherapy for patients with rPC. The 2 regimens had comparable efficacies and acceptable toxicities for patients with rPC, albeit with some differences in baseline characteristics. Notably, the RDI of GnP was relatively lower than that of FFX, although the efficacies of both regimens were similar. This may have been due to the influence of adjuvant chemotherapy. Begg SKS *et al*. referred the sensitivity of patient-derived pancreatic ductal adenocarcinoma cell lines to FFX or GnP (24). The response of both chemotherapy in our clinical study was similar to their vitro data.

We made a comparison of patients with refractory and sensitive relapse as a subanalysis. Because patients with refractory relapse had a poorer OS than those with sensitive relapse, the treatment strategy for patients with rPC might be dependent on the type of relapse. All 6 patients with refractory relapse were treated with GnP, likely to avoid fluoropyrimidine since S-1 was administered as adjuvant chemotherapy to almost all patients per the JASPAC-01 study (9). Therefore, administering FFX to patients with refractory relapse ought to be further investigated.

Our study had several limitations. First, the baseline characteristics of each group exhibited some differences due to the nonrandomized, retrospective nature of the study as well as the relatively small sample size; this suggested that our results were affected by selection bias. To reduce any such bias, we adjusted for confounding factors when performing survival analyses using Cox regression models. Second, FFX was not categorized into original *versus* modified regimens. However, this may be acceptable because a previous study demonstrated the efficacy and safety of the modified FFX (15), while the NAPOLEON study showed no significant difference in effectiveness between the 2 regimens in patients with unresectable pancreatic cancer (data not shown). Third, 6 patients with rPC had refractory relapse; and their treatment may therefore be considered second-line therapy. All 6 patients were treated with GnP owing to their possible resistance to fluorinated pyrimidines; therefore, the efficacy of FFX was not sufficiently evaluated. Finally, although the biomarker of guiding the selection of appropriate chemotherapy might be important (24), selection of chemotherapy in our study was depended on the judgement of each doctor.

This study also had several advantages. First, to our knowledge, it was the first to investigate chemotherapy for patients with rPC, and revealed the efficacy and safety of both FFX and GnP for patients with rPC and those with mPC alike. Second, even if sensitive and refractory relapses are considered distinct, the GnP regimen might be effective for patients with both types of relapses, although it was shown by a number of cases. Third, this was a multi-center study comprising real-world data from practicing clinicians, and its findings regarding chemotherapy are expected to be readily applicable. To build stronger evidence to support this study, further investigation (such as in a prospective cohort study) is warranted.

Conclusion

The effectiveness of chemotherapy for patients with rPC was comparable to that for patients with mPC. Both FFX and GnP may, therefore, be reasonable options for patients with rPC. Moreover, the treatment strategy for patients with rPC might depend on the type of relapse (sensitive *vs*. refractory).

Conflicts of Interest

M.S. received personal fees from Sysmex Corporation; S.A. received personal fees from Taiho Pharmaceutical, Novartis Pharma, Chugai, Bristol-Myers Squibb, Daiichi-Sankyo, and AstraZeneka; A.M. received personal fees from Eli Lilly, Chugai and Takeda; T.S. received personal fees from Taiho Pharmaceutical, Chugai and Takeda; T.O. received grant from Chugai. The remaining authors have no competing interests or financial disclosures to declare.

Authors' Contributions

H.T.: Study conception, study design, data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation. T.O.: Study conceptions, study design, data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript editing. M.S.: Study design, data analysis and interpretation, statistical analysis. S.A.: Data acquisition. S.H.: manuscript editing. A.I.: Manuscript editing. F.K.: Data acquisition. Y.U.: Data acquisition. J.N.: Data acquisition. A.K.: Data acquisition. S.O: Data acquisition. M.F.: Study design, data acquisition. A.M.: Study design, data acquisition. T.H.: Data acquisition. T.S.: Data acquisition. T.M.: Study design. K.M.: Study conceptions, study design, data acquisition, quality control of data and algorithms, data analysis and interpretation, manuscript editing. K.N.: Data acquisition. Y.I: Data acquisition. N.U.: Study design. T.S.: Study conception, study design, data acquisition, quality control of data and algorithms, Data analysis and interpretation, statistical analysis, manuscript editing. All authors: Manuscript reviewing.

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