学位論文

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FOLFIRINOX as First-line Chemotherapy in Japanese Patients Suffering from Metastatic Pancreatic Cancer (KOBE FOLFIRINOX Study)

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Abstract. *Background/Aim: FOLFIRINOX (oxaliplatin, irinotecan, 5-fluorouracil, and leucovorin) combination chemotherapy is the gold-standard therapy for advanced pancreatic cancer. In this study, FOLFIRINOX dosages for Japanese patients were established enabling FOLFIRINOX therapy optimization for efficient use. Patients and Methods: Patients with advanced pancreatic cancer were treated with varying doses of FOLFIRINOX to determine the optimum dosage for highest remission outcomes with the least post-chemotherapy toxicities. Results: Patients given 180 mg of irinotecan and a 400 mg bolus of 5-fluorouracil (5-FU) showed a marked difference in outcome when compared to irinotecan 180 mg given without the 5-FU bolus, with the overall response rate being 28%, a survival time of 6.4 months and progression-free survival time of 4.5 months. Conclusion: The optimum dose of FOLFIRINOX was a dosage combination of oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, l-leucovorin 400 mg/m^2 and 5-FU 2,400 mg/m^2, administered as a continuous 46-h infusion.*

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Pancreatic cancer is the fourth leading cause of cancer-related deaths in Japan, with approximately 36,356 deaths reported in 2019 (1). Most of these patients have locally advanced or metastatic disease and approximately 15-20% of patients are treated surgically (2).

Currently, fluorouracil-containing regimens have been the only treatment for patients with advanced pancreatic cancer (APC). In 1997, a randomized controlled study showed improved survival for patients suffering from APC who were administered gemcitabine compared to patients administered 5-fluorouracil (5FU) only (3), establishing the potential of combination chemotherapy along with 5FU, as a treatment for APC. In a previous randomized control phase III study on patients with APC it was shown that FOLFIRINOX (FFX) consisting of a combination of oxaliplatin, irinotecan, 5FU, and leucovorin had clinical benefits, improving overall survival (OS) of patients to 11.1 months, compared to 6.8 months for patients treated with gemcitabine alone (4). However, in that trial, major grade 3 and 4 adverse events including neutropenia (45.7%), febrile neutropenia (5.4%), thrombocytopenia (9.1%) and anemia (7.8%) were observed. Moreover, in another FFX-related phase II trial on 36 Japanese patients with APC (5), grade 3 and 4 toxicities including neutropenia (77.8%), febrile neutropenia (22.2%), thrombocytopenia (11.1%) and anemia (11.1%) were more prevalent compared to the results of the phase III FFX trials (4).

This observed toxicity in Japanese APC patients was significant enough to question the current recommended dose (RD) of FFX treatment and implies the need to establish an efficient dosage standard that would contribute to maximum therapeutic efficacy with the least possible toxicity. Therefore, this study aimed to evaluate the dose-limiting toxicities (DLTs) of FFX, using a dose escalation/de-

escalation design to determine the maximum tolerated dose (MTD) and RD of FFX for Japanese patients with APC.

Patients and Methods

Patients. Adult patients with histologically and clinically confirmed pancreatic adenocarcinoma, who had inoperable advanced or metastatic tumors, were recruited into this study after obtaining informed consent. Patients were required not to have received any prior chemotherapy or radiation therapy; however, exceptions were made for patients who had undergone prior adjuvant chemotherapy, if more than 6 months had elapsed since the end of therapy. Also, patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1 and wild-type or heterozygous *UGT1A1 *28* or **6*. Normal organ function, as well as blood cell and blood chemistry parameters, defined as neutrophil count ≥2,000/mm^3, hemoglobin ≥10 g/dl, platelet count ≥100,000/mm^3, total bilirubin 1.5 mg/dl, aspartate transaminase and alanine transaminase ≤100 U/l and creatinine clearance ≥60 ml/min or creatinine ≤1.2 mg/dl, were also prerequisites to participate in the trial. Patients with synchronous or previous malignancy other than carcinoma *in situ*, grade ≥2 peripheral sensory neuropathy, grade ≥2 chronic diarrhea, any critical medical conditions including severe mental disorder, serious cardiac disease, interstitial pneumonia, uncontrollable diabetes, active pathological infections, unresolved bowel obstruction, as well as pregnant or breastfeeding patients were excluded from the study. Trial protocols were approved by the Institutional Review Board of Kobe City Medical Center General Hospital and the study was carried out according to the Declaration of Helsinki and Ethical Guidelines for Clinical Studies.

Study design. The primary objective of this study was to evaluate DLTs after 2 cycles of chemotherapy at a fixed FFX dose level designed by us and to determine the RD of FFX as first line chemotherapy in Japanese patients with APC. Secondary objectives included the evaluation of any toxicity, relative dose intensity (RDI), overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) according to RECIST criteria (version 1.1) after the completion of two cycles of chemotherapy. DLT was classified as the occurrence of any one or more of the following adverse reactions until the start of the 3rd cycle of chemotherapy: (i) grade 4 neutropenia lasting for at least 7 days, (ii) febrile neutropenia, (iii) grade 4 thrombocytopenia, (iv) grade 3 or 4 non-hematological toxicities, (v) diarrhea with hyperthermia above 38˚C, (vi) treatment-related death, and (vii) any other unresolved drug-related adverse events not included in the above classifications. Any of the above DLTs resulted in chemotherapy interruption for at least 14 days or more. If the above mentioned adverse events or reactions to the treatment were observed continuously after treatment suspension for 14 days, the patients were removed from the study and not included in the trial anymore. Patients were also allowed to leave the study on personal request or when there was evidence of further disease progression interfering with normal participation in the trial.

This study is registered with the University Hospital Medical Information Network (No. UMIN000013217).

Treatment. Three separate trial dosage regimens were designated as FOLFIRINOX FT-α, FT-β and FT-γ. FT-α consisted of a consecutive 120-min intravenous (*i.v.*) infusion of 85 mg/m^2 oxaliplatin and a 120-min *i.v.* infusion of 200 mg/m^2 *l*-leucovorin, followed after 30 min by a 90-min *i.v.* infusion of 180 mg/m^2 irinotecan and a 400 mg/m^2 *i.v.* bolus of 5-FU, followed by continuous 46-h infusion of 2,400 mg/m^2 of 5-FU. Six patients were treated with FT-α, if 2 or less of these 6 patients experienced a DLT, the RD was determined to be the cut-off dose for treatment. However, if 3 or more of these 6 patients experienced a DLT, this FT-α combination was considered unsuitable and 6 new patients were recruited in a second study group. The patients in the second study group were administered a revised and reduced dose of the combination regimen designated FT-β. FT-β was similar to FT-α with a reduction of irinotecan dose to 150 mg/m^2 and without the 400 mg/m^2 bolus of 5-FU. If 2 or fewer of the 6 patients who received FT-β experienced a DLT, a third study group was established (6 new patients). The third group received a new dose level, designated FT-γ, which was lower compared to FT-α, but higher than FT-β. FT-γ was similar to the FT-β combination, with an increased irinotecan dose of 180 mg/m^2. However, if 3 or more patients treated with FT-β experienced a DLT, the study was discontinued. Thus, if 3 or more of patients from study group 3 experienced a DLT at dose level FT-γ, the RD was determined to be level FT-β, however if 2 or fewer patients at dose level FT-γ experienced a DLT, the RD was determined to be level FT-γ. It should be noted that new patients were recruited in each FFX trial group (FT-α, FT-β, and FT-γ). Patients that developed DLTs that lasted more

Table I. *Baseline characteristics of patients with advanced pancreatic cancer (N=18).*

Characteristic	n (%)
Age (years)*	62 (49-72)
Gender	
Male (%)	10 (55.6)
Female (%)	8 (44.4)
ECOG PS	
0 (%)	6 (33.3)
1 (%)	12 (66.7)
BSA (m^2)*	1.6 (1.33-1.98)
Primary tumor site	
Head (%)	5 (27.8)
Body/Tail (%)	13 (72.2)
UGT1A1 status	
Wild/Wild (%)	11 (61.1)
*6 single hetero (%)	5 (27.8)
*28 single hetero (%)	2 (11.1)
Metastatic sites	
Liver (%)	9 (50)
Lung (%)	8 (44.4)
Peritoneum (%)	6 (33.3)
Lymph node (%)	4 (22.2)
Stent or drainage	
No (%)	14 (77.8)
Yes (%)	4 (22.2)
Primary tumor	
Present (%)	14 (77.8)
Absent (%)	4 (22.2)

ECOG: Eastern Cooperative Oncology Group; PS: performance status; BSA: body surface area, UGT1A1: uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1. *Data presented as median (range).

Table II. *Median relative dose intensity per patient at each dose level.*

Drug	FT-α % (range)	FT-β % (range)	FT-γ % (range)
Oxaliplatin	96.1 (87.5-100)	84.8 (28.2-100)	99.0 (94-100)
Irinotecan	88.1 (50.0-100)	95.3 (83.2-100)	99.9 (99.4-100)
5-FU bolus	75.2 (11.4-100)	-	-
Continuous 5-FU infusion	100 (100)	100 (100)	99.9 (99-100)
l-Leucovorin	100 (100)	100 (100)	100 (100)

than 14 days were moved to a lower dose group; however, they were excluded from the trial.

Before starting chemotherapy, 150 mg of fosaprepitant, a selective antagonist of the neurokinin (NK) 1 neurotransmitter receptor, 0.25 mg of palonosetron, a second generation 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, and 9.9 mg of dexamethasone were administered *i.v.* as a prophylactic to prevent chemotherapy-induced nausea and vomiting. For the treatment of cholinergic syndrome, 0.25 mg of *i.v.* atropine was administered when needed and then administered prophylactically in subsequent cycles; however, the use of granulocyte colony-stimulating factor (G-CSF) was not allowed during this study.

Patient assessment. Patients were routinely examined and their general condition and performance status were monitored during the trial. Laboratory data were also corroborated along with other diagnostics to evaluate any toxicity or other pathological co-morbidities, which may have occurred before the start or during the trial. Patient toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

Results

Patient characteristics. Of the 18 patients enrolled in our study, 33.3% had an ECOG-PS of '0', 27.8% of patients had the head of the pancreas as the primary site of the tumor, 22.2% had a biliary stent, 22.2% experienced recurrence after surgical resection and major sites of metastasis were observed in the liver and lung (50% and 44.4%, respectively). Heterozygotes for the *UGT1A1* genetic polymorphisms *6 and *28 were detected in 27.8% and 11.1% of patients, respectively, while the remaining patients (61.1%) displayed a wild-type genetic polymorphism. Patient characteristics are shown in Table I.

Dose intensity. The median number of treatment cycles administered were 4.5 (range=1-22, 14 days per cycle) and the median recommended dose intensity (RDI) of oxaliplatin, irinotecan, bolus 5-FU and continuous infusion of 5-FU were 75.2%, 88.1%, 96.1%, and 100% respectively, in dose level FT-α. The median RDI of oxaliplatin, irinotecan and continuous infusion of 5-FU was 84.8%, 95.3% and 100% respectively in dose level FT-β, and finally 99%, 99.9% and 99.9% in dose level FT-γ (Table II).

Out of a total of 6 patients in each drug combination group, 2 patients in the FT-α trial group showed chemotherapy-induced general fatigue, 2 patients in the FT-β group developed febrile neutropenia (FN) and grade 4 neutropenia respectively, and 1 patient in the FT-γ group developed chemotherapy-induced general fatigue and thus were put on a lower dose of FFX during the first cycle of treatment. Similarly, during the second cycle, 1 out of a total of 4 patients (2 patients could not receive the next cycle) treated with FT-α developed unresolved drug-related adverse events, 1 out of 6 patients treated with FT-β developed grade 4 neutropenia, and 1 out of 6 patients treated with FT-γ developed general fatigue and were put on a lower FFX dose resulting in chemotherapy interruption for 14 days or more.

Safety. At dose level FT-α, 3 out of 6 patients experienced DLT, with all patients presenting with unresolved drug-related adverse events, resulting in dose interruption for a minimum of 14 days. At dose level FT-β, 2 out of 6 patients experienced DLT, with 1 patient developing grade 4 neutropenia and 1 patient developing febrile neutropenia. Both patients eventually recovered without using G-CSF. At dose level FT-γ, 1 out of 6 patients experienced DLT with unresolved drug-related adverse effects, resulting in dose interruption for a minimum of 14 days. During a maximum of 8 cycles of chemotherapy, safety profiles were evaluated in all patients at each level and no treatment-related deaths were observed. The only major pathologies observed in the 18 patients (6 in each group) were grade 3-4 hematological toxicities, which included neutropenia occurring in 7 (38.9%) patients (2 in FT-α, 4 in FT-β and 1 in FT-γ), leukopenia in 3 (16.7%) patients (1 in FT-α, 1 in FT-β and 1 in FT-γ) and thrombocytopenia in 1 (5.6%) patient (in FT-α). Non-hematological toxicities observed were grade 3-4 anorexia in 1 (5.6%) patient (in FT-α), vomiting in 1 (5.6%) patient (in FT-α), diarrhea in 1 (5.6%) patient (in FT-α), fatigue in 1 (5.6%) patient (in FT-α) and febrile neutropenia in 1 (5.6%) patient (FT-β). All adverse events are listed in Table III.

Efficacy. A complete remission was not observed in any of the patients of the 3 groups. A partial remission response was observed in 3 of patients, stable disease in 1, and progressive

Table III. *Most common adverse events during treatment.*

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematological				
Leukopenia	2 (11.1%)	6 (33.3%)	3 (16.7%)	0
Neutropenia	0	2 (11.1%)	5 (27.8%)	2 (11.1%)
Anemia	14 (77.8%)	1 (5.6%)	0	0
Thrombocytopenia	7 (38.9%)	1.(5.6%)	1 (5.6%)	0
Non-hematological				
Anorexia	4 (22.2%)	5 (27.8%)	1 (5.6%)	0
Diarrhea	3 (16.7%)	0	1 (5.6%)	0
Fatigue	9 (50%)	4 (22.2%)	1 (5.6%)	0
Febrile neutropenia	0	0	1 (5.6%)	0
Hiccough	6 (33.3%)	0	0	0
Nausea	3 (16.7%)	5 (27.8%)	0	0
Peripheral sensory neuropathy	9 (50%)	1 (5.6%)	0	0
Stomatitis	1 (5.6%)	0	0	0
Vomiting	0	0	1 (5.6%)	0

disease in 2 patients at treatment dose level FT-α. At dose level FT-β, the outcome was 0% for partial remission, 3 patients continued to have stable disease and 3 patients had progressive disease. Finally, at dose level FT-γ, 2 patients had partial remission, 3 patients continued to have stable disease and 1 patient had progressive disease. The objective response rate of all patients in the trial was 27.8% and the completion rates after 2 cycles of treatment were 66.7% at level FT-α, 100% at level FT-β and 100% at level FT-γ. The median follow-up period was 6.8 months (range=1.7-27.6) and the median overall survival and progression-free survival were 6.4 months (95%CI=4.5-25.8), and 4.5 months (95%CI=1.7-19), respectively (Figure 1 and Figure 2).

Discussion

Recent clinical trials have shown that modified FFX regimens give promising results in pancreatic cancer (6-11); however, these reports do not suggest a FFX regimen that achieves maximum efficacy while causing the least toxicity to patients suffering from unresectable advanced pancreatic cancer. Thus this study aimed to find the most efficacious and least toxic dosage of FFX for Japanese patients suffering from unresectable APC.

The study results showed that the least DLTs in APC patients occurred at dose level FT-γ, compared to dose levels FT-α and FT-β, indicating that the RD of FFX at dose level FT-γ is the optimum FFX combination for the best treatment outcome in APC patients. This result may have been due to the removal of the 400mg/m^2 bolus of 5-FU bolus in the FT-γ dosage combination. FFX combination FT-γ dosage showed a lower occurrence of adverse effects when compared to the results obtained from the ACCORD11 clinical trial, in which FFX combination was similar to FT-γ, but with a 400mg/m^2 bolus of 5-FU, and 200mg/m^2 leucovorin and a continuous 46-h infusion of 2,400 mg/m^2 5FU (4).

A benefit of the FT-γ dosage treatment was that all patients who reported neutropenia, including advanced grade 3-4 neutropenia and febrile neutropenia, were able to recover without the administration of G-CSF. This was not the case in the ACCORD 11 study (4), where filgrastim (G-CSF) was administered in 42.5% of patients who received FFX treatment. However, it should be noted that the comparison between the current trial and the ACCORD 11 study may be biased by differences in sample size.

Further analyses involving genetic classification in the present study, showed a single heterozygous *UGT1A1* genetic polymorphism (*6/- or -/*28) in 1 out of 6 patients in FT-β, compared to 10 out of 31 and 11 out of 36 patients in two separate phase II studies of modified FFX treatment regimens in Japanese patients with APC (7) and metastatic APC (5), respectively. However, no evidence exists on whether single hetero *UGT1A1* genetic polymorphisms have an impact on the adverse events during FFX treatment and may be an area for further studies.

In the present study, to prevent vomiting, the anti-emetic drug fosaprepitant, palonosetron, and dexamethasone, were administered to all patients intravenously; however the frequency of grade 3-4 vomiting in FT-α-treated patients were not different from that reported in the ACCORD 11 trial. Nevertheless, no patient in the FT-γ group experienced grade 3-4 vomiting. Furthermore, no patient in our FFX FT-γ treatment group experienced grade 3-4 diarrhea, compared to 12.7% of patients who experienced grade 3-4 diarrhea in

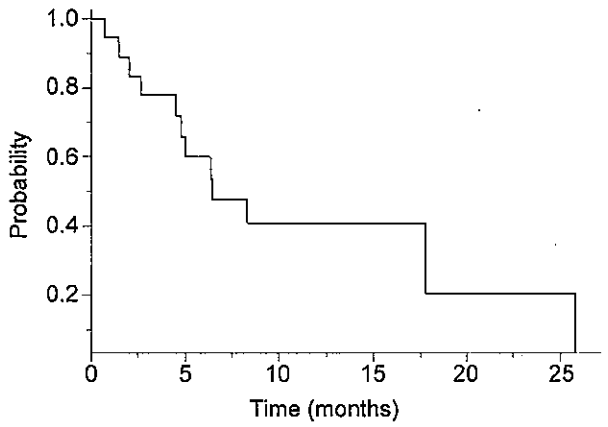

Figure 1. *Kaplan-Meier analysis of overall survival. The median overall survival was 6.4 months (95% confidence interval=4.5-25.8).*

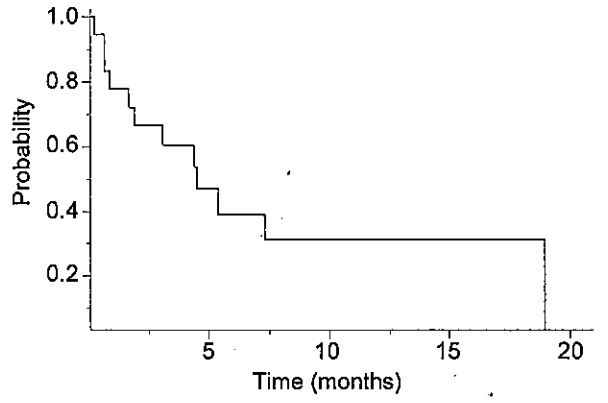

Figure 2. *Kaplan-Meier analysis of progression-free survival. The median progression-free survival was 4.5 months (95% confidence interval=1.7-19).*

the ACCORD 11 study (4). These results suggest that the removal of the 400mg/m^2 bolus of 5 FU in the FFX FT-γ dose might have contributed to the reduced frequency of grade 3-4 vomiting and diarrhea adverse events.

It is important to note that the above observations of reduced diarrhea in our patients may also have been due to the fact that patients having a homozygous (*6/*6, *28/*28) or double heterozygous (*6/*28) *UGT1A1* genetic polymorphisms were excluded in this trial. It has been previously shown that *UGT1A1**28 polymorphism is associated with irinotecan-related diarrhea (12). It is also likely that the prescription of scopolamine butylbromide as an anti-diarrheal prophylactic before starting chemotherapy for all patients may have contributed to the reduction of diarrhea in our patients.

Although this study demonstrated promising results regarding the use of FFX FT-γ dosage for the treatment of APC, there are some limitations to be noted. First, the enrolment of APC patients only from one hospital may have contributed to a patient selection bias. Moreover, patients with homozygous or double heterozygous *UGT1A1* genetic polymorphisms were excluded from this study, which may have contributed to our positive results. Furthermore, examination of hematological and non-hematological baseline parameters was beyond the scope of this current trial, while they were included in the ACCORD11 study for a detailed comparison of FFX regimens and their toxicities (4). Future studies with a larger sample size of patients are warranted to further elucidate the benefits of FFX drug combination FT-γ on Japanese patients with unresectable APC.

Conclusion

An improved FFX regimen, consisting of 85 mg/m^2 oxaliplatin, 200mg/m^2*l*-leucovorin, 180 mg/m^2 irinotecan, and 2,400 mg/m^2 of 5-FU without the 400mg/m^2 bolus of 5 FU showed the best efficacy and least toxicity for the treatment of Japanese APC patients.

Conflicts of Interest

Hironaga Satake has received research funding from Ono Pharmaceutical Co. Ltd.., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and honoraria from Bayer Co., Ltd., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan Co., Ltd., Merck Bio Pharma Co., Ltd., MSD Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Co., Ltd. and Yakult Honsha Co., Ltd. Akihito Tsuji has received honoraria from Chugai Pharma, Takeda Pharmaceutical, Eli-Lilly, Taiho Pharma, Bayer, Bristol-Myers Squibb Japan, Daiichi Sankyo and Merck Serono. Hisateru Yasui has received honoraria from Bayer, Chugai Pharma, Eli Lilly Japan, Merck Biopharma, Taiho Pharmaceutical, Bristol-Myers Squibb Japan, Yakult Honsha and TERUMO. All remaining Authors declare no conflicts of interest.

Authors' Contributions

Yukimasa Hatachi: Corresponding author. Recruitment of patients, and writing of the manuscript; Takeshi Kotake: Creating the study protocol, recruitment of patients, and reviewing of the manuscript; Hironaga Satake: Recruitment of patients, and reviewing of the manuscript; Yoshihirō Okita: Recruitment of patients and of reviewing the manuscript; Hisateru Yasui: Recruitment of patients and reviewing of the manuscript; Akihito Tsuji: Creating the study protocol, recruitment of patients and reviewing of the manuscript.

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