

Clinical Trials Study

Multicenter phase II trial of modified FOLFIRINOX in gemcitabine-refractory pancreatic cancer

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Abstract

AIM

To evaluate the efficacy and safety of modified FOLFIRINOX as a second-line treatment for gemcitabine (GEM)-refractory unresectable pancreatic cancer (PC).

METHODS

This study was a prospective, multicenter, one-arm, open-label, phase II trial. Patients with unresectable PC, who showed disease progression during GEM-based chemotherapy were enrolled. All patients were administered FOLFIRINOX with reduced irinotecan and oxaliplatin (RIO; irinotecan 120 mg/m² and oxaliplatin 60 mg/m²), which was set according to the phase I study of FOLFIRINOX. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events were evaluated. Additionally, changes in quality of life (QoL) were assessed using a questionnaire on QoL.

RESULTS

Between August 2015 and May 2016, a total of 48 patients were enrolled. The median follow-up time was 259 d with a median of 8.5 cycles. The ORR and DCR were 18.8% and 62.5%, respectively, including one patient who showed complete remission. The median PFS was 5.8 mo [95% confidence interval (CI): 3.7-7.9] and median OS was 9.0 mo (95%CI: 6.4-11.6). Neutropenia (64.6%) was the most common grade 3-4 adverse event, followed by febrile neutropenia (16.7%). Although 14.6% of patients experienced grade 3 fatigue, most non-hematologic AEs were under grade 2. In the QoL analysis, the global health status score before treatment was not different from the score at the last visit after treatment (45.43 ± 22.88 *vs* 48.66 ± 24.14, *P* = 0.548).

CONCLUSION

FOLFIRINOX with RIO showed acceptable toxicity and promising efficacy for GEM-refractory unresectable PC. However, this treatment requires careful observation of treatment-related hematologic toxicities.

Key words: Pancreatic cancer; FOLFIRINOX; Clinical Trial, Phase II; Chemotherapy; Gemcitabine refractory

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Core tip: For gemcitabine (GEM)-refractory unresectable pancreatic cancer (PC), there are limited options of second-line chemotherapy regimen. To find new treatment option for GEM-refractory unresectable PC, we conducted a multicenter phase II trial, which evaluated the efficacy and safety of uniquely modified FOLFIRINOX with reduced irinotecan and oxaliplatin. In our results, FOLFIRINOX with reduced irinotecan and oxaliplatin showed acceptable toxicity and promising efficacy. With careful observation of treatment-related hematologic toxicities, this chemotherapy regimen is a promising option for patients with GEM-refractory PC after first-line treatment failure.

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INTRODUCTION

Pancreatic cancer (PC) is among the major causes of cancer-related deaths in the United States^[1]. In South Korea, PC is the eighth highest-diagnosed cancer and the fifth most common cause of cancer-related death^[2]. Metastatic pancreatic cancer (MPC) accounts for 60% of all cases; the median survival of patients with MPC is 3-6 mo. Systemic chemotherapy is pivotal for treating such patients; however, effective regimens remain limited. Recently, two first-line combination regimens-FOLFIRINOX [a combination of oxaliplatin, folinic acid (FA), irinotecan, and 5-fluorouracil (5-FU)] and nanoparticle albumin-bound (nab) paclitaxel in combination with GEM-prolonged survival compared to gemcitabine (GEM) monotherapy and became standard treatments^[3,4]. However, the median progression-free survival (PFS) of these new treatment regimens was only 6.4 and 5.5 mo, respectively.

Proper second-line treatment can improve survival of patients with locally advanced pancreatic cancer (LAPC) or MPC who fail first-line treatment. Although some previous phase III trials showed survival improvement with their study regimens, the standard treatment remains unclear^[5-7].

Patients who received first-line FOLFIRINOX or nab-paclitaxel plus GEM may benefit from a novel second-line treatment, although toxicity should also be considered.

FOLFIRINOX, a standard first-line treatment, has been proposed as a second-line treatment for patients with good performance status who failed GEM-based chemotherapy. However, as the condition of many patients deteriorates after first-line chemotherapy, second-line therapy requires administration at attenuated doses and/or schedules, even in patients who maintain a preserved comorbidity profile.

Standard FOLFIRINOX has limited broad use as a second-line therapy because of toxicity; it includes irinotecan (180 mg/m²), oxaliplatin (85 mg/m²), 5-FU (400 mg/m² administered as a bolus followed by 2400 mg/m² administered as a 46-h continuous infusion), and leucovorin (400 mg/m²) every 2 wk^[3]. Several FOLFIRINOX trials have investigated reducing dosages while maintaining efficacy^[8-10]. However, studies focused on the efficacy and safety of a modified dose of FOLFIRINOX for patients with GEM-refractory PC are still rare. Therefore, we conducted a prospective, multicenter, one-arm, open-label, phase II trial using a modified FOLFIRINOX with reduced oxaliplatin and irinotecan (RIO) to minimize adverse events (AEs). Our aim was to evaluate the efficacy and safety of FOLFIRINOX with (RIO) in patients with unresectable PC who had earlier been treated with a GEM-based regimen until disease progression.

MATERIALS AND METHODS

Study population

This study was a prospective, multicenter, one-arm, open-label, phase II trial and conducted in eight Korean university hospitals. The inclusion criteria for this study were patients between 19 and 75 years old; Eastern Cooperative Oncology Group performance status ≤ 2 ; cytologically or histologically proven unresectable pancreatic adenocarcinoma that progressed after first-line GEM-based chemotherapy; adequate bone marrow function (white blood cell count $\geq 3500/\mu\text{L}$, absolute neutrophil count $\geq 1500/\mu\text{L}$, and platelet count $\geq 100000/\mu\text{L}$); adequate hepatic function (total bilirubin $\leq 1.5 \times$ the upper limit of the normal range [ULN], serum aspartate and alanine transaminase $\leq 3 \times$ ULN, and alkaline phosphatases $\leq 3 \times$ ULN or $\leq 5 \times$ ULN in case of liver metastasis); adequate renal function (serum creatinine ≤ 1.5 mg/dL); and adequate cardiopulmonary function. Patients were excluded if they had a concurrent malignancy other than PC; a serious, uncontrollable medical condition; or a psychiatric disorder. The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written, informed consent was obtained from each participant after potential treatment complications had been fully explained. The institutional review boards at all participating institutions approved this study. This trial is registered with ClinicalTrials.gov, number NCT02440958.

Study endpoints

The primary endpoints were objective response rate [ORR; complete remission (CR) + partial response (PR)] and disease control rate (DCR; CR + PR + stable disease (SD)). The secondary endpoints were PFS, overall survival (OS), changes in quality of life (QoL), and safety. OS was calculated from the date of enrollment until death from any cause. In the absence of an event, data were censored on the last day of survival confirmation. PFS was calculated from the initiation of treatment until either imaging-confirmed disease progression or death from any cause; in their absence, data for such patients were censored on the day of their last imaging procedure.

Determination of study drug dose

In the phase I study of FOLFIRINOX, febrile neutropenia, prolonged (≥ 7 d) severe neutropenia, and severe non-hematologic AEs were not reported at a dose level of 120 mg/m² irinotecan and 60 mg/m² oxaliplatin^[11]. Based on these data, we set the study drug regimen – FOLFIRINOX with RIO – to 120 mg/m² irinotecan (66.6% of standard dose) and 60 mg/m² oxaliplatin (70.5% of standard dose) with standard dose of bolus and infusional 5-FU.

Treatment protocol and dose adjustments

Oxaliplatin was first administered as a 2-h intravenous infusion (IVF); 1 h later, irinotecan was administered as a 90-min IVF. Leucovorin (400 mg/m²) was administered as a 90-min IVF immediately after oxaliplatin and irinotecan. The 5-FU dose was a 400 mg/m² bolus followed by 2400 mg/m² administered over 46 h of IVF. Each cycle of FOLFIRINOX with RIO was administered every 2 wk and repeated until either evidence of progressive disease (PD), significant clinical deterioration, or withdrawal of patient consent. All patients routinely received palonosetron 30 min before the initiation of chemotherapy as a prophylactic anti-emetic agent. Atropine was administered to patients with irinotecan-caused cholinergic reactions. High-dose loperamide was administered for delayed diarrhea, followed by prophylactic oral fluoroquinolones if diarrhea continued for over 48 h. Granulocyte colony-stimulating factor (G-CSF) was administered for severe neutropenia. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) before each cycle. In the event of predefined hematologic or non-hematologic AEs, protocol-specified treatment modifications or delays were performed to minimize additional treatment-related AEs.

For each patient, the study lasted up to 15 cycles with drugs donated by the pharmaceutical manufacturers; patients who completed these cycles without PD were admitted to a post-study phase and continued chemotherapy according to the study protocol at their

own expense. Treatment was discontinued if PD or intolerable toxicity was observed, if the patient withdrew from the study, or at the physician's discretion.

Data assessment

Pre-treatment evaluations included taking a complete medical history, physical examination, and laboratory tests. Evaluations were performed within 2 wk before, and every 2 wk during treatment. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1) based on high-resolution computed tomography scans every 8 wk. QoL was assessed every 8 wk using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)^[12] and its supplement for patients with pancreatic cancer (QLQ-PAN26)^[13]. Additionally, changes in body weight and pain scale were checked every 2 wk. The Korean version of the questionnaire, officially translated and distributed by EORTC, was used. All patients filled-out and submitted the questionnaire by themselves on the day of visit. QoL changes between baseline and the last visit were analyzed, considering that the participation period varied among patients. Scores of all QoL scales range from 0 to 100; a higher score indicates a better functional status or a worse symptom.

Statistical analysis

When this clinical trial was being designed, the previously reported ORR of second-line chemotherapy for unresectable PC with GEM failure ranged from 0% to 11.4%^[5,14-17]. With this background, this trial was performed according to a Simon optimal two-stage design ($P_0 = 0.100$, $P_1 = 0.250$, $\alpha = 0.050$, and $\beta = 0.200$; P_0 and P_1 are the response proportions of a poor and good drug, respectively)^[18,19]. In the first stage, accepting a type I error of 10% and a power of 80%, 46 patients were planned for enrollment. If three or fewer of the 22 enrolled patients demonstrated an objective response, we would terminate the experiment at that stage based on the regimen's low efficacy. Otherwise, the regimen would be recommended for further testing and accrual would continue to 46 patients (assuming a 15% dropout rate).

All patients who received the study regimen at least once were included in the intention-to-treat (ITT) and toxicity analysis populations. All efficacy assessments were based on the ITT analyses. PFS and OS were estimated using Kaplan-Meier methods with 95% confidence interval (CIs). When comparing data (QoL questionnaire, weight, and pain scale) between baseline and last visit, the paired *t*-test was used for normally distributed data while the Wilcoxon signed rank test was used for non-normally distributed data. All statistical analyses were performed using IBM SPSS (version 23.0, IBM Corp., Armonk, NY, United States). A *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of patients

Between August 2015 and May 2016, 48 patients were enrolled. The median age at the time of enrollment was 63.5 years [interquartile range (IQR), 57.5–69.0 years]. All patients had cytologically or histologically confirmed adenocarcinoma according to the inclusion criteria. Also, all patients had LAPC or MPC including 38 patients (79.2%) with accompanying distant metastasis (Table 1). Close to 80% of the patients received GEM plus erlotinib as their first-line GEM-based treatment. Because GEM plus nab-paclitaxel became available in January 2016 in Korea, only one patient was administered this regimen prior to the study.

Treatment exposure

A flowchart of the 48 patients' treatments is shown in Supplementary Figure 1; at the time of analysis, 38 of these patients had died while two patients remained on FOLFIRINOX with RIO. Treatment was discontinued prior to completing 15 cycles in 33 patients, including 14 who showed PD, 10 who had treatment delays for unresolved infections ($n = 2$) or grade 3/4 toxicities ($n = 8$), five who declined further treatment, two who died after treatment (one of septic shock and the other of unknown reasons at another location), one who had acute cerebral infarction, and one who showed radiologic CR. All patients combined received a total of 493 cycles of chemotherapy. The median follow-up time was 259 d (IQR, 103.3–427.8 d), and the median number of chemotherapy cycles per patient was 8.5 (IQR, 3.0–16.5), with a median treatment duration of 145 d (IQR, 30.5–286.3 d). The relative dose intensity (proportion of the administered accumulated dose relative to the planned accumulated dose) of bolus 5-FU, infusional 5-FU, combined bolus plus infusional 5-FU, irinotecan, and oxaliplatin was 93.60% ± 15.86%, 93.60% ± 15.86%, 93.60% ± 15.86%, 95.65% ± 8.16%, and 95.65% ± 8.16%, respectively.

Tumor responses and survival

Tumor responses and survival analysis are shown in Table 2. The ORR and DCR of all patients were 18.8% and 62.5%, respectively. The DCR was 80% in ten LAPC patients, but no CR or PR was reported. Among 38 MPC patients (79.2% of all patients), the ORR and DCR were 23.7% and 57.9%, respectively. A sixty-year-old female patient, who progressed to multiple liver metastasis after GEM monotherapy, achieved radiologic CR after 12 cycle of FOLFIRINOX with RIO. After twelfth cycle, the patient had not experienced disease recurrence on serial radiologic studies without chemotherapy for a year, until peritoneal seeding and liver metastasis were confirmed.

The median PFS was 5.8 mo (95%CI: 3.7–7.9 mo) and the median OS was 9.0 mo (95%CI: 6.4–11.6 mo) for all patients (Figure 1). The PFS rates at 6, 12, and

Table 1 Baseline characteristics

Characteristics of the patients		<i>n</i> = 48	Percent
Age (yr)	median (IQR)		63.5 (57.5-69.0)
	40-49	4	8.3
	50-59	10	20.8
	60-69	25	52.1
	70-79	9	18.8
Sex	Male	23	47.9
	Female	25	52.1
ECOG-PS	0	22	45.8
	1	24	50
	2	2	4.2
Duration since diagnosis (mo)	median (IQR)		7.0 (3.0-12.0)
Location of pancreatic cancer	Head	18	37.5
	Body and tail	17	35.4
	Recurrence after resection	13	27.1
Number of metastatic site	0	10	20.8
	1	18	37.5
	2	14	29.2
	≥ 3	6	12.5
Metastatic sites (> 5%)	Liver	28	58.3
	Peritoneum	16	33.3
	Distant lymph node	8	16.7
	Lung	6	12.5
Level of CA 19-9	Normal	10	20.8
	> ULN	38	79.2
Prior GEM CTx	GEM monotherapy	6	12.5
	GEM + Erlotinib	38	79.2
	GEM + Capecitabine	2	4.2
	GEM + Cisplatin	1	2.1
	GEM + Nab-paclitaxel	1	2.1
Period of prior CTx (mo)	median (IQR)		4.1 (1.9-7.8)
Prior treatment other than CTx	Operation	13	27.1
	CCRT	6	12.5

IQR: Interquartile range; ECOG-PS: Eastern Cooperative Oncology Group-performance status; CA 19-9: Carbohydrate antigen 19-9; GEM: Gemcitabine; ULN: Upper limit of the normal range; CCRT: Concurrent chemo-radiotherapy; CTx: Chemotherapy.

18 mo were 47.9%, 27.1%, and 6.3%, respectively, while the OS rates at 6, 12, and 18 mo were 60.4%, 37.5% and 10.4%, respectively. Eighteen patients (37.5%) survived more than 1 year. The estimated OS from the beginning of first-line treatment was 17.1 mo (95%CI: 10.6–23.6 mo). The median PFS and OS were respectively 5.4 and 8.4 mo for MPC patients, and 8.8 and 12.5 mo for LAPC patients. Analysis of changes in laboratory tests between before and after therapy showed that the median CA19-9 significantly decreased from 366.3 (1–16351) to 311.7 (2–16287) U/mL ($P = 0.041$).

Safety analysis

AEs that occurred in more than 5% of the 48 patients are listed in Table 3. Common AEs observed in more than 20% of patients were neutropenia (68.8%), fatigue (22.9%), nausea and vomiting (66.7%), diarrhea (35.4%), oral mucositis (31.3%), anorexia (20.8%), and fever (20.8%). Of a total of 511 AEs, 358 (70.1%) were considered related to therapy, and 163 (31.9%) were severe AEs (grade 3 or 4). The most common severe AE was neutropenia (64.6%), followed by febrile neutropenia and fatigue (16.7% for both). None of

the patients experienced severe nausea/vomiting or constipation. One patient died of septic shock related to grade 4 neutropenia after treatment.

Changes in QoL

The average body weight was 58.9 ± 9.81 kg at baseline and 59.0 ± 9.83 kg at the last visit. The average pain scale (Visual Analogue Scale) at baseline and the last visit were 2.12 ± 2.31 and 1.90 ± 2.15 , respectively. There were no significant changes in body weight and pain scale ($P = 0.93$ and $P = 0.71$, respectively). QoL questionnaires were available for 31 patients. The global health status scores of the EORTC QLQ-C30 did not worsen after treatment ($P = 0.548$). In general, most functional scores were not significantly decreased except role and cognitive functioning ($P = 0.044$ and $P = 0.015$, respectively) (Supplementary Table 1). Among symptom scores, fatigue and dyspnea were significantly worse than those in the pre-treatment period ($P = 0.021$ and $P = 0.038$, respectively). Among separate QLQ-PAN26 questions, worsening of dry mouth was observed ($P = 0.011$). In patients who achieved disease control ($n = 29$), the global health status score did not worsen after treatment,

Table 2 Tumor responses and survivals (intention-to-treat population)

	All (n = 48)	LAPC (n = 10)	MPC (n = 38)
Response, n (%)			
CR	1 (2.1)	0 (0.0)	1 (2.6)
PR	8 (16.7)	0 (0.0)	8 (21.1)
SD	21 (43.8)	8 (80.0)	13 (34.2)
PD	7 (14.6)	1 (10.0)	6 (15.8)
Could not be evaluated	11 (22.9)	1 (10.0)	10 (26.3)
ORR	9 (18.8)	0 (0.0)	9 (23.7)
DCR	30 (62.5)	8 (80.0)	22 (57.9)
Survival, mo (95%CI)			
Median PFS	5.8 (3.7-7.9)	8.8 (6.0-11.6)	5.4 (2.9-7.9)
Median OS (from 2 nd -line CTx)	9.0 (6.4-11.6)	12.5 (4.9-20.1)	8.4 (5.4-11.4)
Median OS (from 1 st -line CTx)	17.1 (10.6-23.6)	19.1 (13.8-24.4)	16.8 (8.8-24.8)

LAPC: Locally advanced pancreatic cancer; MPC: Metastatic pancreatic cancer; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate; CI: Confidence interval; PFS: Progression-free survival; OS: Overall survival; CTx: Chemotherapy.

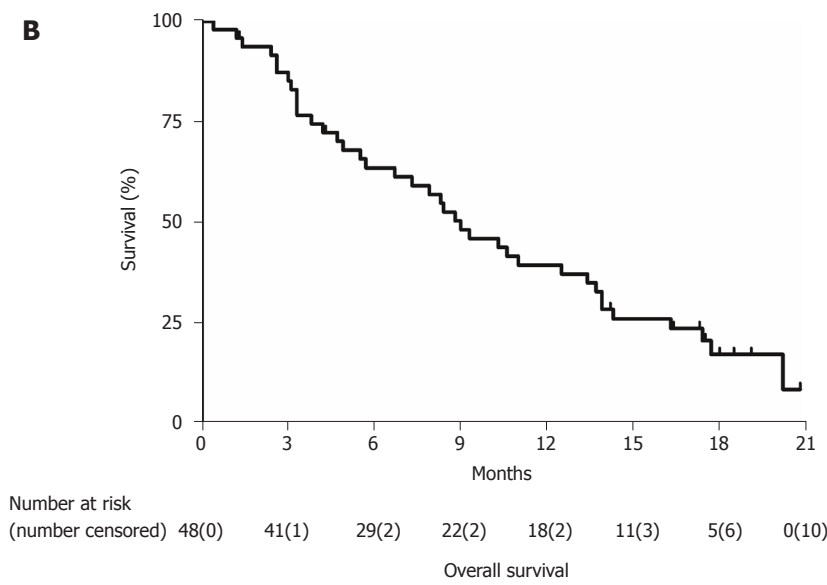
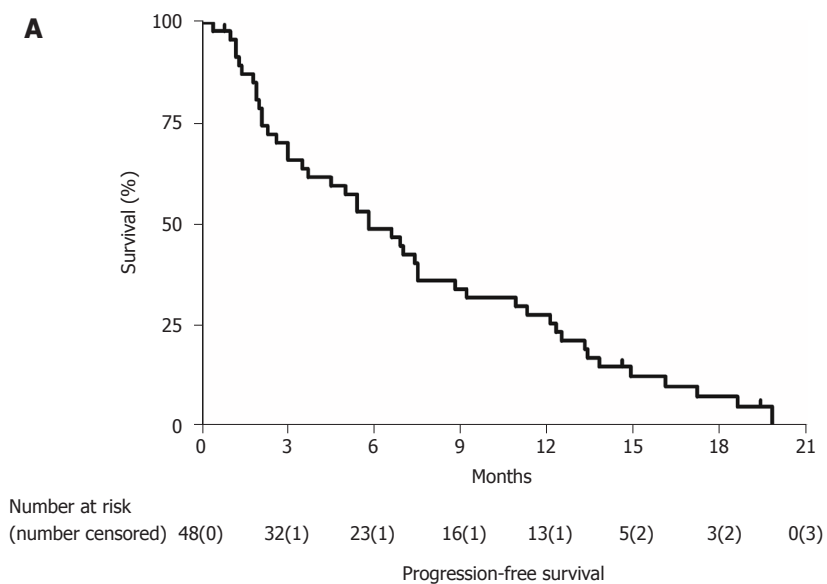


Figure 1 Kaplan-Meier analysis of survival data. A: The estimated median progression-free survival was 5.8 mo (95%CI: 3.7-7.9); B: The estimated median overall survival was 9.0 mo (95%CI: 6.4-11.6).

Table 3 Adverse events ($\geq 5\%$)

N = 48	n (%)	Intensity according to the NCI-CTCAE v4.03			
		Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic					
Fatigue	11 (22.9)	3 (6.3)	0	8 (16.7)	-
Nausea and vomiting	32 (66.7)	17 (35.4)	15 (31.3)	0	0
Diarrhea	17 (35.4)	7 (14.6)	9 (18.8)	1 (2.1)	0
Constipation	8 (16.7)	4 (8.3)	4 (8.3)	0	0
Oral mucositis	15 (31.3)	4 (8.3)	10 (20.8)	1 (2.1)	0
Anorexia	10 (20.8)	9 (18.8)	0	1 (2.1)	0
Peripheral neuropathy	7 (14.6)	6 (12.5)	0	1 (2.1)	0
Biliary tract infection	3 (6.3)	0	0	3 (6.1)	0
Fever	10 (20.8)	1 (2.1)	9 (18.8)	0	0
Hematologic					
Neutropenia	33 (68.8)	0	2 (4.2)	11 (22.9)	20 (41.7)
Thrombocytopenia	6 (12.5)	0	1 (2.1)	1 (2.1)	4 (8.3)
Febrile neutropenia	8 (16.7)	-	-	5 (10.4)	3 (6.3)

NCI: National Cancer Institute; CTCAE: Common Terminology Criteria for Adverse Events.

but some individual items including cognitive function, fatigue, digestive symptoms, and dry mouth were significantly worsened. Only one item (future worries) was significantly improved (Supplementary Table 2). In patients who completed 15 cycles, constipation and pancreatic pain were significantly improved by the end of treatment; only digestive symptoms were aggravated (Supplementary Table 3).

DISCUSSION

FOLFIRINOX with RIO showed an acceptable toxicity profile and promising efficacy as a second-line treatment for GEM-refractory unresectable PC. Although severe neutropenia occurred in almost 65% of participants, other severe AEs, particularly non-hematologic AEs, were infrequently reported. Moreover, the global health status scores of the EORTC QLQ-C30 were not changed significantly after treatment.

Second-line chemotherapy may be considered for many patients^[20]. At present, there is no recognized standard for patients with unresectable PC who experience PD after first-line chemotherapy, and PFS is consistently < 4 mo in patients receiving second-line chemotherapy. A meta-analysis showed that median OS was 6.0 mo with chemotherapy versus 2.8 mo with best supportive care^[21]. Patients whose cancers progress after first-line therapy have difficulty undergoing second-line chemotherapy since they are often older, unwell, and at risk of rapid deterioration^[22].

Only a few prospective trials have shown encouraging results with oxaliplatin plus 5-FU using various doses and schedules^[5,6,14,17,23]. Two phase III trials produced conflicting results. The CONKO-003 trial comparing 5-FU plus FA (FF) and oxaliplatin plus FF (OFF) showed survival benefits of second-line OFF in patients with unresectable GEM-refractory PC^[6]. In contrast, the PANCREOX trial evaluating the modified FOLFOX6 (mFOLFOX6) found no difference in PFS, while the OS

of mFOLFOX6 was inferior to that of FF^[24].

Research on irinotecan plus 5-FU as second-line chemotherapy for PC was also performed^[15,25]. The NAPOLI-1 phase III trial comparing nanoliposomal irinotecan (nal-IRI) alone or combined with FF showed that the combination of nal-IRI and FF was more effective than FF alone, but caused more frequent severe AEs^[7].

A recent comparative systematic review of four randomized trials evaluating oxaliplatin- or irinotecan-containing regimens as post-GEM therapies for patients with unresectable PC showed significant dissimilarity between them; therefore, it is unclear which regimen is best-suited for patients with unresectable PC previously treated with GEM^[26]. Table 4 summarizes clinical trials of second-line treatment for GEM-pre-treated unresectable PC. Our results using second-line FOLFIRINOX with RIO showed results that were superior to those in most previous trials.

Toxicities associated with standard FOLFIRINOX have prompted trials evaluating modifications of FOLFIRINOX^[8-10]. These previous studies of FOLFIRINOX modifications suggested that upfront dose attenuations of standard FOLFIRINOX can improve tolerability without reducing efficacy. A recent phase II trial showed that the efficacy of first-line FOLFIRINOX with reduced doses of the 5-FU bolus and irinotecan was comparable to that of the standard regimen; furthermore, neutropenia, vomiting, and fatigue were significantly reduced^[10]. However, only a few studies have evaluated FOLFIRINOX for patients with unresectable PC after failure of GEM-based chemotherapy; patients' performance statuses are likely to deteriorate after first-line treatment; necessitating second-line dose reductions as in our study. A Japanese phase II trial used modified FOLFIRINOX reducing only irinotecan for 18 MPC patients^[27]. Findings of that trial were consistent with our results except the PFS, which was longer in the present study (2.8 mo vs 5.8 mo).

FOLFIRINOX and nab-paclitaxel plus GEM are two

Table 4 Clinical trials of second-line treatment for gemcitabine pre-treated unresectable pancreatic cancer

Author (yr)	Type of study	Regimen	Patients, n	KPS ≥ 90 or ECOG ≤ 1, %	MPC, %	ORR, %	DCR, %	PFS/TFP, mo	OS, mo
Yoo <i>et al</i> ^[15] 2009	II	Modified FOLFIOX	30	97	100	7	17	6.0 wk	14.9 wk
		Modified FOLFIRI.3	31	100	100	0	23	8.3 wk	16.6 wk
Novarino <i>et al</i> ^[14] 2009	II	Oxaliplatin/5-FU/LV	23	73.9	69.6	0	23.5	11.6 wk ¹	17.1 wk
Pelzer <i>et al</i> ^[5] 2011	III	BSC	23	52.2	69.6	0	NA	NA	2.3
		Oxaliplatin/5-FU/LV (OFF)	23	47.8	73.9	0	NA	NA	4.8 (P = 0.008)
Chung <i>et al</i> ^[23] 2013	II	FOLFOX4	44	NA	100	11.4	40.9	9.9 wk ¹	31.1 wk
Oettle <i>et al</i> ^[6] 2014	III	5-FU/LV (FF)	84	47.6	88.1	NA	NA	2	3.3
		Oxaliplatin/5-FU/LV (OFF)	84	53.9	88.2	NA	NA	2.9 (P = 0.019)	5.9 (P = 0.01)
Zaanan <i>et al</i> ^[7] 2014	Prospective cohort	FOLFOX ²	27	44.4	100	0	36.4	1.7	4.3
Wang-Gillam <i>et al</i> ^[7] 2016	III	5-FU/LV	119	48	100	1	NA	1.5	4.2
		Nal-IRI/5-FU/LV	117	59	100	16	NA	3.1 (P < 0.001)	6.1 (P = 0.01)
		Nal-IRI	151	57	100	6	NA	2.7 (P = 0.1)	4.9 (P = 0.94)
Gill <i>et al</i> ^[24] 2016	III	Modified FOLFOX6	54	88.9	92.6	13.2	44.7	3.1	6.1
		Infusional 5FU/LV	54	94.3	94.4	8.5 (P = 0.36)	55.3	2.9 (P = 0.99)	9.9 (P = 0.02)
Present study	II	FOLFIRINOX with RIO	48 (MPC: 38)	95.8	79.2	18.8 (MPC: 23.7)	62.5 (MPC: 57.9)	5.8 (MPC: 5.4)	9 (MPC: 8.4)

¹Time to progression; First line therapy was GEM alone or FOLFIRI.3 alternating with GEM. KPS: Karnofsky Performance Scale; ECOG: Eastern Cooperative Oncology Group performance status; MPC: Metastatic pancreatic cancer; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression-free survival; TTP: Time to progression; OS: Overall survival; 5-FU: 5-fluorouracil; LV: Leucovorin; NA: Not available; II: Phase II study; III: Phase III study; BSC: Best supportive care; Nal-IRI: Nanoliposomal irinotecan; RIO: Reduced dosage of irinotecan and oxaliplatin.

Table 5 Comparison with previous studies focused on FOLFIRINOX as a second-line therapy

Author (yr)	Study characteristics			Patients characteristics			Treatment outcomes								
	Type	Dose modification	Patients, n	Age, median (range)	ECOG	Cancer status (%)	ORR, %	DCR, %	PFS, mo	OS, mo	NP	Fatigue	Nausea	Diarrhoea	
Assaf <i>et al</i> ^[25] 2011	Retro	Standard	27	63 (45-83)	1-3	MPC (100)	18.5	62.9	3	8.5	56	3.7	NA	11	
Lee <i>et al</i> ^[30] 2013	Retro	Standard	18	57 (44-68)	0-1	MPC (88.9) LAPC (11.1)	27.8	55.6	2.8	8.4	38.9	11.1	NA	38.9	
Kobayashi <i>et al</i> ^[27] 2017	II	Irinotecan 56% or 67%	18	63 (46-68)	0-1	MPC (100)	22.2	61.1	2.8	9.8	66.7	5.6	NA	0	
Present study	II	Irinotecan 67% Oxaliplatin 71%	48	64 (40-79)	0-2	MPC (79.2) LAPC (20.8)	All: 18.8 MPC: 23.7 LAPC: 0.0	All: 62.5 MPC: 57.9 LAPC: 80.0	All: 5.8 MPC: 5.4 LAPC: 8.8	All: 9.0 MPC: 8.4 LAPC: 12.5	64.6	16.7	16.7	0	2.1

AE: Adverse event; ECOG: Eastern Cooperative Oncology Group performance status; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression-free survival; OS: Overall survival; NP: Neutropenia; WHO-PS: World Health Organization performance status; II: Phase II study; Retro: Retrospective study; MPC: Metastatic pancreatic cancer; LAPC: Locally advanced pancreatic cancer; NA: Not available.

of the most effective first-line treatments for MPC, but the appropriate sequence of administration is unclear. A previous study in France concluded that nab-paclitaxel plus GEM appears to be effective, with a manageable toxicity profile, after FOLFIRINOX failure in patients with MPC^[28]. However, studies evaluating the reverse sequence of administration have not been performed to date. Only three studies have been performed evaluating second-line FOLFIRINOX following first-line GEM-based treatment (Table 5)^[27,29,30]. To our knowledge, this study is the first prospective multicenter phase II trial, which evaluated the efficacy and safety of FOLFIRINOX in GEM-refractory PC using

unique dose modification called “FOLFIRINOX with RIO”.

In our study, the relatively higher incidences of severe neutropenia may be related to the patients’ deteriorated physical status after first-line chemotherapy and the lack of prophylactic G-CSF support. For non-hematologic AEs, no grade 3 or 4 vomiting was observed, unlike in the PRODIGE 4/ACCORD 11 trial^[31]. This improved non-hematologic tolerability may be related to the routine administration of prophylactic palonosetron during every cycle of treatment. Peripheral neuropathy was also significantly reduced compared with the previous study, likely because of oxaliplatin dose reduction. In comparison with nal-IRI plus 5-FU regimen of the NAPOLI-1 trial, the preferred second-line therapy for MPC in current guidelines^[31,32], most severe non-hematologic AEs of the present study occurred at lower rates (diarrhea, 13% vs 2.1%; vomiting, 11% vs 0%; anorexia, 4% vs 2.1%)^[7]. However, the rate of severe neutropenia was much higher in the present study (27% vs 64.6%).

Considering QoL, some functional scales such as role and cognitive functioning were significantly reduced in our patients, and some symptom scales such as fatigue and dyspnea were significantly worsened. However, these changes were predictable given our patients’ ages and performance statuses. Global QoL indicators did not significantly deteriorate; moreover, the “physical functioning” QoL score (regarded as one of the strongest prognostic values^[33]) did not significantly worsen throughout treatment.

This study had several limitations. First, it was a non-randomized, single arm trial with a relatively small sample size. A prospective randomized trial including sufficient patients is warranted to provide the clinical recommendation about the treatment sequence for MPC. Second, we included patients with LAPC and MPC who were treated with various prior GEM-based regimens. This heterogeneity in patient population and first-line chemotherapy regimens needs to be improved in future research.

In conclusion, FOLFIRINOX with RIO showed encouraging results in terms of efficacy, with an acceptable safety profile. In addition to nal-IRI plus 5-FU regimen, FOLFIRINOX with RIO may be considered as a treatment option in patients with GEM-refractory unresectable PC. Because the condition of such patients can quickly deteriorate owing to rapid disease progression and treatment toxicity, this regimen may provide acceptable tolerability for patients in terms of patient QoL. However, the presence of hematologic toxicities should be carefully observed, nevertheless, and the routine use of G-CSF should be considered to minimize the risk of hematologic toxicities.

ARTICLE HIGHLIGHTS

Research background

Proper second-line treatment can improve survival of patients with unresectable

pancreatic cancer (PC) who fail first-line treatment with gemcitabine (GEM)-based regimen. Although some previous phase III trials showed survival improvement with their study regimens, the standard second-line treatment remains unclear.

Research motivation

FOLFIRINOX, a standard first-line treatment for PC, has been proposed as a second-line treatment regimen; however, concerns about relatively high toxicity limited broad use of FOLFIRINOX as a second-line therapy.

Research objectives

We evaluated the efficacy and safety of modified dose of FOLFIRINOX as a second-line treatment for GEM-refractory unresectable PC.

Research methods

In this prospective, multicenter, one-arm, open-label, phase II trial, unresectable PC patients, who showed disease progression during GEM-based therapy were enrolled. All patients were administered FOLFIRINOX with reduced irinotecan and oxaliplatin (RIO; irinotecan 120 mg/m² and oxaliplatin 60 mg/m²), which was set according to the previous phase I study of FOLFIRINOX, with the standard dose of 5-fluorouracil (5-FU). The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events, and changes in quality of life (QoL) were evaluated.

Research results

A total of 48 patients were enrolled in eight Korean centers. The ORR and DCR were 18.8% and 62.5%, respectively, including one patient who showed complete remission. The median PFS was 5.8 mo [95% confidence interval (CI): 3.7-7.9] and median OS was 9.0 mo (95%CI: 6.4-11.6). Neutropenia (64.6%) was the most common grade 3-4 adverse event. Although 14.6% of patients experienced grade 3 fatigue, most non-hematologic AEs were under grade 2. In the QoL analysis, the global health status score before treatment was not different from the score at the last visit after treatment (45.43 ± 22.88 vs 48.66 ± 24.14, *P* = 0.548).

Research conclusions

FOLFIRINOX with RIO showed acceptable tolerability for patients in terms of patient QoL and may be considered as a treatment option in patients with GEM-refractory unresectable PC. However, the presence of hematologic toxicities should be carefully observed and the routine use of granulocyte colony-stimulating factor should be considered to minimize the risk of hematologic toxicities.

Research perspectives

Prospective study with larger population comparing the efficacy and safety between FOLFIRINOX with RIO and 5-FU plus leucovorin needs to be conducted.

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