The Efficacy and Safety of Treatment Regimens Used in the First-Line Setting in Metastatic Pancreatic Cancer Patients

A Multicenter Real-Life Study

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Objective: The aim of the study is to compare the efficacy and safety of 3 chemotherapy regimens used as first-line treatments in the real-life management of metastatic pancreatic cancer.

Methods: A total of 218 patients were included in this multicenter study. Gemcitabine (Gem, n = 71), gemcitabine-cisplatin (Gem-Cis, n = 91), and FOLFIRINOX (a combination of leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin [FFX], n = 56) treatments were compared.

Results: Overall response rate was significantly higher in the FFX group (50.0%) than in the Gem (28.2%) and Gem-Cis (27.5%) groups ($P = 0.010$). Median progression-free survival (8.4 vs 4.6 and 5.5 months, respectively, $P < 0.001$) and overall survival (16.4 vs 8.1 and 8.7 months, respectively, $P = 0.002$) were significantly longer in the FFX group than in the Gem and Gem-Cis groups. Toxicity of any grade was noted in 46 (64.8%), 56 (61.5%), and 49 (87.5%) patients in the Gem, Gem-Cis, and FFX groups, respectively ($P = 0.003$).

Conclusions: In our study, FFX regimen provides a significant advantage over the other treatment regimens in terms of response rates and survival. Treatment toxicity was more frequent but manageable with the FFX regimen.

Key Words: efficacy, first-line chemotherapy, FOLFIRINOX, gemcitabine, gemcitabine-cisplatin, metastatic pancreatic cancer

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Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths worldwide. Despite years of efforts, the 5-year relative survival rate in PC remains to be 8% for all stages and declines further to 3% for patients with metastatic disease at the time of diagnosis.[1] One of the major causes of the poor prognosis of PC is that more than half of patients have distant metastases at the time of diagnosis.[2]

Systemic chemotherapy continues to be the basis of the treatment, often in patients with metastatic pancreatic cancer (mPC). Gemcitabine replaced 5-fluorouracil (5-FU) as the first-line option for PC patients with a 1.2-monthly increase in median overall survival (OS) in 1997.[3] However, survival has been limited to 6 months because of the resistance capacity of cancer cells and their surrounding microenvironment to cytotoxicity. Afterward, more aggressive treatment regimens have been developed to overcome these resistance mechanisms.[4]

The first randomized phase 3 study of gemcitabine and cisplatin combination therapy in mPC, relying on different pharmacodynamics properties of chemotherapeutic agents, was conducted in 2002. In the study by Colucci et al,[5] gemcitabine and cisplatin combination therapy was compared with the gemcitabine monotherapy in patients with locally advanced or mPC and the response rate and progression-free survival (PFS) were demonstrated to be significantly better in the combination arm. Later, in 2011, Conroy et al[6] showed that the FOLFIRINOX (5-FU, folinic acid, irinotecan, and oxaliplatin [FFX]) regimen provided a clinically significant PFS and OS advantage compared with gemcitabine, which was an important milestone in the treatment of mPC. After this study, the FOLFIRINOX regimen started to be used as a first-line treatment option for fit patients with good performance status (PS). However, significant toxicities have been reported compared with monotherapy, while the frequency of adverse events has also been reported to be lowered via dose modifications without compromising treatment efficacy.[7]

This multicenter real-life study aimed to compare the efficacy and toxicity outcomes of 3 different chemotherapy regimens used in the first-line treatment of mPC.

MATERIALS AND METHODS

Study Population

A total of 218 patients with mPC at the time of initial presentation were included in this study conducted between January 2015 and September 2020 at 7 different oncology clinics across Turkey. Patients older than 18 years, with histologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma, and stage 4 disease at the time of initial diagnosis were included. Patients with malignancies other than pancreatic cancer, those who underwent surgery, those with a local or locally advanced stage at diagnosis, those who had previously received adjuvant or palliative chemotherapy, and those with a history of radiotherapy were excluded. Data on age, sex, PS, tumor location, metastasis sites, laboratory parameters, treatment modalities, PFS and OS time, and toxicity were retrospectively retrieved from hospital records.

The PS of the patients was determined according to the Eastern Cooperative Oncology Group (ECOG) PS criteria. The study was approved by the Dicle University School of Medicine ethics review board and conducted in compliance with the ethical principles according to the Declaration of Helsinki (approval no: 59/2020).

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Treatment

In the gemcitabine monotherapy group (Gem), gemcitabine 1000 mg/m^2 was administered on days 1, 8, 15, and 30-minute intravenous (IV) infusion every 28 days. In the gemcitabine-cisplatin group (Gem-Cis), gemcitabine 1000 mg/m^2 was administered by 30-minute IV infusion on days 1 and 8, and cisplatin 75 mg/m^2 is administered by IV infusion for 2 hours on day 1 and every 21 days. In the FFX group, the standard regimen is as follows: 85 mg/m^2 of oxaliplatin by IV infusion for 2 hours, 180 mg/m^2 of irinotecan by IV infusion for 90 minutes, and 400 mg/m^2 of leucovorin by IV infusion for 2 hours, followed by bolus 400 mg/m^2 5-FU on day 1 and then administered every 14 days together with 2400 to 3000 mg/m^2 5-FU as infusion for 46 hours. In the modified FFX regimen (mFFX), unlike the standard regimen, a bolus of 400 mg/m^2 of 5-FU was not administered on the first day or the irinotecan dose is administered as 150 mg/m^2. Treatment was continued until the development of progression or unacceptable adverse events. Filgrastim was recommended as primary prophylaxis for FFX and mFFX groups.

Assessments

All patients who were included in the study had pretreatment radiologic evaluation, which had been done with computed tomography. Tumor response was assessed in every 3 cycles or in case of finding a clinical progression. The radiologic responses of the treatment were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) by patients' computed tomographies and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was defined as CR or PR and disease control rate (DCR) was defined as the sum of the PR, SD and CR. Toxicity assessment was performed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Serum carcinoembryonic antigen (CEA) levels lower than 4 ng/mL, serum carbohydrate antigen 19-9 (CA 19-9) levels lower than 37 U/mL, and serum albumin levels higher than 3.5 g/dL were considered as normal.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp, Armonk, NY). Pearson χ^2 and/or Fisher exact tests were used to compare the categorical variables, while Kruskal-Wallis test was used for analysis of numerical variables. Overall survival was calculated as the date of diagnosis until the date of the most recent follow-up or death. Progression-free survival was computed from the date of diagnosis to disease progression or the most recent follow-up or death whichever occurred first. The OS and PFS rates were estimated with the Kaplan-Meier method. Determination of survival by univariate analysis was performed with log rank test. In multivariate analysis, independent factors in predicting survival were analyzed by using the backward method and Cox regression analysis using the probable factors determined in previous analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 218 patients were included in the study. There were 71, 91, and 56 patients in Gem, Gem-Cis, and FFX groups, respectively. The median age at diagnosis was 62 years (range, 30–85 years) overall, 68 years (range, 50–85 years) in Gem group, 62 years (range, 30–81 years) in Gem-Cis group, and 55 years (range, 34–78 years) in FFX group ($P < 0.001$). Forty patients (56.3%) were male in the Gem group, 69 (75.8%) were male in the Gem-Cis group, and 39 (69.6%) were male in the FFX group ($P = 0.029$). The groups were similar in terms of primary tumor location (head, neck, or tail) and liver and lung metastases ($P = 0.422$, $P = 0.082$, and $P = 0.093$, respectively). The highest rate of peritoneal metastasis was noted in the FFX group (37.5%), followed by the Gem (28.2%) and Gem-Cis (14.3%) groups ($P = 0.005$). The highest percentage of ECOG PS 2 patients was noted in the Gem group (39.4%), followed by FFX (16.1%) and Gem-Cis (8.8%) groups ($P < 0.001$). The median number of treatment cycles was higher in the FFX group compared with the other 2 groups (7, 4, and 4, respectively, $P < 0.001$). While there was no significant difference between the groups in terms of median baseline CEA levels ($P = 0.188$), the difference in baseline CA 19-9 level showed a strong tendency toward statistical significance ($P = 0.056$). Baseline albumin levels were lower in Gem and Gem-Cis groups compared with FFX group ($P < 0.001$). Patient and tumor characteristics are summarized in Table 1.

Response to Therapy

Complete response was noted in 1 patient (1.4%) in Gem group and in 2 patients (3.6%) in FFX group. Partial response rate was higher in the FFX group (46.4%, 26 patients) compared with the other 2 groups (28.8% and 27.5%, respectively, $P = 0.051$). Objective response rate was 50% in the FFX group and was higher than ORR achieved in the Gem (28.2%) and Gem-Cis (27.5%) groups ($P = 0.010$). Disease control rate in Gem, Gem-Cis, and FFX groups were 52.1%, 57.1%, and 64.3%, respectively, with no significant difference between the treatment groups ($P = 0.387$; Table 2).

Dose reduction from the first cycle was made in 9 (12.7%), 10 (11%), and 15 (26.8%) patients in the Gem, Gem-Cis, and FFX groups, respectively ($P = 0.027$). In subsequent cycles, dose reductions were made in 4 (5.6%), 13 (14.3%), and 33 (58.9%) patients in the Gem, Gem-Cis, and FFX groups, respectively ($P < 0.001$). In the FFX group, 19 patients (33.9%) were treated with the standard regimen and 37 patients (66.1%) with the modified regimen. The number of patients who could receive second-line treatment was 28 (39.4%), 51 (56%), and 32 (57.1%) in the Gem, Gem-Cis, and FFX groups, respectively ($P = 0.062$).

Survival

The median duration of follow-up was 8.8 months (range, 1.2–52.3 months). Overall mortality occurred in 187 patients (85.8%) and in 69 (97.2%), 82 (90.1%), and 36 (64.3%) patients in Gem, Gem-Cis, and FFX groups, respectively. The median PFS (mPFS) for all patients was 5.7 months (95% CI, 5.2–6.3 months), 4.6 months (95% CI, 3.3–5.8 months) in the Gem group, 5.5 months (95% CI, 4.5–6.5 months) in the Gem-Cis group, and 8.4 months (95% CI, 6.1–10.6 months) in the FFX group ($P < 0.001$). No significant difference was noted between Gem and Gem-Cis groups in terms of PFS ($P = 0.215$). The median OS (mOS) for all patients was 10 months (95% CI, 8.6–11.4 months), 8.1 months (95% CI, 6.5–9.7 months) in the Gem group, 8.7 months (95% CI, 6.2–11.1 months) in the Gem-Cis group, and 16.4 months (95% CI, 7.1–25.7 months) in the FFX group ($P = 0.002$). There was no significant difference between the Gem and Gem-Cis groups in terms of OS ($P = 0.300$; Fig. 1). The mPFS was 8.4 months (95% CI, 5.9–10.8 months) in the group receiving the standard FFX regimen and 8.5 months (95% CI, 5.0–12.0 months) in the group receiving the mFFX regimen, with no significant difference between them in terms of PFS ($P = 0.505$). The mOS was 11.7 months (95% CI, 2.2–21.2 months) in the standard FFX regimen group and 16.4 months (95% CI, 5.5–27.3 months) in the mFFX regimen group with no significant difference between them in terms of OS ($P = 0.460$; Fig. 2).

TABLE 1. Baseline Patient and Tumor Characteristics

Characteristics	Gemcitabine (n = 71)	Gemcitabine + Cisplatin (n = 91)	FOLFIRINOX (n = 56)	*P*
Sex, n (%)				0.029
Female	31 (43.7)	22 (24.2)	17 (30.4)	
Male	40 (56.3)	69 (75.8)	39 (69.6)	
ECOG PS, n (%)				<0.001
0	5 (7)	19 (20.9)	19 (33.9)	
1	38 (53.5)	64 (70.3)	28 (50.0)	
2	28 (39.4)	8 (8.8)	9 (16.1)	
Primary tumor site, n (%)				0.422
Head	39 (54.9)	50 (54.9)	27 (48.2)	
Body	17 (23.9)	20 (22)	20 (35.7)	
Tail	15 (21.2)	21 (23.1)	9 (16.1)	
Liver metastasis, n (%)				0.082
Yes	58 (81.7)	75 (82.4)	38 (67.9)	
No	13 (18.3)	16 (17.6)	18 (32.1)	
Lung metastasis, n (%)				0.093
Yes	25 (35.2)	27 (29.7)	10 (17.9)	
No	46 (64.8)	64 (70.3)	46 (82.1)	
Peritoneal metastasis, n (%)				0.005
Yes	20 (28.2)	13 (14.3)	21 (37.5)	
No	51 (71.8)	78 (85.7)	35 (62.5)	
Age, median (range), y	68 (50–85)	62 (30–81)	55 (34–78)	<0.001
No. cycles, median (range)	4 (1–23)	4 (1–12)	7 (2–22)	<0.001
CEA level, median (range), ng/mL	11.5 (0.3–40,575)	6.4 (0.1–1918)	7.3 (1.4–2627)	0.188
CA 19-9, median (range), U/mL	1030 (0.6–109,321)	788 (0.6–92,474)	496 (0.6–62,415)	0.056
Albumin, median (range), g/dL	3.4 (1.6–4.6)	3.5 (1.6–4.9)	3.9 (2.2–5.2)	<0.001

CA 19-9 indicates carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFIRINOX, oxaliplatin,irinotecan, fluorouracil, and leucovorin.

Prognostic Factors

The univariate analysis revealed the prognostic factors for PFS to be chemotherapy regimens ($P < 0.001$) and albumin level ($P = 0.018$), whereas prognostic factors for OS were chemotherapy regimens ($P < 0.001$), age ($P = 0.024$), ECOG PS ($P = 0.011$), and albumin level ($P = 0.018$; Table 3). In the multivariate analysis, the FFX group was shown to have a PFS advantage over the Gem group, and the level of CEA was also an independent prognostic factor for PFS (HR, 0.54; 95% CI, 0.37–0.87; $P = 0.011$ and HR, 1.54; 95% CI, 1.03–2.31; $P = 0.037$, respectively). In the multivariate analysis, receiving FFX was determined to be associated with a 45% lesser likelihood of mortality compared with receiving Gem (HR, 0.55; 95% CI, 0.34–0.87; $P = 0.010$). In addition, it was observed that those with ECOG PS 2 had a shorter OS than those with PS 0–1 (HR, 1.70; 95% CI, 1.09–2.63; $P = 0.019$; Table 4).

Toxicity

Any toxicity related to the treatment was reported in 151 patients (69.3%) overall and in 46 (64.8%), 56 (61.5%), and 49 (87.5%) patients in the Gem, Gem-Cis, and FFX groups, respectively ($P = 0.003$). Among the grade 1–2 toxicities, those seen more frequently in the FFX group than in the Gem and Gem-Cis groups were as follows: weakness/fatigue (53.6%, 43.7%, and 30.8%, respectively, $P = 0.001$), nausea/vomiting (50%, 25.4%, and 27.5%, respectively, $P = 0.019$), diarrhea (19.6%, 8.5%, and 7.7%, respectively, $P = 0.001$), mucositis (19.6%, 7%, and 3.3%, respectively,

TABLE 2. Response to Treatment

	Gemcitabine (n = 71), n (%)	Gemcitabine + Cisplatin (n = 91), n (%)	FOLFIRINOX (n = 56), n (%)	*P*
Best response				0.051
CR	1 (1.4)	0 (0)	2 (3.6)	
PR	19 (26.8)	25 (27.5)	26 (46.4)	
SD	17 (23.9)	27 (29.7)	8 (14.3)	
PD	34 (47.9)	39 (42.9)	20 (35.7)	
ORR	20 (28.2)	25 (27.5)	28 (50)	0.010
DCR	37 (52.1)	52 (57.1)	36 (64.3)	0.387

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate (CR or PR); DCR, disease control rate (CR or PR or SD); FOLFIRINOX, oxaliplatin,irinotecan, fluorouracil, and leucovorin.

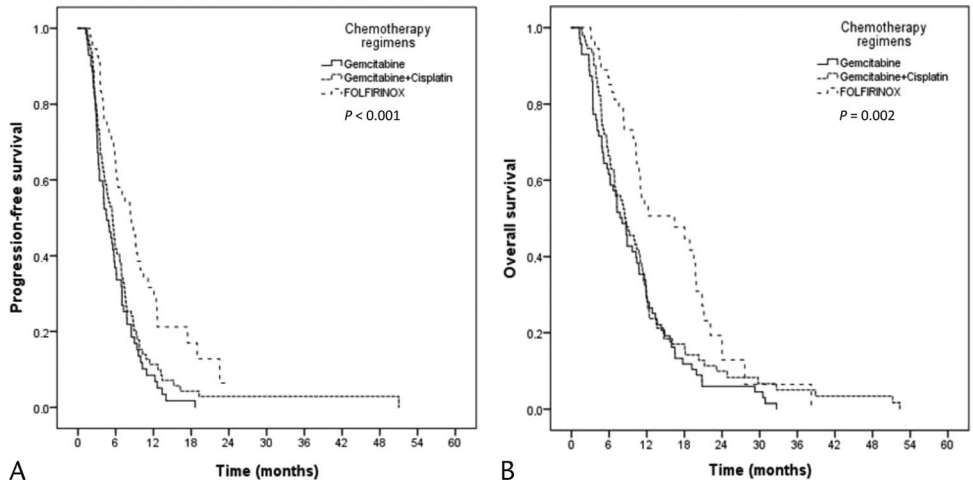

FİGURE 1. Kaplan-Meier curves of PFS (A) and OS (B) according to treatment groups.

$P = 0.001$), and neutropenia (35.7%, 14.1%, and 17.6%, respectively, $P < 0.001$). The rate of thrombocytopenia was not significantly different between FFX, Gem, and Gem-Cis groups (26.8%, 15.5%, and 14.3%, respectively, $P = 0.075$). Grade 1–2 sensory neuropathy and nephrotoxicity were not seen in the Gem group, neuropathy was more common in the FFX group than in the Gem-Cis group (19.6% and 6.6%, respectively, $P = 0.003$), and nephrotoxicity was more common in the Gem-Cis group than in the FFX group (9.9% and 3.6%, respectively, $P = 0.025$). Febrile neutropenia was seen in 1 patient (1.4%) in the Gem group and in 1 patient (1.1%) in the Gem-Cis group, and it was more common in the FFX group with grade 1–2 in 3 patients (5.4%) and grade 3–4 in 4 patients (7.1%, $P = 0.002$). Of the grade 3–4 toxicities, weakness/fatigue and mucositis were seen only in the FFX group (5.4% and 3.6%, respectively). Grade 3–4 diarrhea (10.7%, 0, 2.2%, respectively) and neutropenia (25%, 4.2%, and 5.5%, respectively) were seen more frequently in the FFX group than in the Gem and Gem-Cis groups (Table 5). No treatment-related death was observed.

DISCUSSION

In this study, we evaluated 3 different chemotherapy regimens in terms of efficacy and tolerability in the first-line treatment of pancreatic cancer diagnosed at the metastatic stage. Objective response rate was higher in the FFX group than in the Gem and Gem-Cis groups. There was no statistically significant difference between the DCR of the treatment groups. The mPFS and mOS were longer in the FFX group compared with the other 2 groups. There was no statistically significant difference in mPFS and mOS between patients receiving the standard FFX regimen and those receiving the mFFX regimen. Any grade of toxicity was higher in the FFX group than in the other 2 groups. Among grade 1–2 toxicities, weakness/fatigue, nausea/vomiting, diarrhea, mucositis, and neutropenia were more common in the FFX group compared with the other 2 groups. No significant difference was noted between the treatment groups in terms of thrombocytopenia. Grade 1–2 sensory neuropathy was more common in the FFX group than in the Gem-Cis group, and nephrotoxicity was more common in the Gem-Cis group than in the FFX group. Febrile neutropenia was more common in the FFX group than in the other 2 groups. Among grade 3–4 toxicities, weakness/fatigue and mucositis were seen only in the FFX group. In addition, grade 3–4 diarrhea and neutropenia were more common in the FFX group than in the other groups.

Pancreatic cancer is often diagnosed at the metastatic stage and is associated with a poor prognosis.[8] The main goal of the treatment at this stage is to provide palliative care and to improve survival. Several studies to date have addressed the treatment of metastatic pancreatic cancer, and treatment regimens currently considered as the standard first-line treatments include gemcitabine

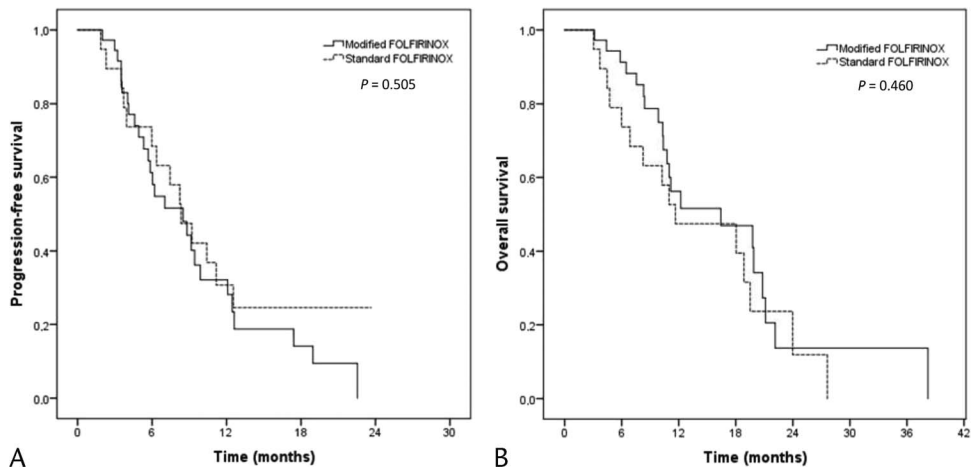

FİGURE 2. Kaplan-Meier curves of PFS (A) and OS (B) according to standard and modified FOLFIRINOX groups.

TABLE 3. Univariate Analysis of PFS and OS

Variables	mPFS (95% CI), mo	*P*	mOS (95% CI), mo	*P*
Chemotherapy regimens		<0.001		0.002
Gemcitabine	4.6 (3.28–5.85)		8.1 (6.47–9.70)	
Gemcitabine + cisplatin	5.5 (4.54–6.50)		8.7 (6.22–11.13)	
FOLFIRINOX	8.4 (6.07–10.62)		16.4 (7.11–25.74)	
Age, y		0.210		0.024
<65	5.9 (5.15–6.62)		10.3 (8.76–11.88)	
≥65	5.0 (3.80–6.18)		7.8 (4.11–11.40)	
Sex		0.405		0.880
Female	5.3 (4.28–6.37)		10.12 (8.25–11.99)	
Male	5.9 (5.35–6.42)		9.9 (7.88–11.84)	
ECOG PS		0.170		0.011
0–1	5.9 (5.21–6.54)		10.3 (8.84–11.80)	
2	3.7 (2.80–4.63)		7.1 (3.23–10.90)	
Primary tumor site		0.938		0.092
Head of pancreas	5.7 (5.22–6.15)		8.2 (6.42–11.00)	
Other	5.9 (4.30–6.29)		11.5 (10.15–12.78)	
Liver metastasis		0.875		0.854
No	5.9 (2.68–9.10)		9.0 (6.98–11.09)	
Yes	5.7 (5.03–6.34)		10.3 (8.50–12.01)	
Lung metastasis		0.918		0.680
No	5.6 (4.66–6.44)		9.7 (8.34–11.10)	
Yes	6.1 (4.93–7.23)		11.34 (8.91–13.76)	
Peritoneal metastasis		0.647		0.981
No	5.6 (4.75–6.40)		10.12 (8.32–11.92)	
Yes	5.9 (4.30–7.47)		9.0 (6.53–11.54)	
Level of CEA		0.174		0.222
Normal	6.9 (5.18–8.62)		10.7 (8.33–13.15)	
Abnormal	5.4 (4.50–6.35)		10.0 (8.34–11.63)	
Level of CA 19-9		0.403		0.762
Normal	5.9 (3.46–8.30)		9.9 (6.95–12.76)	
Abnormal	5.7 (5.16–6.27)		10.3 (8.69–11.94)	
Level of albumin		0.018		0.003
Normal	6.4 (5.41–7.34)		7.9 (5.96–9.75)	
Abnormal	4.5 (2.94–5.99)		11.2 (9.91–12.43)	

CA 19-9 indicates carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFIRINOX, oxaliplatin, irinotecan, fluorouracil, and leucovorin; OS, overall survival; PFS, progression-free survival.

monotherapy, FOLFIRINOX, gemcitabine plus albumin-bound paclitaxel, and gemcitabine plus cisplatin treatments specifically used for hereditary pancreatic cancer patients with DNA repair mutations.[3,6,9,10]

In a study by Colucci et al,[5] the ORR was reported to be significantly higher in Gem-Cis arm than in the Gem arm (26.4 vs 9.2%, $P = 0.020$). However, in another phase 3 study, the ORR was 10.1% in the Gem arm and 12.9% in the Gem-Cis arm, and

TABLE 4. Multivariate Analysis of Potential Prognostic Factors Associated With PFS and OS

	PFS		OS	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Chemotherapy regimens		0.018		0.016
Gemcitabine + cisplatin vs gemcitabine	0.93 (0.60–1.45)	0.754	0.99 (0.65–1.51)	0.978
FOLFIRINOX vs gemcitabine	0.54 (0.37–0.87)	0.011	0.55 (0.34–0.87)	0.010
ECOG PS 2 vs PS 0–1	1.50 (0.95–2.38)	0.084	1.70 (1.09–2.63)	0.019
CEA, abnormal vs normal	1.54 (1.03–2.31)	0.037	—	

CEA indicates carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFIRINOX, oxaliplatin, irinotecan, fluorouracil, and leucovorin; HR, hazard ratio.

TABLE 5. Toxicity Profile of the Treatment Regimens

	Gemcitabine (n = 71), n (%)		Gemcitabine + Cisplatin (n = 91), n (%)		FOLFIRINOX (n = 56), n (%)		
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	*P*
Toxicity							
Weakness/fatigue	31 (43.7)	0	28 (30.8)	0	30 (53.6)	3 (5.4)	0.001
Nausea/vomiting	18 (25.4)	1 (1.4)	25 (27.5)	3 (3.3)	28 (50)	2 (3.6)	0.019
Diarrhea	6 (8.5)	0	7 (7.7)	2 (2.2)	11 (19.6)	6 (10.7)	0.001
Mucositis	5 (7)	0	3 (3.3)	0	11 (19.6)	2 (3.6)	0.001
Neutropenia	10 (14.1)	3 (4.2)	16 (17.6)	5 (5.5)	20 (35.7)	14 (25)	<0.001
Thrombocytopenia	11 (15.5)	1 (1.4)	13 (14.3)	6 (6.6)	15 (26.8)	5 (8.9)	0.075
Sensory neuropathy	0	0	6 (6.6)	1 (1.1)	11 (19.6)	1 (1.8)	0.003
Nephrotoxicity	0	0	9 (9.9)	3 (3.3)	2 (3.6)	1 (1.8)	0.025
Febrile neutropenia	1 (1.4)	0	1 (1.1)	0	3 (5.4)	4 (7.1)	0.002

FOLFIRINOX indicates oxaliplatin, irinotecan, fluorouracil, and leucovorin.

no significant difference was detected ($P = 0.370$).[11] In the pivotal study comparing the FFX and Gem arms, the ORR was reported to be 31.6% and 9.4%, respectively, being significantly higher in the FFX arm compared with the single-agent arm ($P < 0.001$).[6] In our study, the ORR was similar in the Gem (28.2%) and Gem-Cis (27.5%) groups and was significantly higher in the FFX group (50.0%) than in both Gem and Gem-Cis groups ($P = 0.010$).

In a phase 3 study, the mPFS was reported to be 3.9 months in the Gem arm and to be 3.8 months in the Gem-Cis arm with no significant difference between the treatment arms in terms of mPFS ($P = 0.800$). In addition, the mOS was 8.3 and 7.2 months in the Gem and Gem-Cis arms, respectively, and the difference was not statistically significant ($P = 0.380$).[11] In another phase 3 study, the mPFS was 3.1 months in the Gem arm and 5.3 months in the Gem-Cis arm, and it was statistically longer in the combination arm ($P = 0.053$). However, no difference was found in mOS between the Gem and Gem-Cis arms (7.5 vs 6 months, $P = 0.150$).[12] In the first randomized study comparing the Gem and Gem-Cis arms, the mOS was 5 and 6 months, respectively, and no statistically significant difference was found ($P = 0.430$).[5]

In the randomized phase 3 study comparing the FFX and Gem arms, the mPFS was 6.4 and 3.3 months, respectively, and was longer in the FFX arm ($P < 0.001$). The mOS was also longer in the FFX arm than in the Gem arm (11.1 vs 6.8 months, $P < 0.001$).[6] In a retrospective study, the mPFS was 6 months in the FFX arm and 3 months in the Gem arm, and the difference was not statistically significant ($P = 0.100$). In the same study, the mOS was 11 months in the FFX arm and 8 months in the Gem arm, and the difference was statistically significant ($P = 0.030$).[13]

In a retrospective study comparing the standard and modified FFX groups, the mPFS was 8.9 and 8.1 months, respectively, and no statistically significant difference was detected ($P = 0.810$). In addition, the mOS was 13.4 months in the standard FFX group and 12.1 months in the mFFX group, and the difference was not statistically significant ($P = 0.540$).[14] In another study, the mPFS was reported to be 6.2 months in the standard FFX group and 8.7 months in the mFFX group, while the mOS was reported to be 13.1 and 12.9 months in standard and mFFX groups, respectively.[15]

In our study, the mPFS was 4.6 months in the Gem group, 5.5 months in the Gem-Cis group, and 8.4 months in the FFX group ($P < 0.001$). Although there was no statistical difference in PFS between the Gem and Gem-Cis groups, PFS was significantly longer in the FFX group compared with the other 2 groups. The mOS was 8.1 months in the Gem group, 8.7 months in the Gem-Cis group, and 16.4 months in the FFX group ($P = 0.002$). Although there was no statistical difference in OS between the Gem and Gem-Cis groups, the FFX group had longer OS than the other 2 groups. Gem-Cis treatment may provide marginal survival benefit but was not statistically significant and is not routinely used. In our study, the mPFS was 8.4 months in the group receiving the standard FFX regimen and 8.5 months in the group receiving the mFFX regimen, with no significant difference between them ($P = 0.505$). The mOS was 11.7 months in the group receiving the standard FFX regimen and 16.4 months in the group receiving the mFFX regimen, and no statistically significant difference in OS was found between them ($P = 0.460$). Our results were consistent with the literature.

The correct identification of prognostic factors can guide the selection of treatment protocol. Studies on prognostic factors in pancreatic cancer revealed the potential value of several prognostic factors.[16,17] In a study by Heinemann et al,[12] PS was reported to be an independent prognostic factor. In another retrospective study comparing Gem and Gem-Cis treatments, it was reported that survival was shorter in patients with low albumin levels and liver metastases.[18] In a randomized phase 3 study comparing the FFX and Gem arms, synchronized metastases, low baseline albumin level, hepatic metastases, and being older than 65 years were identified as independent adverse prognostic factors for OS.[6] In our study, it was found that the FFX group had a PFS advantage over the Gem group, and the level of CEA was also an independent prognostic factor for PFS ($P = 0.011$ and $P = 0.037$, respectively). There was a 45% decrease in mortality in the FFX group compared with the Gem group ($P = 0.010$), but shorter OS was observed in those with ECOG PS 2 compared with those with PS 0–1 ($P = 0.019$).

In a study by Colucci et al[5] comparing the Gem and Gem-Cis treatment arms, the authors reported that the rates of grade 1–2 nausea/vomiting (51% vs 61%, respectively), diarrhea (9% vs 10%, respectively), mucositis (4% vs 6%, respectively), neutropenia (7% vs 12%, respectively), and thrombocytopenia (28% vs 31%, respectively) were not statistically different between the groups. However, grade 1–2 weakness/fatigue was more common in the combination arm (24% vs 9%, respectively). The weakness/fatigue was not reported among grade 3–4 toxicities, and mucositis was reported in only one patient in the Gem arm and diarrhea in 2 patients in the combination arm. In addition, rate of grade 3–4 thrombocytopenia was reported to be 2% in both arms, neutropenia rate was 18% in the combination arm and 9% in the Gem arm, but no statistical difference was detected.[5]

Conroy et al[6] compared the FFX and Gem arms, and among grade 3–4 toxicities, neutropenia (45% vs 21%, respectively), thrombocytopenia (9.1% vs 3.6%, respectively), diarrhea (12.7% vs 1.8%,

respectively), and sensory neuropathy (9% vs 0%, respectively) were more common in the combination arm. There was no statistical difference between the groups in terms of grade 3–4 weakness/fatigue (23.6% vs 17.8%, respectively) and nausea/vomiting (14.5% vs 8.3%, respectively). In addition, febrile neutropenia was more common in the FFX arm (5.4% vs 1.2%).[6]

In our study, toxicity of any grade was found to be higher in the FFX group than in the other 2 groups. Among the grade 1–2 toxicities, those seen more frequently in the FFX group than in the Gem and Gem-Cis groups included weakness/fatigue (53.6%, 43.7%, and 30.8%, respectively), nausea/vomiting (50%, 25.4%, and 27.5%, respectively), diarrhea (19.6%, 8.5%, and 7.7%, respectively), mucositis (19.6%, 7%, and 3.3%, respectively), and neutropenia (35.7%, 14.1%, and 17.6%, respectively). There was no significant difference between treatment groups in terms of thrombocytopenia. Grade 1–2 neuropathy was more common in the FFX group than in the Gem-Cis group (19.6% and 6.6%, respectively), and nephrotoxicity was more common in the Gem-Cis group than in the FFX group (9.9% and 3.6%, respectively). Febrile neutropenia was more common in the FFX group with grade 1–2 in 3 patients (5.4%) and grade 3–4 in 4 patients (7.1%). Among the grade 3–4 toxicities, weakness/fatigue and mucositis were only seen in the FFX group (5.4% and 3.6%, respectively). The grade 3–4 diarrhea (10.7%, 0, and 2.2%, respectively) and neutropenia (25%, 4.2%, and 5.5%, respectively) were seen more frequently in the FFX group than in the Gem and Gem-Cis groups.

The major limitations of the current study seem to be the retrospective design and the lack of data on the BRCA mutation. In addition, we did not include patients who received nab-paclitaxel therapy, because it was approved later in our country and there was the small number of patients. In addition, even though certain prognostic factors were not evenly distributed, they are shown to not affect PFS. Nonetheless, being a multicenter study individually comparing the 3 treatment arms with complete data on toxicity parameters, the findings achieved in the current real-life retrospective study seem to reflect the similar data obtained from randomized controlled trials. Given the limited number of studies comparing the efficacy and tolerability of 3 treatment regimens as well as FFX and Gem-Cis regimens in the literature, our findings represent a valuable contribution to the literature. Our study population includes only our region, so it is difficult to generalize study results to the worldwide population. Therefore, we suggest that further studies on a larger cohort of patients are needed to confirm our results.

CONCLUSIONS

Our findings indicate that the FFX and mFFX regimens offers a significant advantage over other treatment regimens in terms of response rates and survival. Treatment toxicity was more frequent but manageable with the FFX regimen. No significant difference was noted between Gem and Gem-Cis regimens in terms of efficacy. We also showed that mFFX regimen had similar efficacy to FFX with better tolerability and less adverse effect profile. Therefore, mFFX regimen can be considered as a primary option in the first-line treatment of mPC patients with a younger age and good PS.

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