RESEARCH ARTICLE

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Evaluation of Maintenance Capecitabine Therapy After First-Line Chemotherapy in Metastatic Pancreatic Cancer

Mohamed Abouelfetouh Shehata, Alshimaa Mahmoud Alhanafy, Mohamed Elsherbiny Hassan, Nahla Atef Shabaan, Amira Hosny Hegazy*

Abstract

Objective: To assess the clinical impact of maintenance capecitabine following first-line modified FOLFIRINOX in patients with metastatic pancreatic cancer (mPC), focusing on progression-free survival (PFS), overall survival (OS), quality of life (QoL), and the toxicity profile. **Methods:** This phase II prospective trial, 60 patients with histologically confirmed stage IV pancreatic adenocarcinoma (ECOG PS ≤1, normal organ function, and measurable metastatic disease) who were enrolled after completing modified FOLFIRINOX. Participants were randomized into two groups: Arm A received maintenance capecitabine, and Arm B underwent observation only. **Results:** Baseline patient and disease characteristics were comparable between both groups. The pancreatic head was the predominant tumor site (73.3% in Arm A vs. 86.7% in Arm B). After six months of maintenance therapy, stable disease was reported in 33.3% of Arm A and 0% of Arm B. Toxicity levels were not significantly different. Patients in Arm B demonstrated earlier deterioration in QoL, with median time to decline of 3.2 months compared with 6.9 months in Arm A. Median PFS and OS favored the capecitabine arm (6.13 vs. 3.57 months and 14.20 vs. 10.97 months, respectively). Multivariate Cox regression confirmed treatment arm as the most independent prognostic factor influencing both PFS and OS. **Conclusion:** Maintenance capecitabine after first-line modified FOLFIRINOX in mPC was well tolerated and may enhance PFS and OS while maintaining an acceptable quality of life.

Keywords: Metastatic pancreatic cancer, Maintenance therapy, Capecitabine

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive and lethal malignancies worldwide. Owing to its typically late presentation, most patients are diagnosed at an advanced stage, resulting in markedly poor overall survival (OS) and progression-free survival (PFS) rates compared with other solid tumors [1]. The cornerstone of management for metastatic pancreatic cancer (mPC) is systemic chemotherapy. Historically, gemcitabine served as the standard of care for several years [2]. However, the advent of Modified FOLFIRINOX regimen demonstrated a significant improvement in survival outcomes over gemcitabine (median OS = 11.1 months vs 6.8 months; P < 0.001) [3]. For patients achieving disease control after approximately 3–4 months of induction therapy, several strategies can be considered: discontinuation of treatment with close surveillance, or de-escalation to a maintenance approach [4]. Maintenance strategies have been well established in other chemosensitive malignancies such as colorectal cancer, where continuous full-dose chemotherapy until progression was shown to increase cumulative toxicity without proportional clinical benefit compared with therapeutic pause or de-escalated chemotherapy regimens [5].

In advanced PDAC, two major maintenance strategies have been explored: (1) dose de-escalation through continuation of a reduced number of the induction agents, and (2) switch maintenance, which introduces a different agent or mechanism of action such as targeted therapy [6]. Maintenance approach should aim to sustain tumor control while minimizing cumulative toxicity and preserving quality of life (QoL)-a crucial aspect in this non-curative setting [7].

Accordingly, the present study was designed to evaluate the efficacy and tolerability of maintenance capecitabine following first-line modified FOLFIRINOX in patients with metastatic pancreatic cancer, with special emphasis on progression-free survival, overall survival, quality of life, and treatment-related toxicity.

Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Menoufia University, Shebin El-Kom, Egypt.
**For Correspondence: amirahegazy28@yahoo.com*

Materials and Methods

Patients: This phase II prospective trial enrolled patients diagnosed with stage IV pancreatic cancer between September 2022 to October 2024.

Inclusion criteria

Eligible participants had histologically confirmed PDAC with measurable metastatic lesions based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 [8], were aged between 18 and 69 years, both sexes , had an ECOG performance status ≤ 1 [9], and exhibited adequate hematologic, hepatic, and renal function.. Patients who had previously received adjuvant or neoadjuvant chemotherapy were eligible if the treatment had been completed more than six months before enrollment. Tumor staging followed the AJCC 8th edition (2017) criteria [10].

Exclusion criteria

Patients were excluded if they had endocrine or acinar pancreatic carcinoma, disease progression during induction FOLFIRINOX, uncontrolled diabetes mellitus, peripheral neuropathy greater than grade 1, medical disorders interfering with oral drug administration, brain metastases, or a history of other active malignancies.

Methods

Patients who met the inclusion criteria received 4 months of modified FOLFIRINOX , then randomized using a computer generated system into 2 arms. Arm A received maintenance capecitabine until disease progression or toxicity and arm B kept under follow-up.

Eligible patients were subjected to thorough history (age, sex, PS, comorbidities, personal habits and family history), clinical examination, complete blood count (CBC), liver, kidney function tests before each cycle, baseline investigations: computerized tomography (CT) to the chest, abdomen and pelvis with contrast and pancreatic protocol administration, bone scan if the patient had bony pain or tenderness, or positron emission tomography (PET/CT), endoscopic ultrasound (EUS) or ultrasound guided biopsy for histopathological confirmation and tumor markers: carcinoembryonic antigen (CEA), CA19.9. Baseline calculation of QoL score using European Organization For Research and Treatment (EORTC) QLQ-30 and PAN26 questionnaires was done [11].

In both arms, patients received 4 months of modified FOLFRINOX (Oxaliplatin 85 mg/m^2 Day 1, Leucovorin 400 mg/m^2 Day 1, Irinotecan 135 mg/m^2 Day 1, Flourouracil Bolus: 300mg/m^2 , Continous : 2400 mg/m^2 .Bolus given immediately followed by the infusion over 46 hours), repeated every 2 weeks with follow up CBC ,liver and kidney function tests before every cycle and prophylactic granulocyte colony stimulating factor (GCSF) after each cycle , and prophylactic duloxitine orally to avoid chemotherapy induced peripheral neuropathy were administered. Prophylactic emmolient and urea creams were used to avoid hand and foot syndrome. Then in arm A maintenance capecitabine of 1250 mg/m^2 orally every 12 hours daily from day 1 to day 14 was taken and repeated every 3 weeks till disease progression or dose limiting toxicities or the patients kept under follow up in arm B.

Each patient was evaluated every 2 months by physical examination, whole body CT scan and tumor markers CEA and CA 19-9 during the course of FOLFIRINOX to exclude progression, then every 3 months in both arms or when clinically indicated. Assessment of response was done according to RECIST version 1.1.

QoL was evaluated using EORTC C30 and EORTC QLQ PAN26 that is specific for pancreatic cancer at the baseline, at the end of FOLFIRINOX then every 3 months to assess the time to deterioration of Qol score in both arms. Toxicity was evaluated every cycle during FOLFIRINOX and maintenance capecitabine according to Common Toxicity Criteria of Adverse Events (CTCAE) version 5.0 [12].

Progression free survival (PFS) was calculated from the date of randomization (after the end of induction FOLFIRINOX) to the date of disease progression or death [13]. Overall Survival (OS) was calculated from the date of diagnosis to the date of the last follow-up or the date of death [13].

Ethical Considerations

All participants provided written informed consent prior to study enrollment. The trial protocol received approval from the Ethical Committee of the Faculty of Medicine, Menoufia University (IRB No. 5/2020 ONCO23). The study adhered to the ethical standards of the Helsinki Declaration and was registered at ClinicalTrials.gov (approval No. 1003, September 2022)

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics software version 20.0 (Armonk, NY: IBM Corp). Qualitative variables were expressed as frequencies and percentages, while quantitative variables were summarized as mean ± standard deviation (SD), median, and interquartile range (IQR). The Kolmogorov–Smirnov test was applied to assess the normality of data distribution. Comparisons between groups were performed using appropriate statistical tests: Student's t-test for normally distributed quantitative variables, Fisher's exact test or Monte Carlo correction for categorical variables, Logistic regression analysis for identifying prognostic factors, and Cox proportional hazards model for univariate and multivariate survival analyses. A p-value < 0.05 was considered statistically significant throughout all analyses.

Results

This study included 60 patients, 30 patients in each arm. The median follow up duration was 12.17 months (range from 9.13 to 23.93 months). There were no significant differences between both arms regarding patients and disease characteristics. Most cases in both arms were males (60% in arm A vs 63.3% in arm B). The median age in arm A was 47.50 (44.0–51.0) years and 45.0 (43.0 – 50.0) years in arm B. The mean baseline QoL score was 61.33 ± 2.81 in arm A vs 61.10 ± 2.41 in arm

B. The most common tumor site was head of pancreas (73.3% in arm A vs 86.7% in arm B). The majority of cases were grade III in both arms (80% vs 86.7%), and had liver only metastasis (43.3% vs 53.4%).The median number of liver metastatic lesions was 9 (7 to 10), in arm A and 8 (7 to 10) in arm B. The mean baseline CA19-9 in arm A was 1421.8 ± 1236.1 ng/ml vs 1952.7 ± 1179.3 in arm B. The mean baseline CEA 25.89 ± 27.09 in arm A vs 23.1 ± 20.3 in arm B (Table 1).

After 3 months from randomization, regarding the toxicities, there was significant difference of toxicities between both arms being more in arm A in the form of grade I to II oral mucositis, diarrhea, peripheral neuropathy and hand and foot syndrome (P= 0.011, 0.024, 0.001,< 0.001 respectively). In arm A, 13.3 % of the cases required 25% dose reduction of capecitabine (10 % of the cases developed grade II hand and foot syndrome for the 2nd time and 3.3% of the cases developed grade III hand and foot syndrome for the 1st time). There was significance difference in CA19-9 elevation being more elevated in arm B (70 %) vs 20 % in arm A (P=0.003) (Table 2). As regard the response, arm A had more PR (33.3% vs 0%) and SD (46.7% vs 40%) than arm B, while 60 % of the cases had progressive disease (PD) in arm B vs 20 % in arm A (P <0.001). After 6 months, 20% of the cases in arm A died from deterioration of the general condition vs 53.4% in arm B. There was no significance difference regarding the toxicities in both arm. As regard CA19-9, there was significant elevation in 100 % of the cases in arm B vs 53.3. % in arm A (P <0.001) (Table 2). Regarding the response, 33.3% achieved SD in arm A vs 0% in arm B, while most of the cases in arm A and all of the remaining cases in arm B developed PD (46.7% vs 100% respectively) (P <0.001).

By univariate logistic regression analysis of response at 6 months from randomization. It was found that there was significant correlation between arm A and response (P=0.001). By multivariate analysis, it was found that treatment arms and baseline CA19.9 were the most independent prognostic factors of the response (P=0.002, 0.033) respectively (Table 3).

As regard QOL: there was significant difference in the mean QoL score at 6 months from randomization (82.58 ± 3.80 in arm A vs 91.50 ± 2.56 in arm B) and also significant deterioration of QoL score in arm A versus arm B after 3 and 6 months from randomization, that is translated into earlier deterioration in the QoL in arm B (P = 0.001 and < 0.001) respectively (Table 4). Regarding the functional scale, arm A had a higher score than arm B (that represented a high / healthy level of functioning. Regarding the symptom scale, arm B had a higher score than arm A (that represented a high level of symptomatology / problems). And regarding the global health status, arm A had a higher score than arm B (that represented a better QoL) . The median time to deterioration in the QoL score was longer in arm A (6.9 months from randomization vs 3.2 months in arm B) (Figure 1 A,B, C,D).

There was significant difference in PFS in both arms with the median PFS in arm A was 6.13 (5.956-6.311) months and 3.57 (3.254 – 3.879 in arm B (P value <0.001) (Figure 2). By univariate analysis, there was significant correlation between PFS and arm A, smoking and CA 19-9 elevation at 3 moths from randomization (p value <

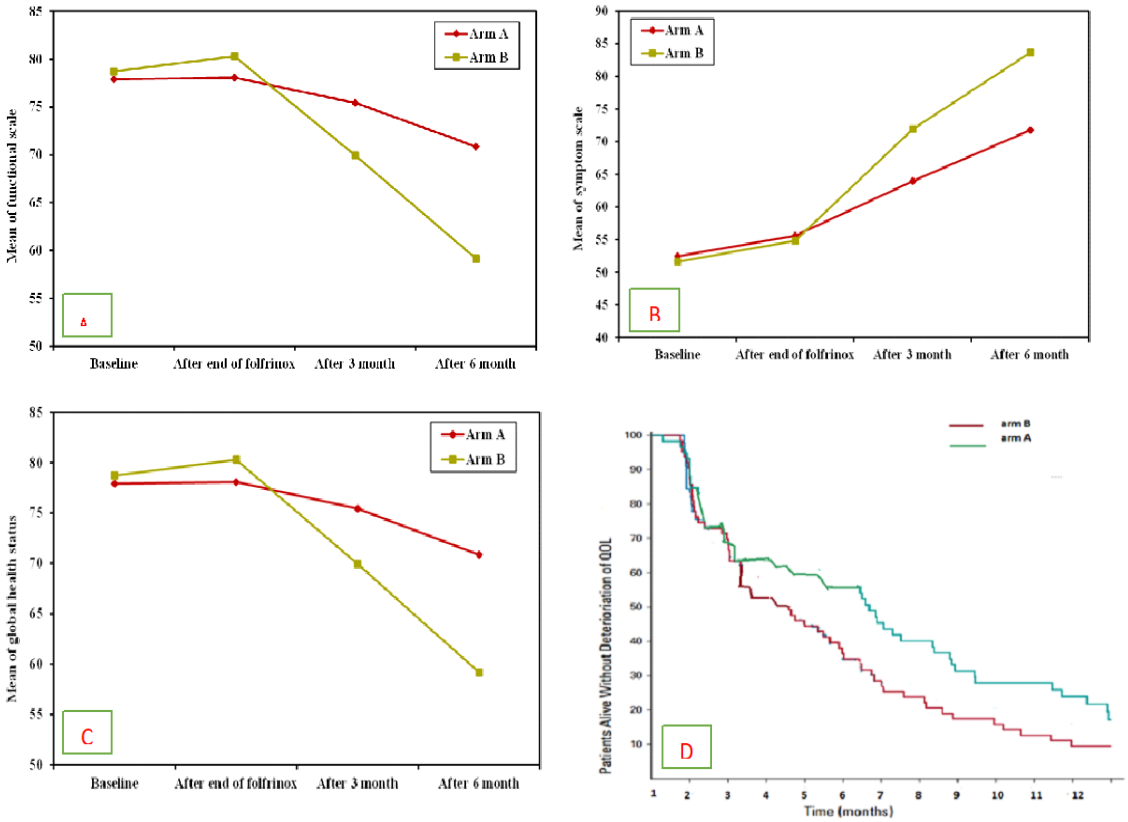

Figure 1. Quality of Life Assessment in Both Groups. A: Functional Scale in both groups. B: Symptom Scale in both groups. C: Global health status Scale in both groups. D:Time without deterioration in the QoL in both groups.

Table 1. Patients' and Disease Characteristics of Both Arms

		Arm A (n = 30)		Arm B (n = 30)		Test of Sig.	P
		No.	%	No.	%		
Gender	Male	18	60	19	63.3	χ^2=	0.791
	Female	12	40	11	36.7	0.071	
Age (years)	Min. – Max.	32.0 – 56.0		40.0 – 55.0		t=	0.259
	Mean ± SD.	42.83 ± 4.38		46.53 ± 4.45		1.14	
	Median (IQR)	47.50 (44.0 – 51.0)		45.0 (43.0 – 50.0)			
PS	0	24	80	19	63.3	χ^2=	0.152
	1	6	20	11	36.7	2.052	
Personal habits	Smoking	11	36.7	9	30	χ^2=0.300	0.584
	Alcohol	0	0	0	0	–	–
BMI baseline	Min. – Max.	19.0 – 29.0		19.0 – 26.0		t=	0.321
	Mean ± SD.	23.33 ± 3.21		22.63 ± 2.08		1.003	
	Median (IQR)	23.0 (21.0 – 26.0)		22.50 (21.0 – 24.0)			
Family history	Pancreas	3	10	2	6.7	χ^2=0.218	FE_p=1.000
	Breast	3	10	2	6.7	χ^2=0.218	FE_p=1.000
	Ovarian	0	0	0	0	–	–
	Colon	0	0	0	0	–	–
	Multiple	1	3.3	1	3.3	χ^2=0.00	FE_p=1.000
Comorbidities	HTN	5	16.7	3	10	χ^2=0.577	FE_p=0.706
	DM	9	30	7	23.3	χ^2=0.341	0.559
	HCV	3	10	2	6.7	χ^2=0.218	FE_p=1.000
	Multiple	5	16.7	3	10	χ^2=0.577	FE_p=0.706
QLQ score baseline	Min. – Max.	56.0 – 69.0		58.0 – 66.0		t=	0.731
	Mean ± SD.	61.33 ± 2.81		61.10 ± 2.41		0.345	
	Median (IQR)	61.0 (60.0 – 63.0)		60.0 (59.0 – 64.0)			
Site of pancreas lesions	Head	22	73.3	26	86.7	FET=	0.396
	Body	6	20	4	13.3	2.613	
	Tail	1	3.3	0	0		
	Body and Tail	1	3.3	0	0		
Tumor grade	II	6	20	4	13.3	χ^2=	0.488
	III	24	80	26	86.7	0.48	
Previous treatment	No treatment	27	90	28	93.3	χ^2=	FE_p=
	Adjuvant chemotherapy	2	6.7	1	3.3	0.218	1
	Neoadjuvant chemotherapy	1	3.3	1	3.3		
	Adjuvant radiotherapy	2	6.7	1	3.3		
Type of chemotherapy	Gemcitabine based	3	100	2	100	–	–
Time between last adjuvant cycle to develop distant metastasis (months)	Mean ± SD.	7.63 ± 1.99		8.67 ± 1.88		t=	0.947
	Median (IQR)	7.5 (7.0 – 8.0)		8.0 (7.0 – 9.0)		0.067	
Whipple operation	No	25	83.3	27	90	χ^2=	FE_p=
	Yes	5	16.7	3	10	0.577	0.706
No. of metastatic organs	1	13	43.4	16	53.4	–	–
	2	10	33.3	9	30		
	≥3	7	23.3	5	16.7		
Site of metastasis	Liver only	13	43.4	16	53.4	–	–
	Liver and Lung	6	20	5	16.6	χ^2=0.000	FE_p=1.000
	Liver and Peritoneum	3	10	2	6.67	χ^2=1.456	FE_p=0.424
	Liver, lung, and peritoneum	7	23.3	5	16.6	–	–
	Liver and bone	1	3.3	2	6.7	–	–

IQR, Inter quartile range; SD, Standard deviation; t, Student t-test; χ^2, Chi square test; FET, Fisher Exact test; P, value for comparing between the two studied group

Table 1. Patients' and Disease Characteristics of Both Arms

		Arm A (n = 30)		Arm B (n = 30)		Test of Sig.	P
		No.	%	No.	%		
No. of liver metastatic lesions	Min. – Max.	7.0 – 14.0		6.0 – 13.0		t=	0.947
	Median (IQR)	9.0 (7.0 – 10.0)		8.0 (7.0 – 10.0)		0.067	
CA19-9 Baseline (ng/ml)	Min. – Max.	200.0 – 5460.0		190.0 – 7450.0		t=	0.676
	Mean ± SD.	1421.8 ± 1236.1		1952.7 ± 1179.3		0.42	
	Median (IQR)	1000.0 (600.0–1880.0)		1250.0 (790.0–2000.0)			
CEA Baseline (ng/ml)	Min. – Max.	7.0 – 98.0		3.0 – 87.0		t=	0.635
	Mean ± SD.	25.89 ± 27.09		23.1 ± 20.3		0.42	
	Median (IQR)	14.30 (3.0 – 45.0)		22.0(4.0–41.0)			

IQR, Inter quartile range; SD, Standard deviation; t, Student t-test; χ^2, Chi square test; FET, Fisher Exact test; P, value for comparing between the two studied group

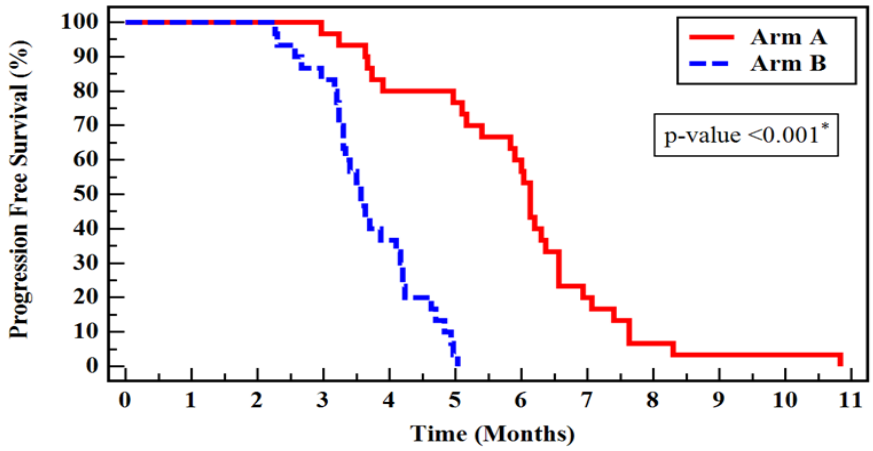

Figure 2. Kaplan Meier Curve of PFS

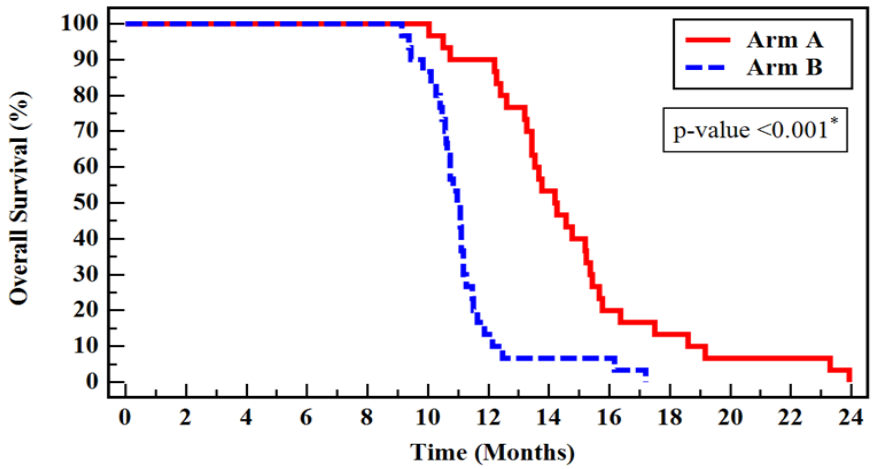

Figure 3. Kaplan Meier Curve of OS

0.001, 0.021 and 0.004) respectively. By multivariate cox regression analysis, it was found that arm A, smoking and CA 19-9 elevation at 3 moths from randomization were the most independent factors of PFS (p value < 0.001, 0.005, < 0.001) respectively (Table 5).

There was significance difference in OS in both arms. The median OS in arm A was 14.20 (12.99 – 15.41) months and 10.97 (10.52 – 11.41) months in arm B (P value <0.001) (Figure 3). By univariate cox regression analysis, there was significant correlation between OS and arm A, previous treatment and whipple operation (P <0.001, 0.004, 0.003 respectively). By multivariate analysis, it was found that arm A was the most independent prognostic factors for OS (p <0.001) (Table 5).

Table 2. Toxicity and Treatment Outcome at 3, 6 Months from Randomization

Data		At 3 months from randomization Arm A (n = 30)		Arm B (n = 30)		Test of Sig.	P
		No.	%	No.	%		
Oral mucositis (grade)	No	23	76.7	30	100	FET=7.920*	0.011*
	I	6	20	0	0		
	II	1	3.3	0	0		
Diarrhea (grade)	No	24	80	30	100	FET=6.462*	0.024*
	I	1	3.3	0	0		
	II	5	16.7	0	0		
Hand &foot syndrome (grade)	No	16	53.3	30	100	FET=17.102*	<0.001*
	I	9	30	0	0		
	II	4	13.3	0	0		
	III	1	3.3	0	0		
Peripheral neuropathy (grade)	No	10	33.3	20	66.6	FET= 0.641	0.001*
	I	15	50	8	26.7		
	II	5	16.7	2	6.7		
Dose adjustment				0	0	χ^2=4.286	^{FE}p=0.112
25% dose reduction			10				
(grade II toxicity 2nd time)		3					
(grade III toxicity 1st time)		1	3.3				
QLQ score	Min. – Max.	66.0 – 92.0		69.0 – 88.0		t= 1.531	0.131
	Mean ± SD.	74.13 ± 7.71		76.70 ± 4.98			
	Median (IQR)	71.0 (69.0 – 75.0)		76.50 (73.0 – 80.0)			
CA19-9 (from the end of FOLFIRINOX)	Stationary	19	63.3	9	30	FET=17.359*	0.003*
	Decreased	5	16.7	0	0		
	Elevated	6	20	21	70		
At 6 months from randomization							
Mucositis (grade)	No	23	95.8	0	0	χ^2=1.017	^{FE}p=1.000
	I	1	4.2	0	0		
Diarrhea (grade)	No	10	41.6	0	0	FET= 3.537	^{FE}p=0.522
	I	2	8.3	0	0		^{FE}p=0.522
	II	2	8.3	0	0		
Hand & foot syndrome (grade)	No	19	79.3	0	0	FET= 5.09	^{FE}p=0.276
	I	4	16.6	0	0		^{FE}p=1.000
	II	1	4.1	0	0		
Peripheral neuropathy (grade)	No	5	20.7	4	28.6	χ^2=2.222	0.112
	I	19	70.3	10	71.4		
Vomiting	No	10	41.6	0	0	χ^2=4.286	^{FE}p=0.112
	I	4	16.6	0	0		
QLQ score	Min. – Max.	75.0 – 89.0	89.0 – 96.0	t=7.787*	<0.001*		
	Mean ± SD.	82.58 ± 3.80		91.50 ± 2.56			
	Median (IQR)	83.0 (80.0 – 85.0)		90.0 (90.0 – 93.0)			
CA19-9 (from 3 months of randomization)	Stationary	8	26.7	0	0	FET=44.415*	<0.001*
	Elevated	16	53.3	14	100		

IQR, Inter quartile range; SD, Standard deviation; t, Student t-test; χ^2, Chi square test; FET, Fisher Exact test; P, value for comparing between the two studied group; SD, stable disease; PD, progressive disease

Discussion

This phase II clinical study was conducted at the Department of Clinical Oncology, Faculty of Medicine, Menoufia University, aiming to explore a practical and well-tolerated maintenance strategy for patients with metastatic pancreatic cancer (mPC), a disease known for its poor prognosis and limited therapeutic options.

Table 3. Univariate and Multivariate Analysis of Response at 6 Months

		Response at 6 months		P	OR (LL – UL 95%C.I)
		Progression	Stable /Regression		
Univariate analysis					
Arms	Arm A	10 (35.7%)	10 (100.0%)	0.001*	3.932 (0.982 – 4.980)
	Arm B	18 (64.3%)	0 (0.0%)		0.167 (0.053 – 0.529)
Gender	Male	9 (24.9%)	19 (55.6%)	0.236	0.415 (0.172 – 1.544)
	Female	10 (35.7%)	16 (44.4%)		0.399 (0.198 – 1.322)
Age (years)	<45	6 (25.0%)	24 (66.7%)	0.676	1.109 (0.897 – 1.235)
	≥45	14 (58.3%)	26 (72.2%)		1.099 (0.899 – 1.987)
PS	I	9 (24.9%)	7 (19.4%)	0.266	2.859 (0.930 – 9.316)
	II	6 (25.0%)	7 (19.4%)		1.999 (0.879 – 9.098)
Smoking	Yes	14 (58.3%)	26 (72.2%)	0.386	1.757 (0.624 – 5.530)
	No	10 (35.7%)	9 (24.9%)		1.654 (0.544 – 5.432)
Family history	Pancreas	4 (10.8%)	0 (0.0%)	0.898	1.864 (0.624 – 5.530)
					1.654 (0.611 – 5.099)
	Breast	3 (8.4%)	1 (2.8%)	0.191	7.100 (0.731 – 67.023)
					7.321 (0.543 – 66.123)
	Multiple	1 (2.8%)	0 (0.0%)	0.89	1.763 (0.624 – 5.530)
					1.444 (0.611 – 5.897)
Comorbidities	HTN	1 (2.8%)	4 (10.8%)	0.753	0.986 (0.191 – 4.110)
					0.899 (0.155 – 5.122)
	DM	1 (2.8%)	9 (24.9%)	0.823	1.135 (0.488 – 3.938)
					1.099 (0.543 – 4.111)
	HCV	1 (4.2%)	1 (10%)	0.374	0.348 (0.036 – 3.319)
					0.411 (0.011 – 3.900)
	Multiple	3 (12.5%)	5 (50.0%)	0.873	0.886 (0.191 – 4.110)
					0.799 (0.211 – 4.222)
Site of pancreatic lesions	Head	18 (75.0%)	30 (83.3%)	0.132	0.610 (0.168 – 2.144)
					0.811 (0.322 – 4.213)
	Body	6 (25.0%)	5 (13.9%)	0.282	2.067 (0.551 – 7.747)
					2.123 (0.544 – 8.444)
	Tail	0 (0.0%)	2 (5.6%)	0.399	2.088 (0.591 – 9.747)
					2.123 (0.654 – 9.900)
Tumor grade	II	7 (29.2%)	9 (25.0%)	0.274	3.153 (0.405 – 16.316)
	III	22 (91.7%)	13 (16.8%)		3.564 (0.322 – 16.78)
Previous treatment		4 (16.7%)	1 (2.8%)	0.194	7.000 (0.831 – 66.023)
					7.908 (0.432 – 65.434)
Whipple operation		5 (20.8%)	3 (8.3%)	0.296	2.695 (0.621 – 12.484)
					2.113 (0.543 – 12.901)
CA19-9 Baseline	Elevation	7 (29.2%)	5 (20.0%)	0.126	1.041 (1.002 – 2.002)
	Normal	21 (91.7%)	5 (20.0%)		1.155 (1.777 – 2.134)
Multivariate analysis of response					
Parameters	Treatment Arms			0.002*	0.025 (0.004 – 0.301)
	CA19-9 Baseline			0.033	1.122 (1.000 – 1.002)

Hosmer and Lemeshow Test (χ^2=3.083; p=0.929); OR, Odd`s ratio; C.I, Confidence interval; LL, Lower limit; UL, Upper Limit; *, Statistically significant at $p \leq 0.05$

Peripheral neuropathy occurred in 66.6% of patients in the maintenance arm compared with 33.3% in the observation arm after three months of randomization. These results are comparable to those reported in the PANOPTIMOX-PRODIGE 35 trial [14], which observed higher rates of neuropathy in the maintenance arm (94.1%) compared with continued FOLFIRINOX (68.6%). The discrepancy in incidence rates between the two studies

Table 4. Quality of Life Score Assessment in Both Arms

QLQ score	Arm A	Arm B	Test of Sig.	p
Baseline	(n = 30)	(n = 30)		
Min. – Max.	56.0 – 69.0	58.0 – 66.0	t=	0.731
Mean ± SD.	61.33 ± 2.81	61.10 ± 2.41	0.345	
Median (IQR)	61.0 (60.0 – 63.0)	60.0 (59.0 – 64.0)		
After end of FOLFIRINOX	(n = 30)	(n = 30)		
Min. – Max.	60.0 – 72.0	61.0 – 70.0	t=	0.305
Mean ± SD.	66.83 ± 2.85	66.13 ± 2.36	1.035	
Median (IQR)	67.0 (65.0 – 69.0)	65.50 (65.0 – 68.0)		
After 3 month	(n = 30)	(n = 30)		
Min. – Max.	66.0 – 92.0	69.0 – 88.0	t=	0.131
Mean ± SD.	74.13 ± 7.71	76.70 ± 4.98	1.531	
Median (IQR)	71.0 (69.0 – 75.0)	76.50 (73.0 – 80.0)		
Deterioration after 3 month	(n = 30)	(n = 30)		
Min. – Max.	0.0 – 42.19	6.06 – 34.92	U=	0.001*
Mean ± SD.	11.13 ± 12.78	16.07 ± 7.84	222.50*	
Median (IQR)	6.15 (4.35 – 9.52)	15.33 (8.70 – 23.08)		
After 6 month	(n = 24)	(n = 14)		
Min. – Max.	75.0 – 89.0	89.0 – 96.0	t=	<0.001*
Mean ± SD.	82.58 ± 3.80	91.50 ± 2.56	7.787*	
Median (IQR)	83.0 (80.0 – 85.0)	90.0 (90.0 – 93.0)		
Deterioration after 6 month	(n = 24)	(n = 14)		
Min. – Max.	13.04 – 37.50	28.57 – 52.38	U=	<0.001*
Mean ± SD.	23.06 ± 6.92	38.24 ± 6.55	16.00*	
Median (IQR)	23.53 (17.26 – 26.98)	38.76 (33.33 – 43.08)		

IQR, Inter quartile range; SD, Standard deviation; t, Student t-test; U, Mann Whitney test; p, value for comparing between the two studied groups; *, Statistically significant at $p \leq 0.05$

Table 5. Univariate and Multivariate Cox Regression Analysis of PFS, OS

		P	HR (LL – UL 95%C.I)
Univariate cox regression analysis of PFS			
+		<0.001*	0.090 (0.037 – 0.216)
Smoking		0.021*	2.998 (1.110 – 3.597)
CA19-9 at 3 month	Stationary	<0.001*	0.099 (0.028 – 0.345)
	Decreased	0.001*	0.069 (0.015 – 0.328)
	Elevated	0.004*	2.991 (0.901 – 9.934)
Multivariate cox regression analysis of PFS			
Treatment Arms		<0.001*	0.059 (0.020 – 0.172)
Smoking		0.005*	2.558 (1.321 – 4.951)
CA19-9 at 3 month of randomization		<0.001*	6.972 (2.686 – 18.095)
Univariate cox regression analysis of OS			
Arm A		<0.001*	0.242 (0.136 – 0.429)
Previous treatment		0.004*	0.238 (0.090 – 0.627)
Whipple operation		0.003*	0.342 (0.156 – 0.752)
Multivariate cox regression analysis of OS			
Treatment Arms		<0.001*	0.173 (0.082 – 0.366)
Family history of malignancy		<0.092	39.745 (6.293 – 251.035)
Previous treatment		0.829	1.080 (0.538 – 2.166)
Whipple operation		0.542	0.784 (0.358 – 1.715)

HR, Hazard ratio; C.I, Confidence interval; LL, Lower limit; UL, Upper Limit *, Statistically significant at $p \leq 0.05$

could be attributed to variations in treatment duration, sample size, study design, and patient characteristics. PANOPTIMOX-PRODIGE 35 trial randomized 276 patients into 3 arms: FOLFIRINOX for 6 months (Arm A), FOLFIRINOX for 4 months followed by LV5FU maintenance (Arm B), or a sequential strategy alternating gemcitabine and FOLFIRI (Arm C).

Chevalier et al. [15] compared several de-escalation strategies after FOLFIRINOX (FOLFOX, FOLFIRI, and LV5FU), revealing that neurotoxicity was most frequent in the FOLFOX maintenance arm (73.7%) compared to LV5FU (9.1%). Also Hann et al. [16] reported only 15% of patients developing neuropathy under LV5FU maintenance. The difference in incidence between our study and others may be partly due to different maintenance agent and the known toxicity profile of this oral fluoropyrimidine which typically produces more hand–foot syndrome and neuropathy compared to 5-FU–based regimens (which causes more hematological and gastrointestinal side effects).

In the present study, 46.6% of patients experienced hand–foot syndrome of grade I–II severity, while 3.3% developed grade III events requiring dose modification in 13.3% of cases. These findings are milder compared with those of Reure J. et al. [17] (single arm study included 30 patients who received maintenance Capecitabine) who reported grade III–IV toxicity in 16.6% of patients, leading to a 35% dose reduction rate. The improved tolerability in our study could be attributed to comprehensive patient education and preventive skin care interventions, which helped mitigate dermatologic adverse effects.

Quality of life assessment showed delayed deterioration in the Capecitabine arm (median 10.9 months from the start of induction therapy vs. 7.2 months in the control arm), consistent with PANOPTIMOX-PRODIGE 35 findings (11.4 vs. 7.2 months). PANOPTIMOX-PRODIGE 35 trial was the only trial that evaluated QoL in the maintenance setting of pancreatic cancer. Although minor increases in neuropathy and dermatologic toxicity were noted, they did not significantly impair patients' global health status or daily functioning. The use of both EORTC QLQ-C30 and EORTC QLQ-PAN26 questionnaires in this study provided a more disease-specific and sensitive evaluation of patient-reported outcomes than earlier trial, which relied solely on generic QoL tools.

Regarding disease control, 33.3% of patients in the maintenance arm achieved stable disease (SD) at six months, compared to none in the control arm, and 46.7% achieved PD vs 100% respectively. These results indicate that capecitabine effectively delayed disease progression. In contrast, PANOPTIMOX-PRODIGE 35 trial reported a slightly higher SD rate of 40.7% and lower PD rate of 23.5% in the maintenance group, while Reure et al. [17] and Hann et al. [16] documented higher progression rates (96.7% and 85%, respectively). Such variation likely reflects differences in sample size, inclusion criteria, and maintenance drug selection.

The median PFS in our study (6.13 months in Arm A vs. 3.57 months in Arm B) aligns with results from Zhang et al. [18] and Petrioli et al. [19], who reported PFS values of 6.2 and 6.4 months with S-1 and gemcitabine maintenance, respectively. It also closely matches findings from Reure et al, and PANOPTIMOX-PRODIGE 35 trial who observed 5 and 5.7 months PFS with Capecitabine and LV5FU maintenance respectively. Moreover it is also compatible with FOLFOX de-escalation arm in Chevalier et al. [15] (6.7 months). However, longer PFS durations were reported in studies employing 5-FU or FOLFIRI maintenance regimens, such as Hann et al. [16] (10.6 vs. 4.9 months), Franck et al. [20] (8 months with FOLFIRI), and Chevalier et al. [15] (9 and 10.1 months with FOLFIRI and 5FU maintenance arms respectively) suggesting that regimen composition and intensity may influence long-term outcomes.

Similarly, the observed median OS of 14.2 months in the Capecitabine arm and 10.97 months in the control arm is comparable to Petrioli et al. [19] (13.4 months) and superior to the maintenance arm of PANOPTIMOX-PRODIGE 35 trial (11.2 months). However, some studies reported longer survival, such as Reure et al. [17] (17 months) and Hann et al. [16] (18.3 months), which may be explained by different study design, sample size, and population characteristics.

Taken together, our findings support capecitabine as a feasible maintenance option in mPC, providing clinical benefit and tolerable safety comparable to previously studied regimens. The oral administration route offers additional convenience and may improve treatment adherence in the outpatient setting.

Nonetheless, this study is limited by its relatively small sample size (60 patients in both groups) and single-center design (Clinical Oncology Department , Menoufia University only). Future large-scale, multicenter randomized trials are warranted to confirm these results. Prospective molecular subtyping (classical vs basal like) is essential to identify biologically distinct subgroups of metastatic pancreatic cancer with differential sensitivity to maintenance therapies. Incorporating transcriptomic classification into future trials may enable personalized treatment strategies and optimize patient selection for fluoropyrimidine-based maintenance approaches. Prospective molecular subtyping is needed to: Match the right maintenance treatment (like capecitabine) to the right patient subgroup before treatment starts so outcomes improve and unnecessary toxicity is avoided.

In conclusion, our findings demonstrated that maintenance Capecitabine following modified FOLFIRINOX was associated with favorable clinical outcomes, including improved progression-free survival (PFS), overall survival (OS), and preserved quality of life (QoL), with manageable toxicity. Given the limited therapeutic options and poor prognosis of advanced pancreatic cancer, integrating a well-tolerated maintenance approach such as Capecitabine could represent a meaningful advancement in disease management.

Author Contribution Statement

all authors contributed equally in the study as regard data collection, follow up of patients, revision of statistical analysis, writing, revision , and editing. We used ChatGPT to assist in language editing. All content was reviewed

and verified by authors.

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Conflicts of interest

There are no conflicts of interest. This manuscript is part of an approved MD student thesis.

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