

Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience

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Key Words

Pancreatic adenocarcinoma · Chemotherapy · FOLFIRINOX · Safety

Abstract

Objectives: The combination of 5-fluorouracil (5-FU), irinotecan and oxaliplatin (FOLFIRINOX) is considered the first-line chemotherapy for fit patients with advanced pancreatic ductal adenocarcinoma (PDAC) but carries an unfavourable adverse event (AE) profile. We retrospectively evaluated the tolerability and efficacy of a modified FOLFIRINOX (mFOLFIRINOX) regimen: intravenous oxaliplatin 85 mg/m², irinotecan 135 mg/m², folinic acid 400 mg/m² and 5-FU infusion 2,400 mg/m² over 46 h, with routine subcutaneous filgrastim on a 14-day cycle. **Methods:** Records of 18 patients with advanced PDAC who received treatment with mFOLFIRINOX were reviewed. Imaging of measurable disease was assessed for response, and survival was measured from the date of commencing chemotherapy to disease progression and/or death. **Results:** Grade 3 or 4 AEs (n; %) included vomiting (5; 28), nausea (4; 22), diarrhoea (3; 17) and

non-neutropaenic fever (3; 17). For patients with stage IV disease, 12/15 (80%) achieved at least stable disease as the best radiological response, with 7/15 (47%) objective responses. In this subgroup, median overall and progression-free survival were 9.3 months (95% CI 8.3–10.4) and 7.2 months (95% CI 4.7–9.6), respectively. **Conclusion:** Compared to full-dose FOLFIRINOX, our modified regimen resulted in lower haematological but only marginally improved non-haematological toxicity rates, with comparable efficacy outcomes. Prospective studies are required to validate these findings.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of cancer-related death in Europe [1] with a 5-year survival rate of 6.9%, the lowest among the 46 most common cancers [2]. The majority of patients have unresectable disease at presentation, and palliative chemotherapy is offered to those patients fit enough to tolerate treatment. Until recently, single-agent

gemcitabine was the international standard of care. In 2011, Conroy et al. [3] reported a clinically significant benefit with the combination of 5-fluorouracil (5-FU), folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) compared to gemcitabine, with a significant median overall survival (OS) advantage of 11.1 versus 6.8 months in patients with stage IV PDAC. Since then, FOLFIRINOX has been adopted as standard first-line combination chemotherapy for PDAC patients with very good performance status [Eastern Cooperative Oncology Group (ECOG) 0 or 1]. The survival gain comes at a cost, as FOLFIRINOX is associated with an unfavourable side effect profile, with significantly more grade 3 and 4 neutropenia (45.7 vs. 21.0%), diarrhoea (12.7 vs. 1.8%) and sensory neuropathy (9.0 vs. 0%) compared to gemcitabine. At full dose, therefore, tolerability remains a concern which has limited the routine use of FOLFIRINOX [4].

Recently, data from retrospective studies have suggested that modifications to the FOLFIRINOX regimen may decrease toxicities without compromising efficacy [5, 6], and a number of studies specifically investigating modified FOLFIRINOX (mFOLFIRINOX) regimens have subsequently been reported in abstract, providing some support for the hypothesis [7, 8]. In the only published study to date evaluating palliative mFOLFIRINOX in advanced pancreatic cancer patients, Mahaseth et al. [9] used a regimen which omitted the bolus 5-FU and incorporated routine haematopoietic growth factor support. The median OS of 60 treated patients was similar to that of the patients treated with the full-dose regimen (9.0 vs. 11.1 months), but in contrast to earlier reports [5, 6], suggesting a much improved toxicity profile with dose attenuation (e.g. <5% incidence of grade 3 and 4 diarrhoea, frequency of grade 3 and 4 non-haematological toxicities of diarrhoea (13%) and nausea was comparable, although fatigue was less common (summarised in table 6). In a recent retrospective neoadjuvant study, Blazer et al. [10] delivered a similar mFOLFIRINOX regimen with a slightly lower irinotecan dose of 160 mg/m², representing an approximately 10% dose reduction. This study also found rates of grade 3 and 4 diarrhoea similar to the full-dose regimen. Further data questioning the value of dose-attenuated FOLFIRINOX in limiting gastrointestinal toxicities have recently been presented by Lee et al. [11] who retrospectively reviewed the outcomes of 27 patients with advanced pancreatic adenocarcinoma, stratified by relative dose intensity (RDI). In this study, there was no significant difference in rates of grade 3/4 diarrhoea and nausea (25 vs. 29%) in the highest and lowest RDI groups (≥80 vs. 50–69%, respectively).

Questions about tolerability therefore remain relevant despite the prospect of comparable efficacy with dose attenuation. At our academic UK institution, we have routinely modified FOLFIRINOX by omitting the bolus dose of 5-FU, reducing irinotecan to 75% of the full dose and including routine haematopoietic growth factor support. We report here the results of a retrospective review of the safety and efficacy of mFOLFIRINOX in advanced pancreatic cancer patients.

Methods

Patient Selection and Treatment

A consecutive cohort of patients with advanced pancreatic adenocarcinoma treated with FOLFIRINOX between July 2011 and May 2014 at Cambridge University Hospitals NHS Foundation Trust (CUH) were identified, and those initiated on or converted to a modified regimen from cycle 2 were eligible for inclusion.

The intended treatment regimen consisted of oxaliplatin 85 mg/m², irinotecan 130–135 mg/m² (72–75% of the full dose), folinic acid 400 mg/m² and 5-FU infusion 2,400 mg/m² over 46 h administered every 14 days. All patients received haematopoietic growth factor support with filgrastim for 7 days with each cycle. Anti-emetic support with ondansetron 8 mg and dexamethasone 8 mg was routinely administered on day 1 of each cycle, and domperidone, ondansetron or aprepitant was prescribed for subsequent days at the discretion of the treating physician. Patients were provided loperamide and instructed to commence this at the onset of diarrhoea.

Treatment toxicities and subsequent dose adjustments were determined following clinical and laboratory evaluation at the beginning of each cycle. Baseline computed tomography (CT) staging was performed within 4 weeks of commencing chemotherapy. Reassessment CT scans were planned for after every four to six cycles. Treatment was discontinued in cases of disease progression or unacceptable toxicity.

Data Analysis

Patient data were collected from review of electronic medical records and paper case notes. Chemotherapy dose intensities were calculated according to the method of Hryniuk and Bush [12]. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. CT scans were reviewed and treatment response assessed as per Response Evaluation Criteria in Solid Tumours (RECIST). Progression-free survival (PFS) and OS were measured as the interval between the day of first treatment and documented radiological or clinical evidence of disease progression, and death, respectively. Data collection was terminated on the July 23, 2014, at which point patients who were alive and/or progression-free were censored for analysis.

Data analysis was on an intention-to-treat basis and carried out using Microsoft Excel and SPSS. Survival analysis was calculated using Kaplan-Meier estimators and adverse event (AE) rates were compared with historical data using Fisher's exact test.

Results

Patient Characteristics

Eighteen patients with advanced PDAC were treated with mFOLFIRINOX between July 2011 and May 2014 (table 1). The majority of patients had stage IV disease ($n = 15$, 83.3%) and tumours localised to the head of the pancreas ($n = 10$, 56.6%) with a median age of 60 years (range 40–77); all had ECOG performance status of 0 or 1.

Treatments

A median of 8.5 chemotherapy cycles was delivered (range 1–12), with median RDI calculated for 16 patients who received more than one cycle (table 2) as follows: 5-FU (83%), oxaliplatin (80%) and irinotecan (64%). A median of two cycles was achieved before further dose reductions were made, which were required for 10 (62%) patients, all of whom had a reduction in their oxaliplatin dose. No chemotherapy drugs were omitted entirely from the planned mFOLFIRINOX treatment regimen.

Two patients who were treated with full-dose FOLFIRINOX in the specified time period were not included in our study cohort. One discontinued therapy after the first cycle due to grade 4 thrombocytopenia and grade 3 nausea; the other patient tolerated two cycles before dose reduction to a modified regimen which was discontinued after a single cycle due to disease progression.

Adverse Events

Treatment-related grade 3 and 4 adverse effects and other toxicity-related events are summarised in table 3 and compared with the toxicity reported with full-dose FOLFIRINOX by Conroy et al. [3]. The incidence of neutropaenia was significantly lower with mFOLFIRINOX compared to the full dose (0 vs. 45.7%, $p < 0.001$), with only 1 episode of febrile neutropaenia. There was a trend towards less severe fatigue which did not meet statistical significance (5.6 vs. 23.6%, $p = 0.129$). There were no significant differences between the rates of other AEs. Eleven patients (61%) experienced one or more grade 3/4 toxicity and three (16.7%) discontinued treatment as a result. Hospital admission was required in seven cases (38.9%) after a median of two cycles (range 1–12), with details presented in table 4. The most common reasons for hospitalisation were uncontrolled gastrointestinal tract toxicities (five cases) and non-neutropaenic fever (four cases). One patient developed severe dysarthria during oxaliplatin infusion which was attributed to oxaliplatin. This resolved spontaneously within hours and did not recur after dose reduction of oxaliplatin.

Table 1. Patient characteristics

Gender	
Male	8 (44.4)
Female	10 (55.6)
Age, years	
Median	60
Range	40–77
ECOG performance status	
0	10 (56.6)
1	8 (44.4)
Disease localisation	
Head	10 (56.6)
Body	1 (5.6)
Tail	3 (16.7)
Resected	4 (22.2)
Disease site	
Metastatic	15 (83.3)
Locally advanced	3 (16.7)
Biliary stent in situ	
Yes	3 (16.7)
No	15 (83.3)
Values are shown as n (%) unless otherwise indicated.	

Table 2. Treatments delivered and dose reductions

Cycles	8.5 (1–12)
Cycles before dose reduction	2 (1–11)
RDI, %	
5-FU infusion	83.0 (65.9–100)
Oxaliplatin	80.5 (53.3–100)
Irinotecan	64.3 (43.0–75.0)
Dose reduction (total patients)	10 (62.5)
5-FU	4 (25)
Oxaliplatin	10 (62.5)
Irinotecan	3 (18.8)
Values are shown as n (%) or median (range).	

Outcomes

With a median follow-up of 8.9 months (range 3.9–24.0), the median OS and PFS for 15 patients with stage IV disease was 9.3 months (95% CI 8.3–10.4) and 7.2 months (95% CI 4.7–9.6), respectively (fig. 1), all of whom received at least three treatment cycles. At least stable disease by radiological criteria was achieved in 12/15 (80.0%) patients, with 7/15 (46.7%) attaining objective partial responses (table 5).

Table 3. Grade 3 and 4 AEs with mFOLFIRINOX compared with prospective AE data reported with FOLFIRINOX (full dose) [3]

	mFOLFIRINOX (n = 18)	Full dose [3]	p
<i>Adverse events</i>			
<i>Haematological (total)</i>			
Febrile neutropaenia	1 (5.6)	9/166 (5.4)	NS
Neutropaenia	0	75/164 (45.7)	<0.001
Thrombocytopenia	0	15/165 (9.1)	NS
Anaemia	0	13/166 (7.8)	NS
<i>Non-haematological</i>			
Vomiting	5 (27.8)	24/166 (14.5)	NS
Diarrhoea	3 (16.7)	21/165 (12.7)	NS
Nausea	4 (22.2)	NR	
Fever (non-neutropaenic)	3 (16.7)	NR	
Fatigue	1 (5.6)	39/165 (23.6)	0.13
Dysarthria	1 (5.6)	NR	
Sensory neuropathy	0	15/166 (9.0)	NS
Elevated alanine transaminase	0	12/165 (7.3)	NS
Thromboembolism	0	11/166 (6.6)	NS
<i>Toxicity-related events</i>			
Acute advice/attendance	6 (33.3)	NR	
Hospitalisation	7 (38.9)	NR	
Treatment discontinuation	3 (16.7)	NR	
Values are shown as n (%). NR = Not reported; NS = not statistically significant, p > 0.05.			

Table 4. Hospital admissions for AEs

Cycle ^a	Admission duration, days	AEs ^b
1	2	Nausea, vomiting, dysarthria
1	14	Febrile neutropaenia, diarrhoea
1	8	NNF, nausea, fatigue
2	6	NNF, nausea, vomiting
4	2	Vomiting
5	9	NNF
12	–	NNF (grade 2)

NNF = Non-neutropaenic fever.

^a Cycle after which hospital admission was required. ^b Grade 3 or 4 unless otherwise indicated.

Table 5. Best radiological responses

Complete response	1 (6.7)
Partial response	6 (40.0)
Stable disease	5 (33.3)
Progressive disease	3 (20.0)

Values are shown as n (%).

Discussion

The FOLFIRINOX regimen was recently established as an active treatment for unresectable pancreatic adenocarcinoma; however, toxicity has been a major limitation to treatment delivery. In the only phase III study reported to date comparing FOLFIRINOX with gemcitabine alone, both median OS (11.1 vs. 6.8 months) and objective response rate (31.6 vs. 9.4%) were significantly improved by combination chemotherapy. The most commonly occurring grade 3/4 toxicities were neutropaenia (45.7%), fatigue (23.6%), vomiting (14.5%) and diarrhoea (12.7%). Limited fully published evidence exists to support the use of mFOLFIRINOX regimens that are intended to attenuate toxicities whilst preserving efficacy [5, 6, 9, 10]. A summary of study characteristics and outcomes is presented in table 6. In the current report, 5-FU bolus omission was combined with irinotecan 25% dose reduction and routine use of haematopoietic growth factor support.

In line with other studies, the outcome measures for patients with metastatic disease were comparable to those reported for patients undergoing full-dose treatment (table 6), with the caveat that efficacy comparisons based on

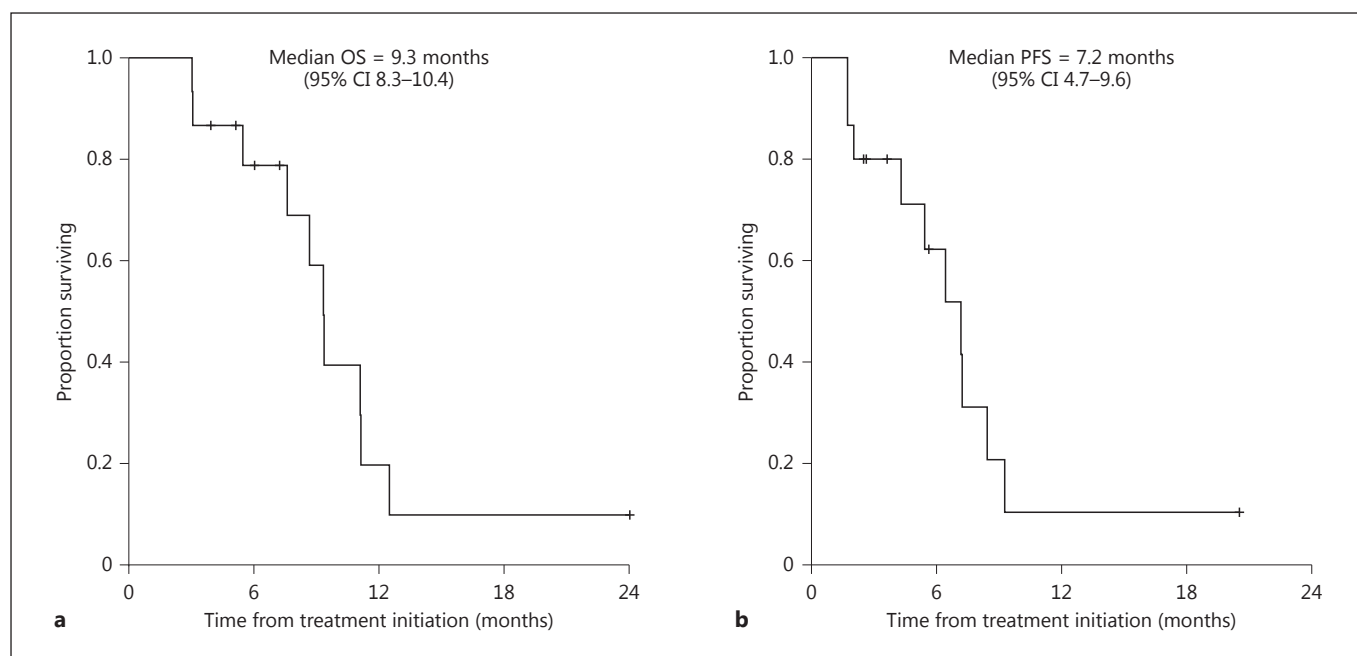


Fig. 1. Kaplan-Meier plots of OS (a) and PFS (b).

overlap in confidence intervals in median survival statistics is suboptimal, and a randomised phase III study would address this more objectively. Neither the median OS nor the PFS reported here were significantly different from those of the study by Conroy et al. [3] (9.3 vs. 11.1 months and 7.2 vs. 6.4 months, respectively).

In addition, the mFOLFIRINOX regimen we employed had a significantly lower haematological toxicity profile compared to the full-dose treatment, with fewer episodes of grade 3/4 neutropaenia. However, the most frequently occurring non-haematological side effects of diarrhoea and vomiting occurred with comparable frequency to full-dose therapy, with a non-statistically significant reduction in the rate of fatigue.

Although two previous retrospective reports of FOLFIRINOX, where the majority of patients received dose-reduced therapy, have suggested much lower rates of fatigue, nausea and vomiting (<6% in each category) [5, 6], the only published study to specifically evaluate mFOLFIRINOX in the palliative setting reported rates not significantly different to the full dose and closer to those observed here [9]. Similarly, a recently presented prospective phase II study of dose-attenuated treatment found only vomiting and fatigue to be significantly reduced in frequency (2.7 vs. 14.5% and 12.2 vs. 23.3%, respectively), with the incidence of other non-haematological side effects including diarrhoea comparable to full-

dose treatment, and final survival data are awaited [8]. An improved toxicity profile has been reported in the neoadjuvant setting [10]; however, rates of diarrhoea were similar to full-dose therapy. Given the likely superior overall fitness of the operable cohort, these data may not be comparable to results of studies within which a majority of patients had metastatic disease.

In all but one study on the toxicity profile of mFOLFIRINOX, the data are retrospective in nature and therefore can be criticised, as precise identification and grading of AEs cannot be assured. Despite this limitation, harder toxicity endpoints may give a less biased picture. In a total of 121 delivered cycles, three patients (17%) discontinued therapy due to adverse effects, and seven (39%) required hospital admission. This hospitalisation rate is similar to that reported by Peddi et al. [5] of 34% (n = 21/61), although the overall toxicity rate was very low in that study (e.g. 3% incidence of diarrhoea). Similarly, Blazer et al. [10] reported a hospital admission rate of 30% (n = 13/43). Randomised prospective studies are required to address these discrepancies, and at present, two phase III trials evaluating mFOLFIRINOX in locally advanced disease (NCT01926197) and the adjuvant setting (NCT01526135) are recruiting.

In summary, the mFOLFIRINOX regimen evaluated here was better tolerated than the full-dose treatment with regard to haematological toxicities and also con-

Table 6. Comparison of studies investigating full-dose FOLFIRINOX and mFOLFIRINOX

Study characteristics	Full dose			mFOLFIRINOX		
	Conroy [3]	Peddi [5]	Gunturu [6]	Mahaseth [9]	Blazer [10]	CUH
Patients, n	166	61	35	60	43	18
Median age, years	61	58	61	63	62.4	60
Stage, %						
Locally advanced	0	37.7	45.7	40	100	16.7
Metastatic	100	62.3	54.3	60	0	83.3
ECOG performance status, %						
0	37.4	NR	69	22	100	56
1	61.9	NR	31	76	100	44
Treatment, mg/m ²						
5-FU bolus	400	400	400	omit	omit	omit
5-FU continuous	2,400/46 h	2,400/46 h	2,400/46 h	2,400/46 h	2,400/46 h	2,400/46 h
Oxaliplatin	85	85	85	85	85	85
Irinotecan	180	180	180	180	165	130
Routine GCSF	no	no	yes	yes	yes	yes
Dose intensity, %						
5-FU bolus	82	57	66	NR	NR	–
5-FU continuous	82	96	100	NR	NR	83
Oxaliplatin	78	96	90	NR	NR	80.5
Irinotecan	81	88	64	NR	NR	64.3
Outcome						
OS, months (95% CI)	11.1 (9.0–13.1)	13.5	11.2	9.0 (7.1–NR)	12.7 ^a (9.6–NR)	9.3 (8.3–10.4)
PFS, months (95% CI)	6.4 (5.5–7.2)	7.5	9.9	8.5 (3.7–11.0)	8.9 ^a (4.5–10.4)	7.2 (4.7–9.6)
ORR, %	31.6	18.2	47	30	23	46.7
Grade 3/4 toxicity, %						
Neutropaenia	45.7	19.7	11.4	3	0	0
Fatigue	23.6	4.9	5.7	13	9.3	5.6
Vomiting	14.5	NR	2.9	8	0	27.8
Diarrhoea	12.7	3.3	2.9	13	14.0	16.7

CUH = Cambridge University Hospitals NHS Foundation Trust; GCSF = granulocyte colony-stimulating factor; NR = not reported; ORR = objective response rate.

^a Results for non-resected patients.

ferred a marginal benefit in non-haematological AE rates, without compromising efficacy. A significant proportion (42.5%) of patients within the initial phase III study of FOLFIRINOX required filgrastim; therefore, the question remains to be answered whether routine addition of filgrastim to full-dose FOLFIRINOX as primary prophylaxis would result in similar tolerability as modified dose regimens. Although some studies have reported significant improvements in side effect profile with dose attenuation, our findings are not in keeping with this. Wide variations in toxicity rates between studies may be accounted for by the limitations of retrospective AE profiling. The high hospitalisation rate observed here and elsewhere serves as a more objective indicator of the toxicity of this combination, and rigorous anti-emetic and anti-

diarrhoeal management is strongly recommended. The potential benefits of mFOLFIRINOX remain to be proven, and the results of ongoing prospective studies are awaited to formally evaluate the safety and outcomes of these regimens.

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Disclosure Statement

The authors have no conflicts of interests to declare.

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