Original Study

FOLFIRINOX for Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma: The Royal Marsden Experience

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Abstract

The study aims were to determine the efficacy and toxicity of FOLFIRINOX (5-fluorouracil, irinotecan, and oxaliplatin) in patients with advanced pancreatic adenocarcinoma treated at the Royal Marsden. Data from 49 patients treated with FOLFIRINOX between 2010 and 2013 were retrospectively reviewed. Efficacy and tolerability were similar to that reported in clinical trials.

Background: Pancreatic ductal adenocarcinoma (PDA) has a very poor prognosis. Treatment with FOLFIRINOX has been shown to improve outcomes, but can be associated with significant toxicity. **Materials and Methods:** A retrospective review was performed of all patients with locally advanced or metastatic PDA treated with FOLFIRINOX at the Royal Marsden between November 2010 and November 2013. Efficacy, tolerability, and potential prognostic factors were evaluated. **Results:** Twenty-seven patients with metastatic PDA and 22 patients with locally advanced PDA were treated with FOLFIRINOX. Patients received a median of 9 cycles (range, 1-26) of FOLFIRINOX. The overall response rate was 41% (20 patients), and a further 17 patients (35%) had stable disease. Thirty-five patients (71%) received FOLFIRINOX in the first-line setting, with a median progression-free survival and overall survival, respectively, of 12.9 months and 18.4 months for patients with locally advanced disease; and 8.4 months and 12.2 months for patients with metastatic disease. The most frequently occurring Grade 3/4 toxicities were neutropenia (29%), fatigue (18%), febrile neutropenia (14%), thromboembolism (12%), and thrombocytopenia (10%). In a univariate analysis, reduction in CA 19-9 of >50% ($P < .001$), normalization of CA19-9 ($P < .001$), surgery after FOLFIRINOX ($P = .004$), and use of prophylactic pegfilgrastim ($P = .005$) were prognostic for overall survival. **Conclusion:** The efficacy and tolerability of FOLFIRINOX for PDA at our institution is similar to that reported in clinical trials. Careful selection of patients and monitoring of response (according to CA19-9) and toxicities can help maximize advantage in this patient population.

Clinical Colorectal Cancer, Vol. 13, No. 4, 232-8
Keywords: CA 19-9, Granulocyte-colony stimulating factor, Nab-paclitaxel, Response, Toxicity

Introduction

Pancreatic cancer has a very poor prognosis, with a 5-year survival of approximately 6%, and only 10% to 20% of patients present with resectable disease.[1] Gemcitabine became the standard of care after a small randomised trial, which demonstrated an improvement in median overall survival (OS) compared with bolus 5-fluorouracil (5.6 vs. 4.4 months; $P = .002$).[2] Gemcitabine has been evaluated in combination with a variety of cytotoxic and targeted agents. For example, the addition of erlotinib was associated with a median improvement in OS of 2 weeks,[3] and a meta-analysis demonstrated a survival benefit from the addition of capecitabine.[4]

Over the past few years, additional treatment options have become available for patients with pancreatic cancer. In 2011, Conroy et al published the results of the landmark phase II/III Partenariat de Recherche en Oncologie Digestive (PRODIGE) 4/Actions Concertées dans les Cancers Colo-Rectaux et Digestifs (ACCORD) 11 trial, which randomized 342 patients to first-line treatment with either gemcitabine or a regimen comprised of 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).[5] This

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Submitted: Jul 4, 2014; Revised: Aug 21, 2014; Accepted: Sep 10, 2014; Epub: Sep 21, 2014

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1533-0028/$ - see frontmatter
http://dx.doi.org/10.1016/j.clcc.2014.09.005

trial demonstrated that FOLFIRINOX was associated with significant improvements in response rate (RR) and progression-free survival (PFS) and a clinically meaningful improvement in OS from 6.8 to 11.1 months ($P < .001$). However, although patients' quality of life improved compared with treatment with gemcitabine, FOLFIRINOX was also associated with significant toxicities, including neutropenia, diarrhea, and peripheral neuropathy. The trial enrolled relatively younger patients with good performance status and therefore there were concerns as to whether the results could be applied to the general patient population outside of the context of clinical trials. More recently, the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) trial has also shown a significant OS benefit for the combination of nab-paclitaxel with gemcitabine (8.5 months vs. 6.7 months; $P < .001$)[6] and this is now another treatment option for many patients. The toxicity profile of gemcitabine/nab-paclitaxel is different to that of FOLFIRINOX and there is ongoing debate on how to select the optimal treatment strategy for an individual patient.

At the Royal Marsden (RM), we have been treating patients with pancreatic cancer with FOLFIRINOX since 2010. We conducted a retrospective review of our experience with FOLFIRINOX in patients with locally advanced (LAPC) and metastatic (MPC) pancreatic cancer. The study objectives were to assess the efficacy and safety of FOLFIRINOX outside of a clinical trial, to assess potential prognostic variables, and to evaluate whether initial treatment with FOLFIRINOX affects response to subsequent lines of chemotherapy.

Materials and Methods

After approval from the institutional review board, we searched the pharmacy section of patients' electronic medical records to identify patients treated with FOLFIRINOX at RM between November 2010 and November 2013. Patients were considered eligible if they received at least 1 cycle of FOLFIRINOX and had histological confirmation of locally advanced or metastatic pancreatic adenocarcinoma.

Standard practice was to start treatment for patients using full-dose FOLFIRINOX, which consisted of oxaliplatin 85 mg/m^2 over 2 hours followed by irinotecan 180 mg/m^2 and leucovorin 400 mg/m^2 given concurrently over 1 hour. This was immediately followed by 5-fluorouracil given as a 400 mg/m^2 bolus and then a continuous infusion of 2400 mg/m^2 over 48 hours. The premedication regimen consisted of intravenous ondansetron and dexamethasone and prophylactic treatment with atropine was given to prevent cholinergic syndrome. Patients received oral dexamethasone and metoclopramide for 3 days and ciprofloxacin 250 mg twice daily for 7 days after chemotherapy. All patients were provided with loperamide and advised to start this at the first sign of diarrhea. The use of prophylactic granulocyte-colony stimulating factor (G-CSF) and dose reductions was at the discretion of the treating physician. Treatment cycles were repeated every 2 weeks until disease progression, unacceptable toxicity, or completion of the planned treatment course.

Clinical information including patient demographic and clinical characteristics, CA19-9, safety/tolerability (measured according to gradable toxicities according to the National Cancer Institute Common Toxicity Criteria version 4.0), hospital admissions, treatment regimes, and patient outcomes were retrospectively collected from patient records. Radiographic response was assessed by S.Y.M. and K.K. according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and compared with the official radiology reports.

Most of the analysis is descriptive, with frequencies and medians being reported. PFS was calculated from the start of treatment with FOLFIRINOX to the date of progression or death. OS was calculated from the start of treatment with FOLFIRINOX to the date of death. Patients who were still alive were censored at the time of last follow-up. Association of survival outcomes with baseline prognostic factors was determined using Cox regression univariate analysis and hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. Factors included in the univariate analysis were sex, age ($\leq$ 60 vs. $>$ 60 years), T-stage, N-stage, extent of disease (LAPC vs. MPC), performance status, line of treatment, number of cycles ($<$ 6 vs. $\geq$ 6), neutrophil/lymphocyte ratio, baseline CA19-9, normalization of CA19-9 (CA19-9 $\leq$ 37 vs. $>$ 37 U/mL), percentage decrease in CA19-9 ($\leq$ 50% vs. $>$ 50% and $\leq$ 90% vs. $>$ 90%), surgery after FOLFIRINOX treatment, and use of prophylactic G-CSF. A multivariate Cox regression model for OS and PFS was developed using a forward stepwise selection method, which included all significant univariate variables ($P < .05$).

Results

Patient Characteristics

Between November 2010 and November 2013, 49 patients with pancreatic adenocarcinoma were treated with FOLFIRINOX at RM. Baseline demographic and clinical characteristics are shown in Table 1. The median age was 60 (range, 34 -76) years and 26 (53%) of the patients were male. Twenty-two patients had LAPC (9 patients had borderline resectable disease and 13 had unresectable disease) and 27 had MPC at the time of treatment with FOLFIRINOX.

Study Treatment and Adverse Events

Patients received a median of 9 cycles of FOLFIRINOX (range, 1-26), with 12 patients receiving $<$ 4 cycles and 22 patients receiving $\geq$ 12 cycles. The reasons for treatment discontinuation are shown in Table 2. The dose of 1 or more components of FOLFIRINOX was reduced in patients (74%), including omission of bolus 5-fluorouracil in 7 patients (14%). The median number of cycles of oxaliplatin was 9 (range, 1-24). Dose delays of $\geq$ 7 days occurred in 23 patients (47%); with 16 patients (33%) having 1 dose delay, 5 patients (10%) having 2 doses delayed, and 2 patients (4%) having 3 doses delayed. Most dose delays were for 7 days (87%) with 13% of dose delays lasting $\geq$ 14 days.

Treatment-related toxicities are summarized in Table 3. There were no deaths related to chemotherapy toxicities. Fourteen patients (29%) had biliary stents in situ at the time of treatment with FOLFIRINOX (7 metal, 2 plastic, 5 stent type unknown), and there was 1 case of cholangitis. Nineteen patients (39%) had 1 emergency hospital admission during treatment with FOLFIRINOX, with a median duration of 4.5 days (range, 4-5 days) and 2 patients (4%) were admitted twice (median duration of second admission, 11.5 days; range, 2-21 days).

G-CSF (pegfilgrastim or filgrastim) was given as primary prophylaxis from cycle 1 onwards in 29 patients (59%), and these

Table 1 Baseline Characteristics of Patients Treated With FOLFIRINOX (n = 49)

Characteristic	n (%)
Sex	
Male	26 (53)
Female	23 (47)
Median Age at Time of FOLFIRINOX Treatment (Range), Years	60 (34-76)
ECOG Performance Status	
0	20 (41)
1	24 (49)
2	5 (10)
Extent of Disease	
Locally advanced	22 (45)
Metastatic	27 (55)
Tumor Location	
Head	30 (61)
Body	9 (18)
Tail	8 (16)
Unknown (previous surgery)	2 (4)
Median CA 19-9 (Range), U/mL	1117 (1-1,058,199)
Previous Surgery	10 (20)
Previous Lines of Chemotherapy for Advanced Disease	
0	35 (71)
1	13 (27)
2	1 (2)
Previous First-Line Advanced Chemotherapy Regimens	
Gemcitabine/capecitabine	10
Gemcitabine/oxaliplatin	1
Gemcitabine	1
Erlotinib	1
Best Response to Previous First-Line Chemotherapy	
Complete response	0
Partial response	1
Stable disease	8
Progressive disease	3

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FOLFIRINOX = 5-fluorouracil, irinotecan, and oxaliplatin.

patients received a higher median number of cycles of FOLFIRINOX (12 vs. 6.5 cycles, $P = .083$). Although patients who received prophylactic G-CSF from cycle 1 and onward had reduced Grade ≥ 3 neutropenia (24% vs. 35%; $P = .524$) and febrile neutropenia (10% vs. 20%; $P = .422$), this was not statistically significant. Of the 20 patients who did not start prophylactic G-CSF from cycle 1, 3 patients (6%) subsequently received G-CSF because of febrile neutropenia and 3 patients (6%) received G-CSF for neutropenia.

Efficacy

In the whole cohort (LAPC and MPC), 1 patient had a complete response and a further 19 patients (39%) had a partial response, with an overall RR (ORR) of 41%. A further 17 patients (35%) had stable disease. In addition to the 1 patient who had a complete response on computed tomography imaging, 4 patients had a complete metabolic response on positron emission tomography imaging. Twenty-five patients (51%) had a reduction in CA 19-9 of > 50% and 15 patients (31%) had a reduction of > 90%. After a median follow-up of 20.6 months, the median PFS and OS for the whole cohort was 9.5 months (95% CI, 7.4-11.5) and 12.9 months (95% CI, 9.3-16.6), respectively. Patients with LAPC had a median PFS and OS of 12.0 and 18.4 months, respectively, and patients with MPC had a median PFS of 6.9 months and an OS of 10.4 months. Thirty-five patients (71%) received FOLFIRINOX in the first-line setting, with a median PFS and OS of 12.9 months (95% CI, 0.5-25.4) and 18.4 months (95% CI, 8.2-28.6) for patients with LAPC and 8.4 months (95% CI, 4.6-12.1) and 12.2 (95% CI, 6.6-17.7) months for patients with MPC (Figures 1 and 2). FOLFIRINOX was given as a second-line treatment in 13 patients (27%) and as a third-line treatment in 1 patient. The median PFS and OS for these 14 patients were 3.9 months and 8.2 months, respectively.

Two patients survived for more than 36 months. One patient with locally advanced, unresectable disease at presentation had a complete pathological response after 12 cycles of first-line FOLFIRINOX, consolidation chemoradiotherapy, and surgery. The second patient had metastatic disease at presentation and had progressive disease after 5 cycles of GEMCAP (gemcitabine and capecitabine). The patient received 14 cycles of FOLFIRINOX in

Table 2 Reasons for FOLFIRINOX Discontinuation

Reason	n (%)
Disease Progression	22 (45)
Completion of Planned Number of Cycles	18 (37)
Disease-Related Complication	3 (6)
FOLFIRINOX Toxicity	2 (4)
Patient Declined Further Treatment	2 (4)
Insufficient Response	1 (2)
Death	1 (2)

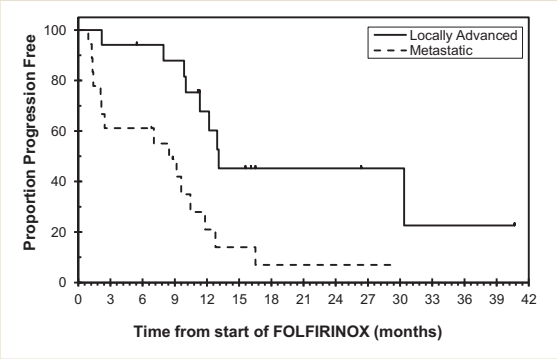
Abbreviation: FOLFIRINOX = 5-fluorouracil, irinotecan, and oxaliplatin.

Table 3 Toxicity After Treatment With FOLFIRINOX

Toxicity	Any Grade, n (%)	Grade 3/4, n (%)
Neutropenia	27 (55)	14 (29)
Fatigue	36 (74)	9 (18)
Febrile Neutropenia	7 (14)	7 (14)
Thromboembolism	7 (14)	6 (12)
Thrombocytopenia	24 (49)	5 (10)
Anemia	30 (61)	2 (4)
Sensory Neuropathy	25 (51)	2 (4)
Diarrhea	20 (41)	2 (4)
Mucositis/stomatitis	11 (22)	2 (4)
Vomiting	7 (14)	2 (4)
Nausea	14 (29)	1 (1)
Other	10 (20)	7 (14)

Abbreviation: FOLFIRINOX = 5-fluorouracil, irinotecan, and oxaliplatin.

Figure 1 Progression-Free Survival for Patients Treated With FOLFIRINOX as a First-Line Therapy (n = 35)



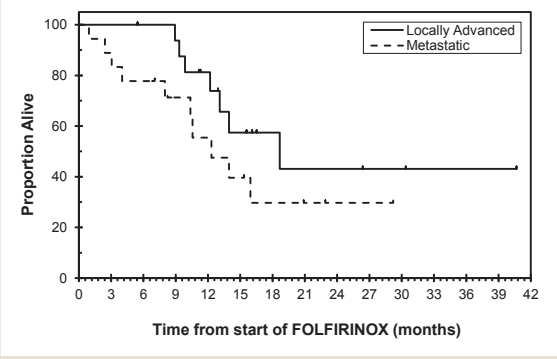
Abbreviation: FOLFIRINOX = 5-Fluorouracil, Irinotecan, and Oxaliplatin.

the second-line setting, with a partial response. After a treatment break, the patient was rechallenged with a further 6 cycles of FOLFIRINOX, with a complete response. This patient subsequently developed disease progression, and did not respond to a second rechallenge with FOLFIRINOX, but achieved stable disease after a rechallenge with GEMCAP.

Prognostic Variables

A univariate analysis (Table 4), demonstrated that extent of disease, number of cycles, use of prophylactic G-CSF from cycle 1, surgery after FOLFIRINOX, line of treatment, percentage reduction in CA 19-9 of > 50% and a CA 19-9 nadir < the upper limit of normal (37 U/mL) were prognostic for PFS and OS. After a multivariate analysis, percentage reduction in CA 19-9 ($P < .001$; HR, 6.3; 95% CI, 2.8-14.0), surgery after FOLFIRINOX ($P = .013$; HR, 12.9; 95% CI, 1.7-96.8), and extent of disease ($P = .009$; HR, 2.7; 95% CI, 1.3-5.5) were significant for PFS; and percentage reduction in CA 19-9 ($P = .003$; HR, 3.4; 95% CI, 1.5-7.6) and surgery after FOLFIRINOX ($P = .044$; HR, 7.9; 95% CI, 1.1-59.8) were also significant for OS.

Figure 2 Overall Survival for Patients Treated With FOLFIRINOX as a First-Line Therapy (n = 35)



Abbreviation: FOLFIRINOX = 5-Fluorouracil, Irinotecan, and Oxaliplatin.

Subsequent Treatment After FOLFIRINOX

After completing treatment with FOLFIRINOX, 15 patients (31%) received consolidation radiotherapy. Thirteen of these patients received 54 Gy in 30 fractions with concomitant capecitabine, 1 patient discontinued chemoradiotherapy after 18 fractions because of the development of acute renal failure, and 1 patient received CyberKnife (38 Gy in 3 fractions) to the pancreatic surgical bed.

Seven patients with LAPC underwent surgery (Table 5), with a PFS of 29.9 months (95% CI, 1.3-58.7). One patient died from liver failure after surgery, which was thought to be due to an ischemic hepatic insult in the perioperative period on a background of steatohepatitis secondary to diabetes and prolonged chemotherapy exposure. In addition, 2 patients with resectable liver metastases underwent surgery, achieving R0 resections. These 2 patients were alive and disease-free at 28 months and 8 months, respectively, after resection.

At the time of the last follow-up, 25 patients (51%) had received 1 or more further lines of palliative chemotherapy. Of these 25 patients, 15 patients (60%) received GEMCAP. Other treatment regimens used were FOLFIRINOX rechallenge (4 patients), nab-paclitaxel (2 patients), gemcitabine (2 patients), gemcitabine/nab-paclitaxel (1 patient), and gemcitabine/erlotinib (1 patient). The ORR to the line of treatment after FOLFIRINOX was 8% (2 patients), with a further 13 patients (52%) having stable disease. At the time of analysis, 5 patients were undergoing their first line of chemotherapy after FOLFIRINOX and 9 patients had received or were currently undergoing their second line of chemotherapy after FOLFIRINOX.

Discussion

The purpose of this study was to evaluate our experience of FOLFIRINOX in patients treated at RM outside of the context of a clinical trial. The efficacy of treatment was comparable with that seen in the PRODIGE 4/ACCORD 11 trial. For patients with MPC, the RR of 41% was greater than the 32% reported by Conroy et al,[5] but was comparable with the 47% reported by another retrospective series.[7] Survival outcomes were also broadly similar, with a PFS of 8.4 months and an OS of 12.2 months in patients with MPC treated in the first-line setting (compared with 6.4 months and 11.1 months in the PRODIGE 4/ACCORD 11 study) and this supports the theory that these outcomes can be achieved outside of a clinical trial setting. As expected, the outcomes for patients with LAPC were better than those for patients with MPC, with a PFS of 12.9 months and an OS of 18.4 months. Again, this was comparable with previously published retrospective series (PFS, 11.7-16.1 months; OS, 17.8 months-not reached).[7-9]

Even though analysis of the quality of life data from the PRODIGE 4/ACCORD 11 trial demonstrated that FOLFIRINOX improved patients' quality of life compared with gemcitabine,[10] one of the main concerns with FOLFIRINOX is the potential level of toxicity associated with this treatment regimen. The toxicities experienced by our patients were broadly similar to those in previous reports, although the incidence of Grade 3/4 diarrhea (4%) was less than that reported by some other studies (2.9%-30%).[5,7,8,11-16] This might be because of dose reductions and prompt supportive care with loperamide. Despite some patients

Table 4 Univariate Analysis of PFS and OS

Covariate	n	PFS			OS		
		Median, Months (95% CI)	Hazard Ratio (95% CI)	*P*	Median, Months (95% CI)	Hazard Ratio (95% CI)	*P*
Age			1.01 (0.53-1056)	.954		0.7 (0.32-1.20)	.353
≤60 Years	19	9.7 (4.8-14.7)			12.0 (8.4-15.7)		
>60 Years	30	9.1 (6.6-11.5)			18.4 (7.4-29.4)		
Extent of Disease			2.68 (1.35-5.30)	.003		2.18 (1.0-4.75)	.044
Locally advanced	22	12.0 (9.2-14.9)			18.4 (11.7-25.2)		
Metastatic	27	6.9 (0-14.1)			10.4 (8.2-12.5)		
Performance Status			1.15 (0.58-2.29) (PS 0 vs. 1)	.694 (PS 0 vs. 1)		0.88 (0.39-1.96) (PS 0 vs. 1)	.747 (PS 0 vs. 1)
0	20	9.7 (4.1-15.4)			12.9 (11.2-14.6)		
1	24	9.9 (8.0-11.8)			18.8 (5.2-32.4)		
2	5	4.6 (3.0-6.2)			6.2 (1.3-11.1)		
Line of Treatment			2.74 (1.38-5.42)	.003		2.39 (1.10-5.20)	.023
First	35	11.2 (8.7-13.6)			13.8 (9.7-17.8)		
≥Second	14	3.9 (0.9-6.9)			8.2 (1.0-15.4)		
Number of Cycles			0.26 (0.08-0.86)	.018		0.15 (0.04-0.52)	.001
<6	3	1.3 (0.7-1.9)			1.3 (0.7-1.9)		
≥6	46	9.9 (7.9-11.9)			13.8 (9.2-18.3)		
Prophylactic G-CSF From Cycle 1			2.18 (1.13-4.19)	.017		2.86 (1.32-6.2)	.005
Yes	29	10.4 (8.3-12.5)			18.8 (13.5-24.1)		
No	20	2.4 (0.0-7.7)			9.2 (6.4-12.0)		
Reduction in CA 19-9			0.18 (0.09-0.37)	<.001		0.23 (0.1-0.52)	<.001
≤50%	24	2.4 (1.4-3.4)			8.8 (7.1-10.5)		
>50%	25	12.0 (9.9-14.2)			18.8 (5.2-32.4)		
Reduction in CA 19-9			0.69 (0.35-1.36)	.277		0.65 (0.29-1.45)	.293
≤90%	34	7.4 (1.5-13.3)			12.2 (7.6-16.7)		
>90%	15	11.7 (9.6-13.8)			15.7 (8.8-22.6)		
CA 19-9 Nadir[a]			3.58 (1.64-7.79)	.001		4.8 (1.86-12.4)	<.001
≤37	18	12.0 (3.7-20.3)			37.1 (10.5-63.7)		
>37	31	7.0 (2.4-11.5)			10.2 (8.0-12.5)		
Surgery After FOLFIRINOX			19.5 (2.6-145.7)	<.001		10.4 (1.41-77.2)	.004
No	40	7.8 (3.7-12.0)			10.4 (7.9-13.0)		
Yes	9	29.9 (1.4-58.5)			NA		

Abbreviations: FOLFIRINOX = 5-fluorouracil, irinotecan, and oxaliplatin; G-CSF = granulocyte-colony stimulating factor; OS = overall survival; PFS = progression-free survival; PS = performance status.
[a]The upper limit of the normal range for CA 19-9 at the Royal Marsden is 37 U/mL.

continuing FOLFIRINOX for ≥ 12 cycles, the rate of Grade ≥ 3 peripheral neuropathy was comparable with previously published series, although oxaliplatin was frequently discontinued after 9 cycles. Although a large proportion of patients (43%) required 1 or more emergency hospital admissions during treatment with FOLFIRINOX, this was broadly comparable with that seen in other retrospective series (32%-36%),[9,13,14] and most patients were discharged within 5 days.

In previously published studies, the rate of Grade 3/4 neutropenia varied from 3% to 57%,[5,7-9,11-17] probably at least partly because of intra- and interstudy variations in G-CSF use. Interestingly, in our study, a univariate analysis showed that patients who received G-CSF had a longer PFS and OS. One potential explanation for this is that G-CSF support might have facilitated longer treatment with FOLFIRINOX and therefore greater treatment efficacy. However, these data should be interpreted with caution because there are a number of potential confounding variables and these results were not confirmed in multivariate analysis (although this analysis was in turn limited because of the small number of patients in our study).

In our patients, dose delays were common, occurring in 47% of patients. This is in keeping with that reported by other series,[16] and for logistical reasons were generally for 7 days. Similarly, dose reductions were also common, occurring in 74% of patients. Although this is more than the 29% to 58% reported in other series,[12,14] this might reflect that most of our patients started treatment with full-

Table 5 Characteristics of the Patients With Locally Advanced Pancreatic Cancer Who Underwent Surgery (n = 7)

Characteristic	n
Extent of Disease at Time of Treatment With FOLFIRINOX	
Borderline resectable	5
Unresectable	2
Median CA 19-9 at Baseline (Range)	119 (17-13,976)
Neoadjuvant Treatment: FOLFIRINOX as a First-Line Treatment	7
Response to FOLFIRINOX on CT Imaging	
Complete response	0
Partial response	6
Stable disease	1
Response to FOLFIRINOX on PET Imaging	
Complete response	3
No PET scan performed	4
Consolidation Chemoradiotherapy (54 Gy in 30 Fractions With Concomitant Capecitabine)	
Yes	6
No	1
Resection Margin	
R0	4
R1	3
Lymph Node Status	
Median number of positive nodes (range)	0 (0-3)
Median total number of nodes (range)	27 (12-42)
Adjuvant Chemotherapy	
Yes (gemcitabine and capecitabine)	1
No	6

The closest borders for the patients who achieved an R0 resection were 1.3 mm, 4 mm, complete pathological response, and not documented. The patient who received adjuvant chemotherapy was the patient who did not receive consolidation chemoradiotherapy.
Abbreviations: CT = computed tomography; FOLFIRINOX = 5-fluorouracil, irinotecan, and oxaliplatin; PET = positron emission tomography.

dose FOLFIRINOX. In contrast, other series commonly used a modified FOLFIRINOX regimen[8] or started treatment for many patients with reduced-dose FOLFIRINOX,[7,14] although the efficacy results were comparable. Furthermore, the median number of treatment cycles was 9, with some patients receiving substantially longer courses of treatment (up to 26 cycles) and therefore oxaliplatin was frequently discontinued or reduced to reduce the risk of persistent peripheral neuropathy. Despite the toxicities experienced by our patients, a lower than expected proportion of patients stopped treatment because of toxicity and a high proportion of patients received 12 or more cycles of FOLFIRINOX. This suggests that the toxicities associated with FOLFIRINOX are manageable with supportive care and dose reductions, allowing treatment to be continued in a large proportion of carefully-selected patients.

Nab-paclitaxel in combination with gemcitabine has recently been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of advanced pancreatic cancer. There is ongoing debate regarding the optimal scheduling of treatment because patients whose disease progresses during first-line therapy might not be fit enough for further chemotherapy and no head-to-head comparison of FOLFIRINOX and gemcitabine/nab-paclitaxel has been performed to date. Some physicians advocate starting with FOLFIRINOX, because patients who undergo first-line treatment tend to be more fit and better able to tolerate treatment toxicities, and the patients treated with FOLFIRINOX in the PRODIGE 4/ACCORD 11 study had a greater RR and longer survival than those treated with gemcitabine/nab-paclitaxel in the MPACT study. In addition, for patients with locally advanced disease, FOLFIRINOX can lead to tumor downstaging and the option of surgical resection, leading to improved patient outcomes.[8,12,18,19] In our study, 9 patients underwent surgery after treatment with FOLFIRINOX. Interestingly, this included 2 patients who had surgery for resectable liver metastases and this has resulted in a prolonged disease-free interval for both patients. Further research is needed to determine whether surgery should be an option for patients with small-volume metastatic disease, a good performance status, and an objective response to treatment.

Second-line chemotherapy after FOLFIRINOX is feasible in selected patients, with 51% of our patients receiving further palliative chemotherapy. This is comparable with the 47% of patients in the FOLFIRINOX arm of the PRODIGE 4/ACCORD 11 study,[5] and greater than the 38% of patients in the gemcitabine/nab-paclitaxel arm of the MPACT study who received second-line therapy.[6] In contrast to the PRODIGE 4/ACCORD 11 study, in which patients commonly received gemcitabine, most of our patients received GEMCAP. Fifty-two percent of patients achieved stable disease with their next line of therapy and although the RR was only 8%, it should be borne in mind that even in the first-line setting, the RR to GEMCAP is only 10% to 17%.[4] There is limited published evidence for the use of gemcitabine/nab-paclitaxel after FOLFIRINOX treatment, apart from case reports that described 2 patients who had good responses,[20,21] but this could be an option if funding is available.

Conversely, other physicians advocate starting with gemcitabine/nab-paclitaxel because of its more favorable toxicity profile, and because persistent peripheral neuropathy secondary to FOLFIRINOX treatment can mean that nab-paclitaxel is not an appropriate second-line treatment option. In the United Kingdom, gemcitabine/nab-paclitaxel is only funded through the Cancer Drugs Fund as a first-line treatment, and therefore FOLFIRINOX would need to be given in the second-line setting for patients to receive both regimens. There are limited data available on the use of FOLFIRINOX as a second-line treatment, and this has typically been used after gemcitabine or GEMCAP chemotherapy rather than gemcitabine/nab-paclitaxel. In our study, 13 patients (27%) received FOLFIRINOX as a second-line treatment and 1 patient was treated with third-line FOLFIRINOX. The PFS and OS of these 14 patients were 3.9 months and 8.2 months, respectively. These results are comparable with the median time to progression/PFS of 2.8 to 5.4 months and OS of 8.2 to 8.5 months reported by other second-line studies of FOLFIRINOX.[11,17]

It is important to identify patients who are most likely to respond to FOLFIRINOX so that the optimal treatment regimen is chosen for each individual patient. In our series, a decrease in CA19-9 of > 50% was associated with improved PFS and OS. This is in keeping with other published reports, which suggest that although

CA19-9 levels were not associated with response according to RECIST,[8] CA19-9 responders had a significantly longer OS[8,17] and a CA19-9 response has also been demonstrated to correlate with improved survival in patients treated with gemcitabine/nab-paclitaxel.[6] Patients who met the PRODIGE 4/ACCORD 11 trial inclusion criteria seemed to have better outcomes than those who did not,[22] and this emphasizes the need for careful selection of patients for treatment with FOLFIRINOX. Indeed, the patients in our study who had a performance status of 2 appear to have had a worse PFS and OS, although because of the small number of patients it was not possible to analyze whether this was statistically significant.

Conclusion

Although our results should be interpreted with caution because of the retrospective nature of our study, our institutional experience shows that outcomes broadly comparable with that seen in the PRODIGE 4/ACCORD 11 trial can be achieved in a non-trial setting in the United Kingdom. Toxicities are significant, but manageable, with only a small proportion of patients stopping treatment because of toxicity. Although FOLFIRINOX can be safely administered as a second-line treatment in selected patients, the optimal scheduling of FOLFIRINOX with other treatment options such as gemcitabine/nab-paclitaxel is as yet undetermined. This requires future study, but in the meantime, the choice of treatment should be tailored to the individual patient and their available treatment options.

Clinical Practice Points

- Advanced pancreatic adenocarcinoma has a poor prognosis. The combination of 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) has been shown to improve outcomes, but can be associated with significant toxicity.
- In this retrospective study, the efficacy and tolerability of FOLFIRINOX for pancreatic adenocarcinoma were similar to that reported in clinical trials.
- With careful patient selection, the toxicities associated with FOLFIRINOX were manageable in routine clinical practice.
- Treatment with FOLFIRINOX facilitated subsequent surgical resection in a proportion of patients whose disease was considered unsuitable for upfront surgery. Patients who underwent surgery after FOLFIRINOX had a longer progression-free and overall survival.
- This study provides more information on the use of FOLFIRINOX in the second-line setting and this may be a treatment option for carefully selected patients.
- A decrease in CA19-9 of more than 50% was associated with improved progression-free and overall survival.

Acknowledgments

We acknowledge support from the NIHR RM/ICR Biomedical Research Centre.

Disclosure

Ian Chau has advisory roles with Merck-Serono, Roche, and Eli Lilly, has received research funding from Merck-Serono and Roche, and honoraria from Roche and Taiho. David Cunningham has received research funding from Amgen, AstraZeneca, Bayer, Celgene, Merck-Serono, Medimmune, Merrimack, Novartis, Roche, and Sanofi. Sheela Rao has advisory and consultancy roles for Merck-Serono, Roche, Eli Lilly, Celgene, and Sanofi. The remaining authors have stated that they have no conflicts of interest.

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