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ORIGINAL PAPER

FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity

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Abstract Although FOLFIRINOX significantly increases survival in metastatic pancreatic cancer (MPC) compared to gemcitabine (Conroy et al. N Engl J Med 364:1817–1825, 2011), toxicities have tempered enthusiasm for its use in full doses. To assess the impact of dose attenuations on toxicity and efficacy, we reviewed our institution's experience with FOLFIRINOX in locally advanced pancreatic cancer (LAPC) and MPC. We performed a retrospective review of dose, toxicity, and efficacy of FOLFIRINOX in all patients with LAPC and MPC treated between June 2010 and July 2011 at Yale. Toxicities in all patients and response rate (RR) and survival in previously untreated MPC were compared to data reported by Conroy. Overall survival (OS) and progression-free survival were estimated by Kaplan–Meier method. Thirty-five patients were treated (16 LAPC; 19 MPC). Twenty-nine patients received dose attenuations with the first cycle. Median relative doses of irinotecan and bolus fluorouracil were less than those reported by Conroy (64 vs. 81 % and 66 vs. 82 %, respectively). RR was 50 % in LAPC and 47 % in MPC, and the latter did not differ significantly from the RR reported by Conroy ($p = 0.19$). OS at 6 and 12 months in MPC was comparable to OS reported by Conroy. Grade 3/4 toxicities were less than reported by Conroy, including fatigue ($p = 0.009$) and neutropenia ($p < 0.0001$). Nine patients experienced transient dysarthria during irinotecan administration. Our findings validate the efficacy and tolerability of FOLFIRINOX in LAPC and MPC and suggest that dose attenuations of irinotecan and bolus fluorouracil improve tolerability without compromising efficacy.

Keywords Pancreatic cancer · FOLFIRINOX · Metastatic pancreatic cancer · Locally advanced pancreatic cancer · Dysarthria

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in men and women [1]. There were an estimated 43,920 new cases and 37,390 deaths from pancreatic cancer in the United States in 2012, and the 5-year survival for all patients with pancreatic adenocarcinoma is <5 % [2]. The vast majority of patients (80–90 %) present with incurable metastatic or locally advanced unresectable disease. Gemcitabine has been the standard of care for treatment of advanced pancreatic cancer for over a decade based on a randomized trial showing an improvement in the one-year survival with gemcitabine compared to fluorouracil (FU) (18 vs. 2 %, $p = 0.0001$) [3]. Although well tolerated, the efficacy of gemcitabine is marginal, with reported response rates of less than 10 % and median survivals of less than 7 months in patients with metastatic disease. Despite promising phase II trials with gemcitabine-based combinations in advanced pancreatic cancer, the addition of cytotoxic drugs (e.g., FU, capecitabine, oxaliplatin, cisplatin, irinotecan) or targeted agents (bevacizumab, cetuximab, erlotinib) to gemcitabine has yielded no meaningful gains in overall survival in multiple randomized trials comparing gemcitabine doublets to gemcitabine alone, till recently [4–13].

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Conroy et al. [14] first reported impressive efficacy and acceptable tolerability of the combination regimen FOLFIRINOX (oxaliplatin 85 mg/m^2 over 2 h, followed by irinotecan 180 mg/m^2 over 90 min and leucovorin 400 mg/m^2 over 2 h, followed by FU 400 mg/m^2 bolus and 2,400 mg/m^2 46 h continuous infusion) in a phase II study in 46 patients with unresectable pancreatic cancer (11 locally advanced, 35 metastatic). In this preliminary study, there were no toxic deaths, and the confirmed response rate was 26 %, including 4 % complete response rate, and median overall survival was 10.2 months. Subsequently, FOLFIRINOX was compared to gemcitabine in a randomized phase III trial in patients with metastatic pancreatic cancer [15]. This study showed significant improvements in overall survival (11.1 vs. 6.8 mo), progression-free survival (6.4 vs. 3.3 mo) and response rate (31.6 vs. 9.4 %) with FOLFIRINOX compared to gemcitabine. However, FOLFIRINOX was associated with significantly more grade 3 and 4 toxicity than gemcitabine (diarrhea, neutropenia, febrile neutropenia, thrombocytopenia and sensory neuropathy). Based on this study, FOLFIRINOX is considered the most effective regimen for metastatic pancreatic cancer, and it is emerging as the new standard of care in appropriate patients with a good performance status. However, given its toxicities, there has been a reluctance to use FOLFIRINOX in full doses, despite the significant increase in efficacy of this regimen compared to gemcitabine.

It is unknown whether the administration of attenuated doses of FOLFIRINOX compromises its efficacy. Moreover, there is a paucity of data regarding the efficacy of FOLFIRINOX in patients with non-metastatic locally advanced pancreatic cancer. We conducted a retrospective review of patients with metastatic or locally advanced unresectable pancreatic cancer treated with FOLFIRINOX at Yale's Smilow Cancer Center to assess the efficacy and the toxicities of this regimen as it is used in an academic practice with routine dose attenuations.

Methods

Design

We conducted a retrospective review of all patients with locally advanced unresectable and metastatic pancreatic cancer treated with FOLFIRINOX at Yale's Smilow Cancer Center between June 2010 and July 2011. We evaluated patient characteristics, toxicities, response rate (RR), progression-free survival (PFS), and overall survival (OS) based on review of the patients' medical records and imaging studies. Toxicities in the entire Yale cohort (locally advanced and metastatic patients), and patient characteristics and RR in the metastatic cohort, were compared to the FOLFIRINOX-treated group as reported by Conroy et al. [15].

Treatment

Full dose FOLFIRINOX consisted of oxaliplatin 85 mg/m^2 over 2 h, followed by irinotecan (IRI) 180 mg/m^2 over 90 min and leucovorin (LV) 400 mg/m^2 over 2 h, followed by FU 400 mg/m^2 as a bolus and 2,400 mg/m^2 as a 46 h continuous infusion. Dose modifications were made at the treating physician's discretion. All patients received peg-filgrastim with the first cycle and subsequent cycles in the absence of severe leukocytosis. Patients routinely received palonosetron, aprepitant, and dexamethasone for emesis prophylaxis.

Assessment

Patients were evaluated for toxicities at the start of each cycle with history, examination, performance status, complete blood count, and metabolic panel. Response assessment imaging was obtained after every 4–6 cycles of treatment. All scans were systematically reviewed by the investigators (KSG, JRT) for response by RECIST.

Duration of treatment and follow-up

Treatment was discontinued at the discretion of the treating physician for unacceptable toxicity, progression of disease, or pursuit of alternative therapies, including surgical resection or radiotherapy for locally advanced disease. Patients were followed for PFS and OS.

Statistics

Toxicities in the entire Yale group were compared with the toxicities in the FOLFIRINOX-treated group as reported by Conroy et al. [15]. One-sample proportion test was used to compare the proportion of grade 3 and 4 adverse events (AEs). Patient characteristics and RR of the Yale metastatic cohort were compared with the FOLFIRINOX-treated group as reported by Conroy et al. [15]. One-sample Wilcoxon signed rank test or Fisher's exact test was used to compare patient characteristics. One-sample proportion test was used to compare the RR in previously untreated metastatic patients. OS and PFS analyses were performed using Kaplan–Meier method. Two patients in the metastatic cohort who had received prior chemotherapy for metastatic disease were excluded from RR and survival analysis.

Results

Patient characteristics

21Between June 2010 and July 2011, 35 patients with advanced pancreatic adenocarcinoma were treated with

FOLFIRINOX at the Yale Smilow Cancer Center, including 16 with locally advanced unresectable disease and 19 with metastatic disease. The demographics and disease characteristics are shown in Table 1. Compared to the series reported by Conroy et al. [15] in previously untreated patients with metastatic disease who received FOLFIRINOX, more patients with metastatic disease in our cohort were female ($p = 0.006$) and had ECOG PS of 0 ($p = 0.003$). In our 19 patients with metastatic disease, 2 had received prior adjuvant chemotherapy, 1 had received prior neoadjuvant chemoradiotherapy, and 2 had received prior chemotherapy for metastatic disease.

Dose modifications and supportive care

Dose modifications were at the discretion of the treating physician. Only 6 of 35 patients received full doses of each drug of FOLFIRINOX with the first cycle. In the remaining 29 patients, dose attenuations with the first cycle were as follows: IRI was reduced in 27 and omitted in 1, OX was reduced in 10, bolus FU was reduced in 9 and omitted in 7, LV was decreased in 11, infusional FU was reduced in 3. The median number of cycles received was 11 (range 1–28). The median relative doses of each drug (in comparison with the median relative doses in FOLFIRINOX-treated patients reported by Conroy et al. [15]) were as follows: OX 90 % (vs. 78 %), IRI 64 % (vs. 81 %), bolus FU 66 % (vs. 82 %), and infusional FU 100 % (vs. 82 %). 34 of 35 patients received peg-filgrastim with the first cycle and subsequent cycles, except in the event of severe leukocytosis, at the discretion of the treating physician.

Efficacy

Response

Response rates in patients with locally advanced and metastatic disease are shown in Table 2. Two of 19 patients with metastatic disease were excluded from the analysis, as they had received prior chemotherapy for metastatic disease. The RR (CR + PR) in the entire group (locally advanced and metastatic) was 48 %, with 1 CR and 15 PR in 33 patients. In patients with metastatic disease, the RR was 47 % and did not differ significantly from the RR of 32 % reported by Conroy et al. in FOLFIRINOX-treated patients ($p = 0.19$). In patients with locally advanced disease, the RR was 50 %, and two patients were able to undergo resection after 4 and 6 cycles. One of these patients had a near pathologic complete response with 2 mm of residual tumor.

Progression-free and overall survival

The survival data are shown in Table 3 and Fig. 1. For the entire cohort of patients (locally advanced and metastatic), the median PFS was 16.1 months, and the median OS has not been reached.

In patients with metastatic disease, the median PFS and OS were 9.9 and 11.2 months, respectively. The PFS in the metastatic cohort at 6 and 12 months was 76 and 35 %, respectively, and the OS at 6 and 12 months was 82 and 50 %, respectively. By comparison, the OS at 6 and 12 months was 75.9 and 48.4 %, respectively, in the FOLFIRINOX-treated patients as reported by Conroy et al. [15].

In patients with locally advanced disease, the median PFS and OS have not been reached. The PFS for locally advanced disease at 6 and 12 months was 94 and 77 %, respectively, and the OS at 6 and 12 months was 94 and 83 %, respectively.

Adverse events

Treatment-related grade 3 and 4 toxicities are summarized in Table 4. There were no toxic deaths attributable to FOLFIRINOX. The incidence of grade 3 or 4 fatigue (5.7 vs. 23.6 %, $p = 0.009$) and neutropenia (11.4 vs. 45.7 %, $p < 0.0001$) was significantly decreased in our cohort compared to the FOLFIRINOX-treated patients as reported

Table 1 Patient demographics and characteristics

Characteristic	Total ($n = 35$)	Locally advanced ($n = 16$)	Metastatic ($n = 19$)	Historical data[15] ($n = 171$)	p value*
Age	61 (48–77)	60 (51–77)	62 (48–76)	61 (25–76)	0.81^{+}
Male	13 (37 %)	8 (50 %)	5 (26 %)	106 (62 %)	0.006^{++}
Female	22 (63 %)	8 (50 %)	14 (74 %)	65 (38 %)	
ECOG PS					
0	24 (69 %)	10 (62 %)	14 (74 %)	64 (37 %)	0.003^{++}
1	11 (31 %)	6 (37 %)	5 (26 %)	106 (62 %)	
Prior therapy	5 (14 %)	0 (0 %)	5 (26 %)	0 (0 %)	
Tumor location					
Head	20 (57 %)	8 (50 %)	12 (63 %)	67 (39 %)	0.05^{++}
Other	15 (43 %)	8 (50 %)	7 (37 %)	104 (61 %)	

* Comparison between the Yale metastatic group and historical control group of FOLFIRINOX-treated patients reported by Conroy et al. [15]

$^{+}$ One-sample Wilcoxon signed rank test

$^{++}$ Fisher's exact test

Table 2 Objective response

	Total ($n = 33$)	Locally advanced ($n = 16$)	Metastatic ($n = 17$)	Historical data[15] ($n = 171$)	p value*
CR	1 (3 %)	1 (6 %)	0 (0 %)	1 (0.6 %)	
PR	15 (45 %)	7 (44 %)	8 (47 %)	53 (31 %)	
SD	13 (39 %)	7 (44 %)	6 (35 %)	66 (39 %)	
PD	2 (6 %)	0 (0 %)	2 (12 %)	26 (15 %)	
CR + PR	16 (48 %)	8 (50 %)	8 (47 %)	54 (32 %)	0.19
CR + PR + SD	29 (88 %)	15 (94 %)	14 (82 %)	120 (70 %)	0.43

* Comparison between the Yale metastatic group and historical control group of FOLFIRINOX-treated patients reported by Conroy et al. [15]. p values are based on one-sample proportion test

Table 3 Survival

	Overall survival			Progression-free survival		
	Median (mos)	6-month	12-month	Median (mos)	6-month	12-month
All patients ($n = 33$)	Not reached	88 %	68 %	16.1	85 %	57 %
Metastatic ($n = 17$)	11.2	82 %	50 %	9.9	76 %	35 %
Locally advanced ($n = 16$)	Not reached	94 %	83 %	Not reached	94 %	77 %

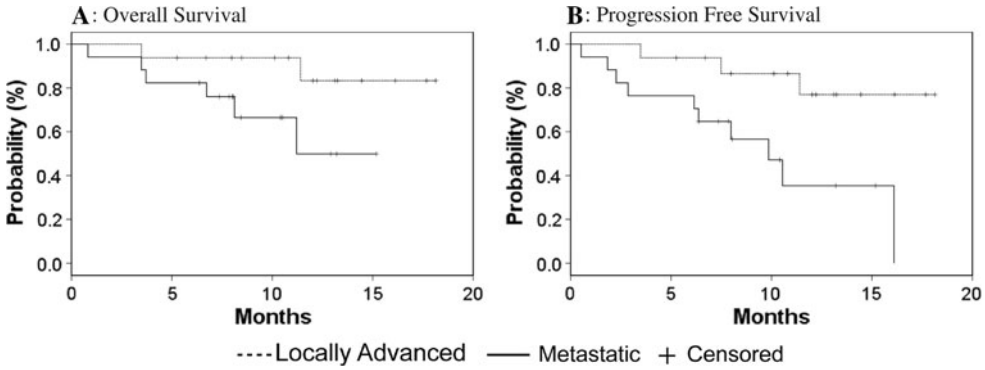

Fig. 1 Kaplan–Meier survival estimates of overall survival (**a**) and progression-free survival (**b**) of patients with locally advanced (*dotted line*) and metastatic (*solid line*) pancreatic cancer

by Conroy et al. [15]. There was a non-significant trend toward a lower incidence of febrile neutropenia, anemia, thrombocytopenia, vomiting, diarrhea, and neuropathy compared to the FOLFIRINOX-treated patients as reported by Conroy et al. [15]. Grade 3 or 4 diarrhea in our patient population was just 2.9 % compared to 12.7 % in the FOLFIRINOX-treated patients as reported by Conroy et al. [15].

In our study, there were nine cases of acute onset of dysarthria and other neurological symptoms during the FOLFIRINOX infusion. These symptoms included dysarthric speech, facial or perioral paresthesias, leg cramps, ataxia, and blepharospasm. In all cases, the onset of these neurological symptoms was temporally associated with the irinotecan infusion. The symptoms remitted with interruption of the irinotecan infusion, and in some cases, recurred with re-challenge. In all cases, the symptoms resolved completely without specific intervention other than transient interruption of the irinotcan infusion and/or administration of anticholinergic agents (atropine and/or diphenhydramine). The first two patients in whom these symptoms developed were hospitalized for neurological work up to rule out a cerebral vascular event; subsequent patients were managed as out-patients in the infusion center. Dose reduction of irinotecan and/or pre-medication with anticholinergics, at the discretion of the treating physician, prevented or mitigated the severity of these neurologic symptoms in subsequent cycles in all patients.

Discussion

Our single institution retrospective study validates the efficacy of FOLFIRINOX in unselected patients with locally advanced and metastatic pancreatic cancer. The majority of the patients treated at our institution received attenuated doses of FOLFIRINOX with the first and subsequent cycles of treatment, and the median relative doses

Table 4 Adverse events

Grade 3/4 event	Yale ($n = 35$)	Historical data[15] ($n = 171$)	p value*
Hematologic			
Neutropenia	4 (11.4 %)	75/164 (45.7 %)	<0.0001
Febrile neutropenia	1 (2.9 %)	9/166 (5.4 %)	1.0
Thrombocytopenia	1 (2.9 %)	15/165 (9.1 %)	0.37
Anemia	0 (0 %)	13/166 (7.8 %)	0.11
Non-hematologic			
Fatigue	2 (5.7 %)	39/165 (23.6 %)	0.009
Diarrhea	1 (2.9 %)	21/165 (12.7 %)	0.12
Vomiting	1 (2.9 %)	24/166 (14.5 %)	0.05
Neuropathy	0 (0 %)	15/166 (9.0 %)	0.07

* Comparison between the Yale group and historical control group of FOLFIRINOX-treated patients reported by Conroy et al. [15]. p values are based on one-sample proportion test

of IRI and bolus FU were lower than those reported in the FOLFIRINOX-treated group reported by Conroy et al. [15]. Nonetheless, our findings suggest that the efficacy of FOLFIRINOX was not compromised by these dose modifications. The RR of 47 % in our patients with metastatic disease was not significantly different from the RR of 32 % in the FOLFIRINOX-treated patients as reported by Conroy et al. [15]. Moreover, the observed PFS and OS at 6 and 12 months, as well as the median OS and PFS, in our patients with metastatic disease were also comparable to the survivals reported by Conroy et al. [15] in the FOLFIRINOX-treated patients.

Although FOLFIRINOX is associated with a significant increase in response rate and overall survival in metastatic pancreatic cancer compared to gemcitabine, the toxicities of FOLFIRINOX have tempered enthusiasm for its use in full doses in community and academic centers [15]. Our study suggests that incorporation of modest dose attenuations of IRI and bolus FU in the majority of patients, in conjunction with routine use of growth factor support with the first and subsequent cycles, is associated with less toxicity than observed in the FOLFIRINOX-treated patients reported by Conroy et al. [15]. We observed a significant decrease in the incidence of grade 3 or 4 fatigue and neutropenia, and a trend toward decreased incidence of febrile neutropenia, anemia, thrombocytopenia, diarrhea, vomiting, and neuropathy in our cohort compared to the FOLFIRINOX-treated patients reported by Conroy et al. [15]. The improved tolerability of FOLFIRINOX in our institution's cohort of patients may be related to the dose modifications, routine use of growth factor support, or the use of aggressive anti-emetic and anti-diarrheal regimens. In addition, a higher percentage of our patients had an ECOG PS of 0 compared to the FOLFIRINOX-treated patients reported by Conroy et al. [15]. Interestingly, 57 % of our patients had carcinoma of the head of the pancreas, compared to 39 % of patients reported by Conroy et al. Although 31 % of our patients had biliary stents for obstruction, we observed only one case of cholangitis.

The optimum treatment of locally advanced unresectable pancreatic cancer remains uncertain. Current therapeutic options include chemoradiation or chemotherapy alone. Meta-analyses comparing chemotherapy with chemoradiation showed no survival benefit and increased toxicity for chemoradiotherapy compared to chemotherapy [16–18]. The combination of gemcitabine and oxaliplatin was compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer in the GERGOR/GISCAD randomized trial. Despite an increased RR in locally advanced disease with gemcitabine/oxaliplatin compared to gemcitabine (27 vs. 14 %), the overall survival was identical at 10.3 mo in both arms [7]. In a subsequent randomized ECOG trial comparing conventional gemcitabine, gemcitabine fixed-dose rate (FDR) infusion, and gemcitabine/oxaliplatin in advanced pancreatic cancer, there was no difference in RR, PFS, or OS between any of the regimens, and the median survival was just 9.2 months in locally advanced disease [8].

Although FOLFIRINOX has superior efficacy compared to gemcitabine in patients with metastatic pancreatic cancer, there are limited data regarding its efficacy and tolerability in locally advanced pancreatic cancer. In the initial phase II trial of FOLFIRINOX, only 11 patients had locally advanced disease, and in these patients, the RR was 27 % and median OS was 15.7 mos [14]. In our cohort of 16 patients with locally advanced pancreatic cancer treated with FOLFIRINOX, we observed a response rate of 50 % and a disease control rate of 94 %, confirming impressive efficacy of FOLFIRINOX in locally advanced disease. The RR in our cohort of locally advanced pancreatic cancer is higher than that reported for gemcitabine-based regimens and is similar to the RR reported by Conroy et al. [15] in FOLFIRINOX-treated patients with metastatic disease. The PFS for locally advanced disease at 6 and 12 months was 94 and 77 %, respectively, and the OS at 6 and 12 month was 94 and 83 %, respectively. Two of our 16 patients with locally advanced disease were able to undergo resection, and one patient had near complete

pathological response. Our findings suggest that the efficacy and tolerability of FOLFIRINOX in locally advanced pancreatic cancer is similar to its efficacy in the metastatic setting and support the use of FOLFIRINOX as initial therapy in patients with locally advanced or borderline disease.

We report nine cases of acute onset of dysarthria and other neurological symptoms (facial or perioral paresthesias, leg cramps, ataxia, and blepharospasm) during the FOLFIRINOX infusion. The onset of these symptoms was temporally associated with the irinotecan infusion. In all cases, the symptoms resolved completely without specific intervention other than transient interruption of the irinotecan infusion and/or administration of anticholinergic agents (atropine or diphenhydramine). In some cases, the symptoms recurred with re-initiation of the irinotecan infusion, but resolved with administration of anticholinergic agents. Neurotoxic effects of irinotecan are uncommon, and only four cases have been reported in the literature [19–22]. The mechanism by which CNS toxicity occurs after irinotecan infusion is not well understood. Harel et al. [23] proposed that irinotecan causes increased cholinergic activity by binding to the active site of acetylcholinesterase causing its functional inhibition. Cholinergic receptors are found more in the brainstem nuclei and using cholinergic agents result in a surge of hypoglossal nerve activity [24, 25], which might explain the dysarthria associated with irinotecan toxicity. This mechanism could be related to cholinergic oversensitivity of the neurons in the hypoglossal nerve nucleus. Atropine has not been shown to prevent dysarthria, and all the reported cases showed that these symptoms were reversible and severity did not worsen upon re-challenging with irinotecan [26]. Since oxaliplatin is routinely administered prior to irinotecan in the FOLFIRINOX regimen, we speculate that oxaliplatin may enhance the neurotoxic effects of irinotecan, thereby increasing the incidence of this rare side effect of irinotecan.

Conclusions

In this single institution retrospective study, the routine use of modest dose attenuations of FOLFIRINOX, in conjunction with growth factor support, was associated with improved tolerability compared to full dose FOLFIRINOX as reported by Conroy et al. Our findings suggest that these modest dose attenuations do not reduce the efficacy of FOLFIRINOX in metastatic pancreatic cancer patients. Moreover, the efficacy of FOLFIRINOX in locally advanced disease was comparable to its efficacy in metastatic disease. Given the number of patients in our series and the limitations of a retrospective study, our findings require further substantiation. Prospective trials are needed to validate the efficacy and tolerability of modifications of FOLFIRINOX in metastatic pancreatic cancer. In patients with locally advanced and borderline disease, we need to better define the activity of FOLFIRINOX and its role and safety in the neoadjuvant setting.

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Conflict of interest None.

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