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Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas

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Abstract

Background—For patients with metastatic pancreatic cancer, FOLFIRINOX (fluorouracil [5-FU], leucovorin [LV], irinotecan [IRI], and oxaliplatin) has shown improved survival rates compared with gemcitabine but with significant toxicity, particularly in patients with a high tumor burden. Because of reported response rates exceeding 30 %, the authors began to use a modified (m) FOLFIRINOX regimen for patients with advanced nonmetastatic disease aimed at downstaging for resection. This report describes their experience with mFOLFIRINOX and aggressive surgical resection.

Methods—Between January 2011 and August of 2013, 43 patients with borderline resectable pancreatic cancer (BRPC, $n = 18$) or locally advanced pancreatic cancer (LAPC, $n = 25$) were treated with mFOLFIRINOX (no bolus 5-FU, no LV, and decreased IRI). Radiation was used based on response and intended surgery. Charts were retrospectively reviewed to assess response, toxicities, and extent of resection when possible.

Results—The most common grade 3/4 toxicity was diarrhea in six patients (14 %) with no grade 3/4 neutropenia or thrombocytopenia. Resection was attempted in 31 cases (72 %) and accomplished in 22 cases (51.1 %) including 11 of 25 LAPC cases (44 %). Vascular resection was required in 4 cases (18 %), with R0 resection in 86.4 % of the resections. Complications occurred in 6 cases (27 %), with no perioperative deaths. The median progression-free survival period was 18 months if the resection was achieved compared with 8 months if no resection was performed ($p < 0.001$).

Conclusion—Neoadjuvant mFOLFIRINOX is an effective, well-tolerated regimen for patients with advanced nonmetastatic pancreatic cancer. When mFOLFIRINOX is coupled with aggressive surgery, high resection rates are possible even when the initial imaging shows locally advanced

disease. Although data are still maturing, resection appears to offer at least a progression-free survival advantage.

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, with 43,290 new cases and 37,390 deaths annually.¹ Surgical resection is the only curative option, with 15 % of patients having resectable disease at presentation. With treatment, the median overall survival time for unresectable, locally advanced disease is 9.2–13.5 months.^{2–4} After curative resection, more than 80 % of patients experience recurrence due to distant metastatic failure.^{5–7} Complete resection of all gross and microscopic disease (i.e., R0) results in a median survival time of 22–23 months.^{7–9} Although the true impact of microscopic margins is not fully known, it stands to reason that patients destined to have the longest survival are those for whom resection with curative intent is feasible.

Neoadjuvant chemotherapy with or without chemoradiation for localized disease allows for systemic control and improves the chances of resection, particularly when the possibility of complete resection is unclear [e.g., for borderline resectable pancreatic cancer (BRPC) or locally advanced pancreatic cancer (LAPC)]. The optimal regimen in this setting is tolerable and offers both systemic and local control. Recently, FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², and fluorouracil given as a bolus of 400 mg/m² followed by a 46-h continuous infusion of 2,400 mg/m² given every 2 weeks) was compared with gemcitabine (1,000 mg/m² weekly for 7 weeks, then every 3 out of 4 weeks) in a phase 3 trial (ACCORD-11) involving patients with metastatic pancreatic cancer.¹⁰ In this trial, FOLFIRINOX exhibited a statistically significant increase in the overall response rate versus gemcitabine alone (31.6 vs. 9.4 %; $p < 0.001$), with a significant increase in grade 3 or higher neutropenia (45.7 vs. 21 %), febrile neutropenia (5.4 vs. 1.2 %) despite growth factor use in 42.5 % of the patients, thrombocytopenia, diarrhea, and neuropathy.

Based on this data, our multidisciplinary pancreas cancer team at Ohio State University (OSU) instituted a plan to treat patients with BRPC and LAPC using a modified version of FOLFIRINOX (mFOLFIRINOX) to improve tolerability without having a negative impact on response, with the goal of resection. The mFOLFIRINOX regimen comprised a lower dose of irinotecan, elimination of the bolus fluorouracil and leucovorin, and addition of prophylactic pegfilgrastim starting with cycle 1 (Table 1). This report reviews our experience with mFOLFIRINOX for patients with advanced nonmetastatic pancreatic cancer.

METHODS

Study Design

This retrospective study reviewed all patients with BRPC or LAPC treated at OSU with mFOLFIRINOX between January 2011 and August 2013. The study was approved by the institutional review board at OSU.

Eligibility Criteria

Patients were confirmed as having met the following criteria before initiation of therapy: no radiographic evidence of metastatic disease, age older than 18 years, histologic or cytologic diagnosis of pancreatic adenocarcinoma confirmed as BRPC or LAPC, an Eastern

Cooperative Group performance status (PS) of 0 or 1, and adequate organ function. Resectability was determined by the multidisciplinary team including pancreatic surgeons, medical oncologists, radiation oncologists, endoscopic ultrasonographers, and diagnostic radiologists after review of baseline contrast-enhanced pancreas protocol computed tomography (CT) scans or magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS).

The criteria used to determine resectability was based on the consensus statement of the American Hepato-Pancreato-Biliary Association, the Society for Surgery of the Alimentary Tract, the Society of Surgical Oncology, and the Gastrointestinal Symposium Steering Committee.¹¹ Patients with abutment of the portal vein or superior mesenteric vein (SMV), even with mild deformation of the vein and without clear invasion or encasement by cross-sectional imaging or EUS, were not included because they were considered resectable.

Treatment Administration

Because the maximal response typically is reached within 3–4 months after therapy with mFOLFIRINOX and in an attempt to minimize cumulative toxicities, additional cycles of therapy were not routinely administered. After 3–4 months, if a tumor still was localized but not clearly resectable, a shortened course of chemoradiation was administered. This regimen consisted of gemcitabine 1,000 mg/m²/week with radiation (36 Gy in 15 daily fractions).¹² On days 1 and 15, oxaliplatin 85 mg/m² could be added to gemcitabine with radiation (30 Gy in 15 daily fractions) at the oncologist's discretion.¹³

Study Assessments

Patients were seen every 2 weeks, and toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 (CTCAE v4). Toxicities were evaluated, graded, and recorded in the patient's medical record prospectively at each visit by a trained registered nurse staff and subsequently verified by a medical oncologist and a clinical oncology pharmacist. Resectability was assessed at 2-month intervals by the multidisciplinary pancreas cancer team. All surgical specimens for resected tumors were assessed by a gastrointestinal pathologist. An R0 resection was defined as no tumor within 1 mm of the resection margin. After curative resection or progression, further therapy was administered at the discretion of the treating oncologist, and patients were followed at 3-month intervals with routine cross-sectional imaging as clinically indicated.

Statistical Analysis

The data collected included demographics, safety/toxicity, response, resection rate, perioperative outcomes, pathology findings, progression-free survival (PFS), and overall survival (OS). This study defined PFS as the time from initial treatment to the first evidence of radiographic progression or disease-related death and OS as the time from initial treatment to death resulting from any cause. Using Kaplan–Meier methods, PFS and OS curves were created and compared based on resection status by log-rank analysis. In this report, BRPC and LAPC are presented separately for informative purposes only. Survival analyses were run using Stata, version 12.1 (Stata Corporation, College Station, TX, USA).

RESULTS

Patient Characteristics (Table 2)

Between 1 January 2011 and 15 August 2013, 43 patients with advanced nonmetastatic pancreatic cancer received mFOLFIRINOX. The median age of the patients was 62.4 years (range, 40–81 years). Of the 43 patients, 18 had BRPC and 25 had LAPC. All the patients were considered not clearly resectable based on vascular involvement shown by CT/MRI and/or EUS. Nodal involvement or indeterminate liver, lung, or peritoneal lesions were not the indicator for initiation of mFOLFIRINOX.

Gemcitabine-based chemoradiation was administered to 53 % of all the patients including 44 % of those with BRPC and 60 % of those with LAPC. Three patients (1 BRPC and 2 LAPC) received oxaliplatin with gemcitabine and radiation, as described earlier. Two patients with LAPC received low-dose gemcitabine (300 mg/m²) with radiation during 5–6 weeks before their transfer to OSU and then were treated with mFOLFIRINOX. Notably, one patient with BRPC was started with four treatments of FOLFOX due to elevated enzymes and bilirubin, then received two cycles of mFOLFIRINOX after normalization of liver enzymes subsequent to biliary stenting.

Tolerability and Toxicity (Table 3)

Of the 43 patients, 13 were hospitalized for treatment- or disease-related issues during therapy. Of these 13 patients, 7 were admitted for cholangitis (6 of these patients had biliary stents, and none of these 7 patients had concomitant neutropenia). The remaining admissions were due to cholecystitis ($n = 1$), small bowel obstruction ($n = 1$), diarrhea/dehydration/ gastroenteritis ($n = 3$), or bleeding ulcer ($n = 1$).

No episodes of febrile neutropenia, grade 3/4 neutropenia, or thrombocytopenia occurred with mFOLFIRINOX. Overall, the rates of grade 3/4 toxicity were low, with diarrhea and fatigue being the most common. Of the 43 patients, 18 (42 %) had dose reductions of mFOLFIRINOX for toxicities including neurotoxicity, diarrhea, dehydration, and fatigue. The average number of 14-day cycles completed per patient was 4.9 (Table 2). During therapy, three patients died of pneumonia, myocardial infarction, and stroke, respectively. These were considered unrelated to treatment and associated with no other significant toxicities.

Response (Figs. 1, 2; Table 2)

Nine patients (23 %) showed radiographic responses. Fairly dramatic responses were observed in a few patients, including the reopening of nearly occluded portal veins in two patients. Stable disease was seen by CT/MRI in 25 patients (63 %), with disease progression only in 6 patients (15 %). After chemoradiation, radiographic response was seen in one additional patient, whereas three patients showed progression. Of the patients with an initially elevated CA19-9, 70 % had reduced levels.

A total of 31 patients underwent surgical exploration, with 22 successfully resected. Nine patients had an aborted attempt at resection including one patient with occult metastatic

disease (BRPC) and eight patients with unresectable disease (5 LAPC and 3 BRPC). In 12 cases, surgery was not performed for various reasons including persistent radiographic evidence of unresectable disease ($n = 3$), new metastatic disease ($n = 4$), patient preference ($n = 2$), and death as described earlier ($n = 3$).

The operations undertaken included pancreaticoduodenectomy for 13 patients (5 LAPC, 8 BRPC), distal subtotal pancreatectomy for 7 patients (6 LAPC, 1 BRPC), and total pancreatectomy for 2 patients (BRPC). Vascular resections were required for four patients. Three patients (all LAPC) underwent resection of the celiac axis, with none requiring revascularization of the hepatic artery or gastrectomy. Resection of the SMV with primary anastomosis was required for one patient (BRPC). No perioperative deaths occurred. Six patients experienced complications including two grade A pancreatic fistulas that resolved spontaneously, one *Clostridium difficile* colitis, one bile leak with abscess that required reoperation, one wound infection, and one gastric perforation 30 days after subtotal pancreatectomy with celiac axis resection that was managed successfully without reoperation. The perforation was thought to be iatrogenic due to thermal injury because of its delayed presentation and otherwise healthy mucosa seen on endoscopy.

Negative surgical margins were achieved in all but three patients (Table 2). These all were focally positive at the uncinate/superior mesenteric artery (SMA) interface. Microscopic invasion was seen in the vessel wall of the tumor requiring SMV resection, but none of the three arterial resections showed evidence of invasion into the adventitia. In two patients, no residual tumor (pCR) was found in the final resected specimen. Both of these were considered as BRPC cases initially due to encasement of the portal vein/SMV. In both cases, a dramatic radiographic response was seen, with reopening of a nearly occluded SMV (Fig. 3, Appendix). No patients had R2 resection (gross residual tumor). Of the 22 resected patients, 17 went on to receive additional postoperative chemotherapy (gemcitabine based in 13 and fluorouracil based in 4 cases).

At this writing, after a median follow-up period of 13.3 months (range, 4.5–34.8 months), 18 patients have died due to disease, 14 patients are alive and without evidence of progression, and 1 patient has been lost to follow-up evaluation. The median PFS for the patients who underwent resection was 18 months compared with 8 months for those who had no resection (Fig. 1). Of the patients with R0 resection that had progressed at the time of this analysis, the recurrence patterns included local ($n = 1$) and distal ($n = 6$) recurrence. The median overall survival time for the entire group was 21.2 months. The median overall survival time for the patients who underwent resection has not been reached to date and is 12.7 months for those unable to undergo resection (Fig. 2).

DISCUSSION

Pancreatic cancer is a universally lethal disease, with surgical resection offering the only chance for cure. Even at early stages, most patients present with LAPC or BRPC. Because most patients with early-stage disease will die of systemic disease, an aggressive systemic approach has become favored, with the role of chemoradiation remaining controversial.¹⁴ Given that standard FOLFIRINOX has significant toxicities that may affect dose intensity,

we chose to modify the regimen, with the goal to improve its tolerability and maintain or improve on its efficacy. This formed the basis of our approach, and to our knowledge, this is the largest study describing the role of FOLFIRINOX in this particular setting.

Our experience showed mFOLFIRINOX to be tolerable, with no episodes of febrile neutropenia or grade 3/4 neutropenia compared with the historical 5.4 and 47.5 %, respectively.¹⁰ Whereas ACCORD III was dominated by tumors in the body and tail of the pancreas, with only 14.3 % initially having biliary stents in place (i.e., nonjaundiced patients), our rates for grade 3/4 toxicity remained low even for patients with a high rate of biliary stenting (37.3 % initially). Still, even with this modified approach, 13 patients (30.2 %) were hospitalized during therapy for treatment- or disease-related toxicity, with cholangitis in stented patients representing almost half of the admissions.

Future studies should consider antibiotic prophylaxis for patients with initial biliary stenting before therapy. In addition, while mFOLFIRINOX toxicity was improved, we were able to demonstrate very promising activity for this approach that included a shortened course of chemoradiation for select patients.

Hosein et al.¹⁵ previously described their institutional experience using standard FOLFIRINOX for 18 patients (14 LAPC, 4 BRPC). Similar to our strategy, they selectively included chemoradiation (50.4 Gy in 28 fractions with gemcitabine 600 mg/m² weekly) after induction chemotherapy. They reported a 22 % rate of grade 3/4 neutropenia and a 17 % rate of febrile neutropenia despite the use of pegfilgrastim for 89 % of the patients. Their overall R0 rate was 44 %. Faris et al.¹⁶ reported on 22 LAPC patients treated with FOLFIRINOX followed by fluoropyrimidine-based chemoradiation (50.4 Gy during 28 fractions) that resulted in a resection rate of 22.5 %. They reported a grade 3/4 neutropenia incidence of 18 %, with 32 % of patients hospitalized for treatment-related toxicities.

In our experience, radiographic responses were uncommon, but lack of response was not a deterrent to attempted resection with curative intent. As part of our initial multidisciplinary review, decisions were made as to the goals of neoadjuvant therapy. If tumor response was required, chemotherapy response was maximized before consideration of chemoradiation. This was most commonly relevant for tumors at the root of the mesentery involving jejunal branches of the SMV, SMA, or both for which complete tumor extirpation was not feasible nor vascular reconstruction possible. All patients were taken to the operating room willing to undergo major vascular resection, although surprisingly, this was rarely necessary. For the vast majority, even when preoperative imaging exhibited persistent vascular encasement, tumor could be dissected free from the adjacent vessel. As such, vascular resection was necessary in only four cases. In all three celiac axis resections, the adventitia was not invaded by final microscopic evaluation. Single-vein resection was performed for a patient with short-segment occlusion. In all other instances of apparent arterial involvement, the tumor could be “unwrapped” from the artery. Intraoperative frozen section analysis was always performed in these circumstances to confirm that no viable tumor was being left behind. In one patient with 360° encasement of the proximal 3 cm of the SMA, all the perivascular tissue removed was fibrotic, so no vascular resection was performed. At this writing, the patient remains free of recurrence 13 months after surgery. With this aggressive approach,

51 % of tumors were resected, including 44 % of LAPC. Negative margins were achieved in 86 % of those resected.

Finally, this aggressive approach begs the question whether resection adds to survival or merely represents a selection bias of better-performing patients and tumors. Herein lies the primary weakness of this retrospective review. Whereas we report our general approach to these advanced nonmetastatic tumors, therapy was (and continues to be) tailored to the individual and modified as needed through ongoing multidisciplinary review. This study was not protocol driven, so it clearly introduced unforeseen factors. Our promising median PFS result of 18 months for resected patients must account for those aggressive tumors that progressed in the face of advanced therapy and never made it to resection. However, even our preliminary PFS of 8 months for patients unable to undergo resection is better than that for historical gemcitabine-based doublets or gemcitabine induction before chemoradiation in the locally advanced setting.^{2,17}

CONCLUSION

The use of a modified FOLFIRINOX regimen for patients with advanced nonmetastatic pancreatic cancer results in fewer hematologic toxicities and maintains an impressive resection rate in the neoadjuvant setting. The willingness to attempt resection with this approach often shows that major vascular resection is not always necessary to achieve R0 resection. Given our relatively short follow-up period, it is unknown whether we have truly provided cure for patients previously defined as incurable, but an 18-month median PFS for resected patients is interesting and suggests that ongoing investigation is worthwhile.

APPENDIX

See Appendix Fig. 3.

FIG. 3 Radiographic response to mFOLFIRINOX. Magnetic resonance imaging (MRI) (*top panel*) before therapy and computed tomography (CT) (*bottom panel*) after 2 months of mFOLFIRINOX show reopening of the nearly occluded superior mesenteric vein (SMV) (*arrow*), with complete resolution of tumor (T) with residual calcification

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Fig. 1. Kaplan–Meier progression-free survival (PFS) by resection status. **The upper boundary of the 95 % confidence interval (CI) for the resected group could not be estimated due to insufficient events below the median for this group. *NR* not reached

Fig. 2.

Kaplan–Meier overall survival (OS) by resection status. **The upper boundary of the 95 % confidence interval (CI) could not be estimated due to insufficient events below the median. NR not reached

TABLE 1

The mFOLFIRINOX regimen

	Dose	Administration	Frequency
Chemotherapy			
Irinotecan	165 mg/m ²	IVPB during 90 min	All given every 2 weeks for 4–8 treatments total
Oxaliplatin	85 mg/m ²	IVPB during 2–4 h	
Fluorouracil (5-FU)	2,400 mg/m ²	Continuous infusion during 46 h	
Supportive care			
Fosaprepitant	150 mg	IVPB during 30 min	30 min before chemotherapy
Palonosetron	0.25 mg	IV push during 3 min	
Dexamethasone	12 mg	Orally	
Dexamethasone	8 mg	Orally	Once daily for 3 days after each treatment
Pegfilgrastim	6 mg	Sub-Q	Day 4 (24 h after cessation of 5-FU pump)

The dose of irinotecan is lower than that used in the phase 3 (ACCORD-11) trial, and no bolus 5-FU nor leucovorin was administered. All patients received the growth factor pegfilgrastim with the first and all subsequent cycles unless it was deemed in subsequent cycles as not needed due to dose reductions of the cytotoxic agents for other toxicities

5-FU 5-fluorouracil, *IVPB* intravenous piggyback (drug administration), *IV* intravenous

TABLE 2

Summary of patient characteristics and responses to therapy

Characteristic	Total (<i>n</i> = 43) <i>n</i> (%)	LA (<i>n</i> = 25) <i>n</i> (%)	BR (<i>n</i> = 18) <i>n</i> (%)
Mean age (years)	62.4 ± 9.4	62.6 ± 10.0	62.2 ± 8.7
Performance status (ECOG) 0–1	43 (100)	25 (100)	18 (100)
Male	23 (53.5)	12 (48)	11 (61)
Tumor location			
Head	25 (58)	9 (36)	16 (89)
Body/tail	18 (42)	16 (64)	2 (11)
Vascular involvement			
Arterial	15 (35)	13 (52)	2 (11)
Venous	11 (25.5)	2 (8)	9 (50)
Both	17 (39.5)	10 (40)	7 (39)
Mean mFOLFIRINOX cycles: <i>n</i> (range)	4.9 (1–14)	5.3 (1–14)	4.4 (1–8)
Chemoradiation	23 (54)	15 (60)	8 (44)
Median baseline CA19-9: <i>n</i> (range)	335.97 (<15.00– 10,943.97)	184.80 (<15.00– 1,355.05)	650.88 (<15.00– 10,943.97)
CA19-9 reduction ^a	26/37 (70)	13/20 (65)	13/17 (76)
Radiographic response (CR + PR) ^b	9/40 (23)	2/23 (9)	7/17 (41)
Surgical exploration	31 (72)	16 (64)	15 (83)
Resected	22 (51)	11 (44)	11 (61)
Vascular resection	4/22 (18)	3/11 (27)	1/11 (9)
Negative margins	19/22 (86)	10/11 (91)	9/11 (82)

LA locally advanced, BR borderline resectable, ECOG Eastern Cooperative Oncology Group, CR complete response, PR partial response

^aLA locally advanced, BR borderline resectable, ECOG Eastern Cooperative Oncology Group, CR complete response, PR partial response

^bThree patients died before restaging scans

TABLE 3

Toxicities during modified FOLFIRINOX therapy based on the presence or absence of a biliary stent

Dose-limiting toxicities	Biliary stent ^a		No biliary stent		All patients	
	(n = 18)	(n = 25)	(n = 43)			
	n (%)	n (%)	n (%)			
Grades	1 & 2	3 & 4	1 & 2	3 & 4	1 & 2	3 & 4
Neutropenia	–	–	–	–	–	–
Neutropenic fever	–	–	–	–	–	–
Thrombocytopenia	–	–	1 (4.0)	–	1 (2.3)	–
Neuropathy	3 (16.7)	–	7 (28.0)	–	10 (23.3)	–
Diarrhea	5 (27.8)	3 (16.7)	9 (36.0)	3 (12.0)	13 (30.2)	6 (14.0)
Fatigue	7 (38.9)	1 (5.6)	11 (44.0)	3 (12.0)	18 (41.9)	4 (9.3)
Nausea	3 (16.7)	–	11 (44.0)	2 (8.0)	14 (32.6)	2 (4.7)
Vomiting	2 (11.1)	–	3 (12.0)	–	5 (11.6)	–
Mucositis	1 (5.6)	–	5 (20.0)	–	6 (14.0)	–
Dehydration	–	2 (11.1)	1 (4.0)	2 (8.0)	1 (2.3)	4 (9.3)
Hyperbilirubinemia	2 (11.1)	2 (11.1)	–	–	2 (4.7)	2 (4.7)
Cholangitis without neutropenia	6 ^b (33.3)	–	1 (4.0)	–	7 (16.2)	–

^a Of the 18 patients with biliary stents, 16 had them placed before initiation of any treatment. The stents were plastic in 9 patients (with 2 of these ultimately converted to metal) and metal in 8 patients, and 1 patient had a percutaneous external drain

^b Three patients had metal stents, and three patients had plastic stents at occurrence of cholangitis