Modified FOLFIRINOX Regimen With Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma

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Objectives: FOLFIRINOX (5-fluorouracil [5-FU], oxaliplatin, and irinotecan) as compared with gemcitabine in pancreatic cancer (PC) has superior activity and increased toxicity. The bolus 5-FU contributes to the toxicity. We hypothesized that the elimination of bolus 5-FU and use of hematopoietic growth factor will improve the safety profile without compromising the activity of FOLFIRINOX.

Methods: Sixty patients with PC treated with modified FOLFIRINOX (no bolus 5-FU) were reviewed. Patients were divided into metastatic or nonmetastatic (locally advanced or borderline resectable) disease. Toxicity, response rate, progression-free survival, and overall survival were evaluated.

Results: Nonmetastatic and metastatic disease were present in 24 (40%) and 36 (60%) patients, respectively. The incidence of grade 4 neutropenia, grade 3/4 diarrhea, and fatigue were 3%, 13%, and 13%, respectively. Response rate was 30%. The median progression-free survival for nonmetastatic disease was 13.7 months (95% confidence interval [CI], 9.6–24.6 months), and that for metastatic disease was 8.5 months (95% CI, 3.7–11.0 months), respectively. The median overall survival for nonmetastatic disease was 17.8 months (95% CI, 9.9 months to not estimable), and that for metastatic disease was and 9.0 months (95% CI, 7.1 months to not estimable), respectively.

Conclusions: Modified FOLFIRINOX has an improved safety profile with maintained efficacy in metastatic PC. Modified FOLFIRINOX has promising activity in nonmetastatic disease.

Key Words: FOLFIRINOX, pancreas cancer, borderline resectable, locally advanced, toxicity, bolus 5-FU

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Pancreatic cancer (PC) is the fourth leading cause of cancer mortality in the United States.[1] Complete surgical resection remains the only treatment with curative potential; however, only 10% to 20% of patients with PC present with resectable disease.[2] The management of this small subset of patients usually involves resection followed by chemotherapy or chemoradiotherapy. Approximately 30% of patients present with locally advanced unresectable or borderline resectable disease.[2] Although there is no consensus on the best management approach for this group of patients, chemotherapy and radiation are often used initially in an attempt to enable tumor resection. The majority of patients present with advanced disease where the objective of therapy is palliative. Systemic chemotherapy has a central role in the management of patients presenting with advanced stage disease.[3] Until recently, gemcitabine was the standard-of-care treatment for patients with PC in the above settings.[3]

Conroy et al[4] compared FOLFIRINOX (5-fluorouracil [5-FU], Leucovorin, oxaliplatin, and irinotecan) with gemcitabine in metastatic PC in a randomized phase III trial. Median overall survival (OS) and progression-free survival (PFS) were significantly higher in the FOLFIRINOX arm (11.1 and 6.4 months) compared with gemcitabine arm (6.8 and 3.3 months). The response rate (RR) for FOLFIRINOX was 31% versus 9% for gemcitabine. The FOLFIRINOX regimen was associated with significantly higher toxicity including myelosuppression, fatigue, diarrhea, and vomiting. The trial included a heavily selected group of patients with relatively younger age, an excellent performance status, and a high proportion of tumors in the pancreatic body or tail. The toxicity profile and the patient selection raised the concerns whether the results of the trial would be generalizable to a nontrial setting and to patients who have tumors in the pancreatic head requiring biliary stents. The high RR observed with FOLFIRINOX in metastatic disease raises the possibility of using this regimen in earlier-stage disease to downstage tumors for resection. There is limited experience regarding the role of FOLFIRINOX in patients with either borderline resectable or locally advanced unresectable PC.

Our group at Emory University has adopted a modified FOLFIRINOX regimen in both locally advanced unresectable and metastatic PC patients with good performance status. The modifications to the FOLFIRINOX regimen include discontinuation of the bolus 5-FU and administration of growth factors to all patients. For patients with locally advanced disease, FOLFIRINOX is administered until best response, and then patients are evaluated for concurrent chemoradiotherapy. The objective of this retrospective study was to evaluate the safety and efficacy of the modified FOLFIRINOX regimen. The second objective was to provide a preliminary evaluation of the efficacy of FOLFIRINOX in patients with borderline or locally advanced unresectable PC.

MATERIALS AND METHODS

Selection Criteria

After approval from the institutional review board, the tumor registry of Emory University was queried to identify patients carrying a diagnosis of PC between June 2010 and June 2012. Patients were considered eligible if they received at least 1 dose of modified FOLFIRINOX for PC. The charts of eligible patients were reviewed for age, sex, race, Eastern Cooperative Oncology Group performance status, pathological diagnosis, tumor stage, tumor location, stent status, CA-19-9, complete blood counts with differentials, treatment regimens, number of cycles and duration of treatment with modified FOLFIRINOX, imaging results, adverse events, and outcome events such as disease response,

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The authors declare no conflict of interest.

TABLE 1. Baseline Characteristics of Patients With Pancreatic Cancer Treated With Modified FOLFIRINOX

Variable	n (%) or Median (Range)
Age, y	63 (36–78)
Sex	
Female	34 (57%)
Male	26 (43%)
Race	
White	40 (67%)
African American	18 (30%)
Other	2 (3%)
Stage	
II	4 (6%)
III	20 (34%)
IV	36 (60%)
Prior surgery/prior adjuvant	6 (10%)/5 (8%)
Location of primary	
Head	42 (70%)
Body	12 (20%)
Tail	6 (10%)
Stent	
No	38 (67%)
Percutaneous drain	2 (3%)
Yes	20 (33%)
Plastic	6 (10%)
Metal (uncovered)	5 (8%)
Metal (covered)	9 (15%)
Performance status	
0	13 (22%)
1	46 (76%)
2	1 (2%)

progression, recurrence, or death. The results of imaging studies were reviewed by 2 physicians independently and were compared with official radiology reports.

Chemotherapy

The modified FOLFIRINOX regimen included oxaliplatin 85 mg/m^2 in water with 5% dextrose intravenously (IV) over 2 hours, leucovorin 400 mg/m^2 in normal saline IV over 90 minutes concurrently with irinotecan 180 mg/m^2 in normal saline IV over 90 minutes, and 5-FU 2400 mg/m^2 in water with 5% dextrose via continuous intravenous infusion over 46 hours. Patients did not receive bolus 5-FU. On day 3 after chemotherapy, pegfilgrastim 6 mg was administered subcutaneously to each patient. Each cycle of therapy consisted of days 1 and 15 treatments. Complete blood counts were performed before administration of chemotherapy on days 1 and 15.

The premedication regimen consisted of intravenous serotonin 5-HT$_3$ receptor antagonists and dexamethasone. Atropine was given to patients who had cholinergic reactions from irinotecan. All patients had teaching regarding adverse effects and management plan from a specialized nurse in the gastrointestinal oncology clinic. Patients received oral dexamethasone and serotonin 5-HT$_3$ receptor antagonists at home for 3 days after chemotherapy. Antidiarrheal medications were provided to patients before initiation of chemotherapy. Patients were asked to start on these medications at the first sign of diarrhea.

Study Design

Tumor response was evaluated by Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1.[5] Imaging studies (computed tomography scan or magnetic resonance imaging) were performed at baseline and every 8 weeks to assess the tumor burden. Adverse events were graded using National Cancer Institute Common Toxicity Criteria (version 4.0). Response by CA-19-9 was defined as a CA-19-9 nadir 50% or less of CA-19-9 baseline value. In patients with biliary obstruction, baseline CA-19-9 was measured after stent was placed and bilirubin normalized. Progression-free survival was measured from beginning of therapy until either date of first documented progression or death. Survival was measured from beginning of therapy until date of death or loss to follow-up.

Statistical Analysis

Baseline characteristics of patients with PC treated with modified FOLFIRINOX were summarized. For the response by RECIST criteria, the response by CA-19-9, and grade 3 or 4 toxicity, incidence rates and their 95% confidence intervals (CIs) based on exact tests were calculated. The relationship between the response by CA-19-9 and the response based on RECIST criteria was examined by Fisher exact test. The survival functions for OS and PFS were estimated by the Kaplan-Meier method, and log-rank test was used to assess the difference in survival between different cohorts.[8] A Cox proportional hazards models[9] were fitted to test whether the RR by RECIST criteria and the response by CA-19-9 were a significant predictor of OS. A waterfall plot analysis was performed to illustrate patient's percent change in tumor size. The significance levels are set at 0.05 for all tests. The SAS statistical package V9.3 (SAS Institute, Inc, Cary, NC) was used for data analyses.

RESULTS

Patient Characteristics

From June 2010 to June 2012, 60 consecutive patients with PC were treated with at least 1 dose of modified FOLFIRINOX. The baseline patient characteristics are included in Table 1. Median age was 63 years (range, 36-78 years). The majority of the

TABLE 2. Grade 3/4 Toxicities of Patients With Pancreatic Cancer Treated With Modified FOLFIRINOX Regimen

Variable	n (%)
Hematologic	
Neutropenia*	2 (3)
Thrombocytopenia	3 (4)
Nonhematologic	
Diarrhea	8 (13)
Fatigue	8 (13)
Nausea/vomiting	5 (8)
Neuropathy	3 (4)
Allergic reaction†	2 (5)
Mucositis	1 (3)
Infection‡	3 (4)

*Grade 4 only.

†Allergic reaction to 5-FU

‡Infection with without neutropenia. Two were stent related.

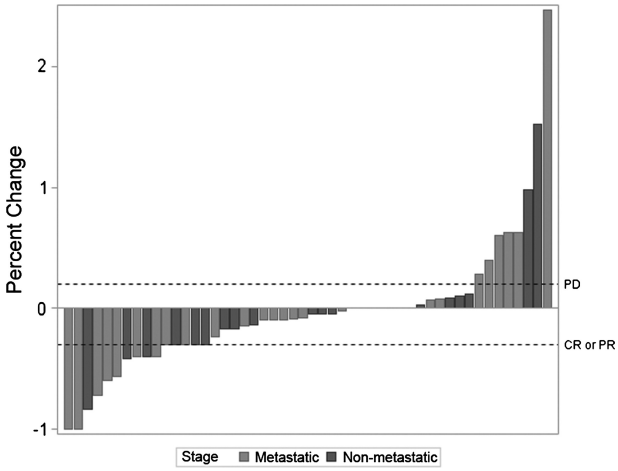

FIGURE 1. Waterfall plot depicting the change in tumor size from baseline in 50 patients with PC treated with modified FOLFIRINOX. Blue bars represent patients with stage II/III disease. Red bars represent patients with stage IV disease. Horizontal black dot lines denote −0.3 and 0.2, which mark the response status of CR (complete response) or PR (partial response) and PD (progressive disease), respectively.

patients (76%) had an Eastern Cooperative Oncology Group performance status 1. At the time of treatment, 36 patients (60%) had metastatic disease. The patients with stage II disease had involvement of the portal vein resulting in having borderline resectable disease. The pancreatic primary tumor was located in the head, body, and tail of the pancreas in 42 (70%), 12 (20%), and 6 (10%) patients, respectively. Biliary stent was placed in 20 patients (33%) and included plastic stents (6), uncovered metal stents (5), and covered metal stents (9).

Treatment Delivered

A total of 209 cycles (418 doses) of modified FOLFIRINOX were administered. Patients received a median of 3 cycles (range, <1–10 cycles). Fifteen patients are still receiving FOLFIRINOX. The 4 patients with stage II disease received 2 to 6 cycles of FOLFIRINOX followed by chemoradiotherapy (3 with capecitabine and 1 gemcitabine). Two have undergone surgical resection with negative resection margins and negative lymph node disease. Ten of the 20 patients with stage III disease completed chemoradiotherapy (8 capecitabine and 2 gemcitabine) after a median of 3 cycles of FOLFIRINOX. Four of these 10 patients underwent surgical resection with negative margins in 3 patients and negative lymph node in 4 patients. Therefore, a total of 6 (42%) patients of 14 treated with FOLFIRINOX followed by chemoradiotherapy were sufficiently down-staged for resection. Of the patients with stage II/III disease, 2 (11%) did not receive chemoradiotherapy because of progression of disease after 2 cycles of therapy.

Safety

Overall modified FOLFIRINOX was safe. Twenty-four patients (40%; 95% CI, 0.28-0.54) had at least 1 grade 3 or 4 toxicities. The incidence of grade 3 or 4 toxicity appeared similar in the patients with stents (45%) as to patients without stents (40%). For nonhematologic, grade 3 toxicities (Table 2) included diarrhea, 8 (13%); fatigue, 8 (13%); nausea/vomiting, 2 (3%); peripheral neuropathy, 3 (4%); allergic reaction to 5-FU infusion, 2 (3%); and mucositis, 1(2%). Three patients (4%) developed grade 3 infections, which included 2 stent-related infections. Hematologic toxicity (Table 2) included grade 3 thrombocytopenia in 2 patients and grade 4 neutropenia in 2 patients. No febrile neutropenia was observed. Eighteen patients required dose reduction. Four patients had only oxaliplatin held due to neuropathy. Five patients had only irinotecan held or reduced due to diarrhea. Nine patients had dose reduction of all agents.

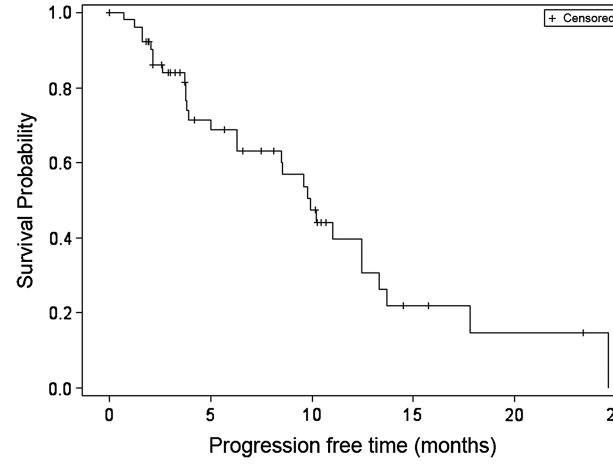

FIGURE 2. Progression-free survival of 60 patients with PC treated with modified FOLFIRINOX. Median PFS time is 9.9 (months) (95% CI, 6.3–12.43).

Response by RECIST and CA-19-9

Fifty patients were evaluable for RR by RECIST criteria. Of the 10 inevaluable patients, 2 had no measurable disease, and 8 received less than 2 cycles (4 due to toxicity, 3 still on therapy, and 1 lost to follow-up). The best response for individual patients is depicted in a waterfall plot in Figure 1. Two patients had complete response, and 13 had partial response for an overall RR of 30% (95% CI, 0.18–0.45). Twenty-seven patients (54%; 95% CI, 0.39–0.68) had stable disease. Eight patients (16%; 95% CI, 0.07–0.29) had progressive disease.

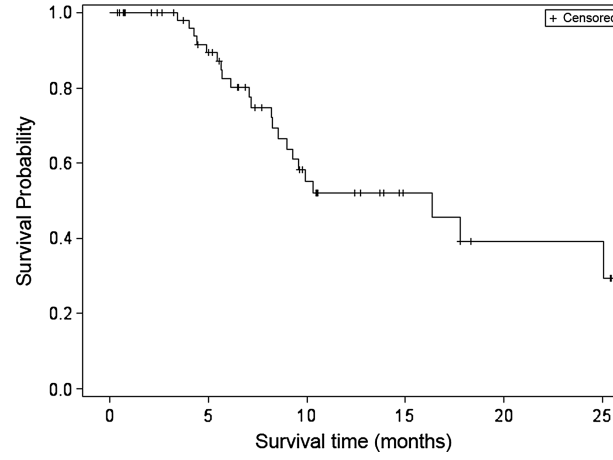

FIGURE 3. Overall survival of 60 patients with PC treated with modified FOLFIRINOX. Median OS time is 16.4 months (95% CI, 8.5 months to not estimable).

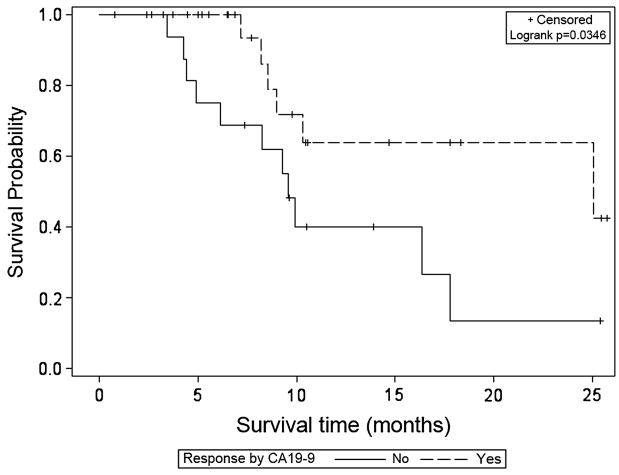

FIGURE 4. Overall survival in 44 patients with PC treated by modified FOLFIRINOX. Patients are divided according to response by CA-19-9. Significant difference in OS is observed between responders and nonresponders. Median OS time is 25.0 months (95% CI, 8.5 months to not estimable) for patients with response by CA-19-9, and it was 9.6 months (95% CI, 4.9–17.8 months) for patients with nonresponse by CA-19-9.

Forty-four patients were evaluable for response by CA-19-9. The 16 inevaluable patients included 8 patients who received less than 2 cycles (detailed above) and 8 patients with normal baseline CA-19-9. Twenty-five patients (57%; 95% CI, 0.41–0.72) showed a greater than 50% decline in CA-19-9 level from baseline. Change in CA-19-9 levels was not associated with the response per RECIST criteria ($P = 0.121$).

PFS and OS

Thirty-one patients were censored for PFS. The PFS and OS are shown in Figures 2 and 3. The median PFS among all patients was 9.9 months (95% CI, 6.3–12.4 months). The median PFS for patients with nonmetastatic and metastatic disease was 13.7 months (95% CI, 9.6–24.63 months) and 8.5 months (95% CI, 3.77–11.03 months), respectively. Thirty-eight patients were alive at the time of the analysis. The median OS among all patients was 16.4 months (95% CI, 8.5 months to not estimable). The median OS for patients with nonmetastatic and metastatic disease was 17.8 months (95% CI, 9.9 months to not estimable) and 9.0 months (95% CI, 7.1 months to not estimable), respectively. Univariate analysis revealed significant associations of response by RECIST with OS ($P = 0.039$) (Table 3). The hazard ratio for OS in patients with response by CA-19-9 compared with nonresponders was 0.36 (95% CI, 0.13–0.97; $P = 0.035$) (Table 3). Responders by CA-19-9 had a median OS of 25.0 months compared with 9.6 months for nonresponders (Fig. 4).

DISCUSSION

The purpose of this study was to evaluate our modified FOLFIRINOX regimen on PC patients with borderline resectable, locally advanced, and unresectable disease. The results of the PRODIGE 4–ACCORD 11 trial demonstrated the superiority of FOLFIRINOX to gemcitabine in stage IV PC.[4] Two concerns that remained after this trial were the generalizability of the results and the safety of the regimen. In our series, patients with metastatic disease treated with modified FOLFIRINOX regimen had an overall RR, median PFS, and OS of 30%, 8.5 months, and 9.0 months, respectively. The RR, median PFS, and OS reported in the randomized trial were 32%, 6.4 months, and 11.1 months, respectively.[4] The RR and PFS, which are directly related to the efficacy of the treatment, were similar in our series to those reported in the PRODIGE 4–ACCORD 11 trial. The inferior OS in our series is most probably related to the high censoring rate (38 patients are still alive) and relatively short follow-up. The modification to the FOLFIRINOX regimen did not appear to negatively impact its efficacy.

Overall our modified regimen was well tolerated. The toxicities were reversible. The regimen was safely administered to patients with tumors in the pancreatic head and with biliary stents. The majority of patients who developed grade 3 or 4 toxicities were able to receive the regimen again with dose reductions. The modified FOLFIRINOX regimen appears to have an improved safety profile especially with respect to neutropenia, fatigue, and vomiting. The lower incidence of neutropenia and absence of febrile neutropenia are due to the discontinuation of bolus 5-FU and the administration of prophylactic pegfilgrastim. The incidence of diarrhea, infection, thrombocytopenia, and neuropathy appears comparable to that reported for FOLFIRINOX. The current series included only patients with good performance status and normal baseline organ function. This highlights the importance of proper selection of patients for treatment with modified FOLFIRINOX regimen.

Our series included 24 patients with stages II and III PC. The median PFS and OS in patients with stage II/III were 13.7 and 17.8 months, respectively. There is no consensus on the treatment of patients with stage II/III PC. Our group uses an approach of chemotherapy upfront in patients with stage II/III PC. Patients who do not progress after initial chemotherapy are considered for chemoradiotherapy. This approach has been previously evaluated by the GERCOR group.[6] In our series, approximately 10% of patients progressed after initial therapy with FOLFIRINOX. This appears to be lower than the 29% rate previously reported for gemcitabine.[6] Fourteen patients completed concurrent chemoradiotherapy after the initial FOLFIRINOX regimen confirming the safety of the sequential therapy approach.

TABLE 3. Univariate Survival Analysis on OS

Covariate	Level	n	Hazard Ratio	95% CI Low	95% CI Up	Hazard Ratio *P*	Log-Rank *P*
Best response	Complete or partial response	15	0.309	0.094	1.017	0.053	0.039
	SD	27	0.273	0.088	0.849	0.025	
	Progressive disease	8	Reference	—	—	—	
Response by CA-19-9	Yes	25	0.355	0.130	0.967	0.043	0.035
	No	19	Reference	—	—	—	

Six (42%) of the 14 patients treated with sequential FOLFIRINOX followed by chemoradiotherapy underwent surgical resection. Hosein et al[7] reported a single institutional experience with neoadjuvant FOLFIRINOX in unresectable or borderline resectable PC. Their rate of R0 resection was 44%. The rate of resection in both series suggests that neoadjuvant therapy with FOLFIRINOX is a promising strategy raising the need to evaluate modified FOLFIRINOX-based sequential regimens in prospective trials in nonresectable locally advanced disease as well as borderline resectable disease.

Evaluation of response is a clinically challenging problem in patients with PC. In our series, patients who had a greater than 50% decline in their CA-19-9 after receiving FOLFIRINOX had a significantly longer median OS (25.0 vs 9.6 months). A potential role for monitoring CA-19-9 in clinical practice would be in patients with stage II/III disease to help in selecting patients who have good prognosis to receive additional radiotherapy or surgery. The role of the nadir CA-19-9 in such a setting would require validation in prospective clinical trials.

In conclusion, modified FOLFIRINOX regimen is well tolerated and has significant activity in metastatic PC. In patients with stage II or III disease, treatment with modified FOLFIRINOX followed by concurrent chemoradiotherapy appears to have promising activity with respect to resectability and survival.

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