# **Modified FOLFIRINOX Regimen as Front-Line Therapy for Metastatic Pancreatic Adenocarcinoma**

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**Abstract: Purpose**: we conducted this prospective study of using modified FOLFIRINOX regimen [5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin] as a front-line therapy for metastatic pancreatic cancer (MPC) patients aiming at a safer therapy with maintained efficacy. **Patients and Methods**: A prospective phase II single-arm study including 28 patients with MPC treated with modified FOLFIRINOX regimen between March 2016 and October 2017 was conducted at our department. Modified FOLFIRINOX regimen consisted of oxaliplatin 85 mg/m2, irinotecan 135 mg/m2, and leucovorin 400 mg/m2 infused intravenously (IV) on day 1, and 5-FU 2400 mg/m2 infused IV over 46 hours on days 1–2 with cycles repeated every 2 weeks. **Results**: The median follow-up period for all patients was 10.75 (range 5.5–18) months. Only 4 (14.3%) patients were alive at the time of data analysis. The median overall survival (OS) and progression free survival (PFS) times were 10.5 (95% CI, 8.4–12.6) and 7.7 (95% CI, 6.8-8.6) months respectively. The 1-year OS and PFS rates were 39.3% and 10.7% respectively. The objective response rate (ORR) was 28.6%, and the disease control rate (DCR) was 67.9%. Grade 3 adverse events occurred in 9 (32.1%) patients with the incidence of grade 3 neutropenia was 21.4%. No grade 4 adverse events or treatment-related death were recorded. **Conclusions:** The front-line modified FOLFIRINOX regimen has an acceptable safety profile with maintained efficacy in MPC.

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**Key Words:** Metastatic pancreatic cancer, chemotherapy, FOLFIRINOX, modified FOLFIRINOX

**1. Introduction**

Pancreatic ductal adenocarcinomas metastasize early and resistance to conventional therapy such as radiation therapy (RT) and chemotherapy (CT) and most patients presented with advanced stages, so that globally pancreatic cancer (PC) is considered one of the highest fatal malignant tumors [1].

About 50% of the PC patients have distant metastases and 30% have locally advanced disease at the time of diagnosis [2]. The 5-year survival rate of PC patients was 8% and was only 3% for the advanced stage [3].

Historically, in 1997, Burris et al. [4] recorded an improvement in overall survival (OS) with gemcitabine (GEM) compared to the traditional 5-fluorouracil (5-FU) therapy for patients with metastatic PC [5]. Since that date, GEM-based CT regimens have been considered the standard therapy for both adjuvant and palliative settings; however, treatment with GEM monotherapy has low effect on survival and minimal response rates (RR).

In French phase II/III study, comparing GEM versus FOLFIRINOX regimen for MPC patients. The results showed significant improvements in the median PFS (3.3 vs. 6.4 months respectively) and OS (6.8 vs. 11.1 months respectively), as well as an increased RR (9.4% vs. 31.6% respectively) [6]. Following this study, a Japanese phase II study of the FOLFIRINOX regimen for MPC conducted with Okusaka et al. [7] showed equivalent efficacy.

Concerning the safety profile, significantly higher rates of grade 3 or 4 toxicities (neutropenia, sensory neuropathy and diarrhea) associated with FOLFIRINOX regimen compared to GEM were reported [6]. Also, in the Japanese study the FOLFIRINOX regimen adverse effects, particularly the hematological toxicities were high [7]. As a result of the higher FOLFIRINOX regimen toxicity, there is a need for more treatment delays and dose reductions. So that FOLFIRINOX regimen is preferred to use in patients with very good performance status (PS) [8].

Many trials had conducted aiming at the reduction of FOLFIRINOX regimen adverse effects with maintaining its efficacy. Using dose modifications of the original FOLFIRINOX regimen, Mahaseth et al. [9] by omitting 5-FU bolus reported a significantly decreased incidence of adverse events with a similar median OS compared to the full FOLFIRINOX dose. Similarly, Stein et al. [10] demonstrated that reduction of irinotecan and bolus 5-FU doses by 25% resulted in significantly reduced incidence of high grade neutropenia, fatigue, and vomiting with a relatively high RR of 35.1%.

Based on the previous studies, although FOLFIRINOX regimen can be considered an effective therapy for MPC patients; its high toxicity remains a concern. Dose modification of the initial FOLFIRINOX regimen might reduce the serious adverse effects with maintaining its efficacy. Thus, we conducted this prospective phase II study of using modified FOLFIRINOX regimen for MPC patients as a front-line therapy aiming at a safer therapy with maintained efficacy.

**2. Patients and methods**

**Study design**

This study was a prospective phase II single-center study, involving 28 MPC patients who received modified FOLFIRINOX regimen as a front-line regimen between March 2016 and October 2017 at Clinical Oncology Department, Tanta University Hospital. The study was approved by the Medical Ethics Committee of the Faculty of Medicine, Tanta University, and written informed consent was obtained from all participants. The primary endpoints of this study were OS and tolerability of the patients. Secondary endpoints were the overall response rate (ORR), disease control rate (DCR) and progression-free survival (PFS).

**Inclusion criteria**

All included patients were older than 18 years. They should have a cytologic or histologic diagnosis of pancreatic adenocarcinoma with good PS (0 or 1) according to Eastern Cooperative Oncology Group (ECOG). All patients should have at least one measurable metastatic lesion with adequate hematological, liver, and renal functions.

**Exclusion criteria**

Any patient with prior CT or RT; ≥grade 2 peripheral sensory neuropathy; active infection; uncontrolled diabetes; other malignancies; or other serious comorbid diseases were excluded from the study.

**Diagnostic work up**

All patients included in the study should have a full medical history and complete physical examinations with PS evaluation. Imaging studies included; abdomen-pelvis computed tomography (CT) scan or magnetic resonance imaging (MRI), chest CT scan and bone scan (when indicated). Laboratory tests included; complete blood counts (CBC), blood chemistry profile, serum cancer antigen (CA) 19.9 and carcinoembryonic antigen (CEA) tumor markers.

**Treatment**

The FOLFIRINOX regimen was modified by irinotecan dose reduction to be 75% of the full dose of FOLFIRINOX regimen reported in the Prodige 4/Accord 11 study [6] with the omission of the 5-FU intravenous (IV) bolus. The modified FOLFIRINOX regimen was planned as follows: a 2-hours IV infusion (IVI) of oxaliplatin (85 mg/m2), followed by 2- hours IVI of leucovorin (400 mg/m2), concomitantly with an additional 1.5- hours IVI of irinotecan (135 mg/m2), on day 1 and a subsequent IVI of 5-FU (2400 mg/m2) over 46 hours on days 1–2.

Each cycle was planned to be repeated every 2 weeks. All patients routinely administered dexamethasone and ondansetron for emesis prophylaxis. Granulocyte-colony stimulating factor (G*-*CSF) for 5 consecutive days after CT was only administered as primary prophylaxis of neutropenia for patients with neutrophile count nearby the lower normal value and also for patients developed ≥grade 3 neutropenia during the treatment course.

Progression of the disease, intolerable adverse events of CT or patient refusal was the reasons for discontinuation of the treatment protocol. Patients who received at least 2 cycles of the planned treatment protocol were included in the data analysis. The treatment protocol was discontinued when delayed ≥3 weeks due to high-grade toxicity.

**Assessments**

Before the start of each CT cycle, all patients were evaluated for adverse effects with a full medical history, physical examination, PS assessment, and laboratory investigations. Adverse effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Tumor response was assessed radiologically according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [11] with tumor marker estimation every 6 weeks.

Overall survival was defined as the time interval between the diagnosis to the date of death of any cause or the date of the last follow-up. Progression-free survival was defined as the time interval between the start of CT to the first documentation of disease progression or death.

**Statistical analysis**

Categorical data were described by frequency distribution with the percentage. Data were presented as mean±SD, median, and range. The median OS and PFS were calculated with the corresponding 95% CI (confidence interval).Overall survival and PFS rates were analyzed utilizing the Kaplan-Meier method. All data were analyzed using SPSS software, version 21 (SPSS Inc, Chicago, IL, USA).

**3. Results**

**Patient characteristics**

Patients’ age ranged from 41 to 65 years (median 60 years), with 57.1% of the patients had PS 1. Obstructive jaundice was the first presentation in 17.9% of patients with 14.3% had a biliary stent. The head of the pancreas as a primary tumor site was represented in 46.4% of patients. The most frequent metastatic site was the liver (71.4%), with 10 patients (35.7%) had multiple metastatic organ involvement. Median serum CA19-9 and CEA values were 356 (range, 145–1750) U/mL and 4.6 (range, 1.3–15.4) ng/mL, respectively. Baseline level of CA 19-9 was >1000 U/mL in 10 (35.7%) patients (Table 1).

**Treatment**

None of the included patients achieved complete response (CR). Eight (28.6%) patients achieved partial response (PR), 11 (39.3%) patients had stable disease (SD), and 9 (32.1%) patients had progressive disease (PD). The ORR (CR+PR) was 28.6%, and the DCR (CR+PR+SD) was 67.9% (19 of 28 patients) (Table 2).

A total of 127 cycles were delivered to 28 patients with a median of 4 cycles (range, 2–10 cycles). The treatment protocol was discontinued in 15 (53.6%) patients. The main reason for discontinuation was disease progression (32.1%). Out of 9 patients who suffered from grade 3 adverse events, 6 (21.4%) patients had treatment discontinuation while the other 3 (10.7%) patients had treatment delay till the toxicity was corrected. Neutropenia was the most frequent toxicity cause of both dose discontinuation and treatment delay.

**Outcomes**

At the end of the study with 10.75 months median follow-up period for all patients (range 5.5–18 months), only 4 (14.3%) patients were alive. As regards the survival outcome, the median OS and PFS times were 10.5 (95% CI, 8.4–12.6) and 7.7 (95% CI, 6.8-8.6) months respectively. The 1-year OS and PFS rates were 39.3% and 10.7% respectively (Fig. 1 & 2).

Out of the 15 patients who discontinued their treatment, nine patients received second-line therapy most commonly in the form of GEM monotherapy (7 patients) while the remaining 6 patients did not receive any further therapy.

In 7 out of 8 patients who achieved PR, serum CA 19-9 values were normalized or decreased while in patients with PD, no improvement of serum CA 19-9 level was found.

**Adverse events**

No grade 4 adverse events were recorded. Nine (32.1%) patients developed grade 3 toxicities, among which 6 (21.4%) patients had neutropenia with 2 (7.1%) of them developed febrile neutropenia, 1 (3.6%) patient had grade 3 thrombocytopenia. As regard grade 3 non-hematological toxicities, 2 (7.1%) patients had fatigue and each of vomiting and diarrhea were represented in only 1 (3.6%) patient (Table 3). None of the patients developed grade 3/4 sensory neuropathy or thromboembolism. Five (17.9%) patients received G-CSF prophylactically with the first CT cycle as the neutrophil count was nearby the lower normal value. Further 6 (21.4%) patients developed grade 3 neutropenia received G-CSF support in later cycles. Totally, 11 (39.3%) patients received G-CSF treatment before or after CT.

**Table (1): Baseline characteristics of 28 patients with MPC**

|  |  |
| --- | --- |
| **Characteristic** | **No (%)** |
| **Age (years)**  Median (Range)  ≤ 60  > 60 | 60 (41-65)  15 (53.6)  13 (46.4) |
| **Gender**  Male  Female | 18 (64.3)  10 (35.7) |
| **ECOG PS**  0  1 | 12 (42.9)  16 (57.1) |
| **Presenting symptoms**  Jaundice  Pain  Weight loss | 5 (17.9)  22 (78.6)  13 (46.4) |
| **Biliary stent**  Yes  No | 4 (14.3)  24 (85.7) |
| **Tumor location**  Head or uncinated process  Body or tail | 13 (46.4)  15 (53.6) |
| **Metastatic sites**  Liver  Lymph Nodes  Peritoneal  Lung  Bone | 20 (71.4)  13 (46.4)  5 (17.9)  4 (14.3)  2 (7.1) |
| **Number of sites involved**  1  2  ≥3 | 18 (64.3)  7 (25)  3 (10.7) |
| **Serum CA19-9 (U/mL)**  Median  Mean±SD  Range | 356.0  698.4±559.2  145-1750 |
| **Serum CEA (**ng/mL**)**  Median  Mean±SD  Range | 4.6  4.9±3.0  1.3-15.4 |

**Table (2): Clinical treatment response of 28 patients with MPC**

|  |  |  |
| --- | --- | --- |
| **Clinical response** | **No** | **(%)** |
| **CR** | 0 | (0) |
| **PR** | 8 | (28.6) |
| **SD** | 11 | (39.3) |
| **PD** | 9 | (32.1) |

|  |
| --- |
| OS |
| **Figure 1:** Overall survival of all patients. |

|  |
| --- |
| PFS |
| **Figure 2:** Progression-free survival of all patients. |

**4. Discussion**

Metastatic PC patients have extremely short survival with few established treatment modalities in such highly lethal clinical condition [12]. These patients may be selected for systemic CT with the aim of survival prolongation, minimizing symptoms and improving or at least maintaining the quality of life (QoL) [13].

Compared to GEM monotherapy, FOLFIRINOX regimen can produce a significant improvement of the survival with remarkable efficacy in MPC patients. However, the considerable FOLFIRINOX regimen toxicity largely limits its application [6].

**Table (3): Treatment adverse events of modified FOLFIRINOX regimen**

|  |  |  |
| --- | --- | --- |
| **Adverse events** | **Grade 1/2**  **No (%)** | **Grade 3**  **No (%)** |
| **Hematologic**  Neutropenia  Febrile neutropenia  Thrombocytopenia  Anemia | 11 (39.3)  1 (3.6)  4 (14.3)  8 (28.6) | 6 (21.4)  2 (7.1)  1 (3.6)  0 (0) |
| **Non-hemotologic**  Infection  Mucositis  Fatigue  Nausea  Vomiting  Diarrhea  Peripheral sensory neuropathy  Anorexia | 4 (14.3)  7 (25)  6 (21.4)  14 (50)  4 (14.3)  5 (17.9)  2 (7.1)  9 (32.1) | 0 (0)  0 (0)  2 (7.1)  0 (0)  1 (3.6)  1 (3.6)  0 (0)  0 (0) |

In practice, when high-grade toxicity developed with FOLFIRINOX regimen, the treatment plan is to reduce the dosage or discontinue the CT [14]. The high toxicity rates for initial FOLFIRINOX regimen reported in previous studies has led to an unwillingness of the majority of clinicians to prescribe this regimen and have encouraged widespread use of a modified FOLFIRINOX regimen in most oncology centers.

Many researchers tried to improve patients' tolerance to FOLFIRINOX regimen through various ways of modification. Mahaseth et al. [9] by omitting 5-FU bolus and using G-CSF at the same time can maintain the efficiency of FOLFIRINOX regimen with a significant reduction of the incidence of serious adverse effects (grade 3/4 diarrhea and neutropenia). Stein et al. [10] recorded that the incidence of neutropenia, fatigue, and vomiting were significantly reduced when the doses of both 5-FU bolus and irinotecan were reduced by 25% of the standard dose. Another modification strategy for MPC includes applying of oxaliplatin plus 5-fluorouracil and folinic acid (OFF) with the removal of irinotecan and it may be advantageous for MPC patients [15].

The present study prospectively investigated the safety and efficacy of an attenuated dose of FOLFIRINOX regimen using upfront dose reductions of the irinotecan by 25% of the standard dose and omission of 5-FU bolus as a front-line therapy for MPC. Our findings suggested that upfront dose attenuation of irinotecan and bolus 5-FU improved tolerability without compromising efficacy.

As regards the treatment outcome in this study, the ORR was 28.6% and the DCR was 67.9%. The median OS and PFS were 10.5 and 7.7 months, respectively. In comparison to the previous studies, Li et al. [12] in a Chinese study utilized modified FOLFIRINOX regimen by reducing oxaliplatin and irinotecan to 85% and 75% of the full dose, respectively, and omitting the 5-FU IV bolus for treatment of 62 MPC patients and reported ORR was 32.5% and DCR was 60%, median OS and median PFS were 10.3 months and 7.0 months, respectively. Mahaseth et al. [9] reported ORR was 32.5% and the median OS and PFS rates for MPC patients were 9 and 8.5 months respectively but they only removed 5-FU IV bolus from the standard FOLFIRINOX regimen. In a Japanese phase II multi-institutional study of modified FOLFIRINOX regimen for 68 CT-naïve patients with MPC, the ORR and DCR were 37.7% and 78.3% respectively. The median OS and PFS were 11.2 and 5.5 months respectively [16]. Yoshida etal. [17] conducted a multicenter prospective phase II study of first-line modified FOLFIRINOX (by reduction of irinotecan and leucovorin doses with the omission of 5-FU IV bolus) for unresectable advanced PC. The ORR was 38.7% withmedian OS and PFS were 14.9 and 7.0 months, respectively. In another multicentre phase II study, Stein etal.[10] assessed the impact of FOLFIRINOX regimen dose attenuation in MPC and reported that the efficacy of modified FOLFIRINOX regimen was comparable with FOLFIRINOX regimen with 35.1% ORR and the median OS and PFS were 10.2 and 6.1 months respectively.

Ghorani et al. [18] treated a small number of patients (18 patients) with MPC and recorded 47% ORR with 9.3 and 7.2 months median OS and PFS, respectively. Bai et al. [19] reported 55.2% ORR for 29 MPC patients treated with first-line modified FOLFIRINOX therapy (irinotecan 135 mg/m2, oxaliplatin 68 mg/m2, 5-FU 2400 mg/m2, leucovorin 400 mg/m2).

As regards the adverse events recorded in the present study, grade 3 treatment-related adverse events were as follows: neutropenia, 21.4%; febrile neutropenia, 7.1%; thrombocytopenia, 3.6%; fatigue, 7.1%; vomiting and diarrhea, 3.6% for both. In our study, 6 (21.4%) patients received G-CSF as a supportive treatment during the treatment CT cycles. In addition, 5 (17.9%) patients started on a prophylactic G-CSF from the first cycle, Thus 39.3% of our patients received G-CSF.

Among different studies, there were wide variations in the profile of the treatment adverse events as a result of different schedules of the drugs doses modification and different percent of patients administered hematopoietic growth factors. Stein et al. [10] recorded grade 3 and 4 toxicities were as follows: diarrhoea,16.2% (grade 3 only); neutropenia and fatigue, 12.2%; thrombocytopenia, 9.5%; anaemia, 5.4%; alanine aminotransferase (ALT) elevation, thromboembolism and febrile neutropenia, 4.1%; vomiting and peripheral neuropathy, 2.7%. Ghorani et al. [18] reported that grade 3 or 4 adverse events included vomiting (28%), nausea (22%), diarrhea (17%) and non-neutropenic fever (17%). Also Li et al.[12] reported the commonest grade 3 and 4 toxicities were neutropenia and ALT elevation (29% and 14.5% respectively). Also, Mahaseth et al.[9] reported the incidence of grade 4 neutropenia, grade 3/4 diarrhea, and fatigue were 3%, 13%, and 13%, respectively.

Ozaka et al.[16] recorded the incidence of grade 3 or higher neutropenia was 47.8%. On the other hand, Yoshida et al.[17] recorded a very high incidence of grade 3 or 4 adverse events included neutropenia (83.9%). Also, recorded febrile neutropenia (16.1%), peripheral sensory neuropathy (9.7%), thrombocytopenia (6.5%), diarrhea (6.5%), anorexia (6.5%), and vomiting (3.2%).

Von Hoff et al.[20] reported that GEM plus nab*-*paclitaxel regimen provide another choice for treating MPCas this regimen significantly improved PFS and OS [20]. In Goldstein et al.[21] phase III trial that included 861 MPC patients received nab-paclitaxel plus GEM or GEM alone, the median OS was 8.7 months in the combined arm [21]. Thus, the outcome of our patients (median OS; 10.5 months) treated with modified FOLFIRINOX regimen is considered a relatively better compared to GEM plus nab-paclitaxel regimen. However, Chan et al.[22] reported that the FOLFIRINOX regimen seems to be more effective than GEM/nab*-*paclitaxel for treating MPC.

In summary, our results suggests that, regardless of the FOLFIRINOX dose attenuation, patients can still benefit from FOLFIRINOX regimen with ORR and survival rates comparable to the treatment outcome reported in of Conroy et al. [6] study (ORR; 31.6%, median OS; 11.1 months, and median PFS; 6.4 months) with considerable lower incidence of grade 3 and 4 neutropenia associated with full dose FOLFIRINOX regimen (neutropenia; 45.7%). In addition, while standard FOLFIRINOX regimen as a front-linetherapy for MPChas found to be a more cost-effective therapy compared with GEM as reported by Chan et al.[22], the modified FOLFIRINOX protocol seems to be costly better than the standard FOLFIRINOX regimen. The small number of our patients with lack of an assessment of the QoL constituted the main limitations of this study.

**Conclusions**

The modified FOLFIRINOX regimen has an acceptable safety profile with maintained efficacy in MPC. Prospective multicenter studies with a large number of patients are required to validate these findings.

**Conflict of Interest**

The authors declare no conflict of interest

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