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Original Article

# First line modified Folfirinox versus gemcitabine for advanced pancreatic cancer: A single institution retrospective experience

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ABSTRACT

*Background:* Advanced pancreatic cancer (APC) is a highly lethal malignancy which has one of the worst treatment outcomes. Modified (m)FOLFIRINOX is an intense but a proven treatment approach with a survival benefit for APC. Although mFOLFIRINOX demonstrated survival benefit compared with gemcitabine monotherapy, the standard treatment in previous years, toxicity is a difficult aspect of this treatment.

*Methods:* A retrospective analysis of patients referred to Medical Oncology Clinics of Ankara Oncology Research and Training Hospital with the diagnosis of inoperable locally advanced or metastatic pancreatic cancer and treated with mFOLFIRINOX or gemcitabine monotheraphy from March 2013 to April 2018 was performed.

*Results:* Forty three patients and 37 patients were included in mFOLFIRINOX and gemcitabine groups, respectively. The mean age of the patients was 53.74 years (range: 32–69) and 65,7 years (range: 47–82) for mFOLFIRINOX and gemcitabine, respectively (95% CI, $p < 0.001$). All patients, except one, had ECOG performance status of 0 or 1 in mFOLFIRINOX group. In contrast, nine patients had ECOG performance status of 2 in the gemcitabine group (95% CI, $p = 0.002$). When the patients were evaluated for response, 11 (25.6%) and 6 (16.2%) had partial remission with mFOLFIRINOX and gemcitabine, respectively. Median PFS and OS was 5,73 (95% CI, 2,57-8,90) months and 8.77 (95% CI, 6.54–10.99) months with mFOLFIRINOX and 2,77 (95% CI, 2,29-3,24) months and 5.80 (95% CI, 3.08–7.92) months with gemcitabine, respectively. mFOLFIRINOX regimen was more toxic than gemcitabine regimen. The incidences of all-grade neutropenia, neuropathy, and emesis were more prominent in the mFOLFIRINOX group.

*Conclusion:* mFOLFIRINOX is a difficult regimen for both patients and physicians with significant toxicity with a greater survival benefit. The survival benefit was modest in this real-life experience. Patient selection bias and small sample size of this retrospective study should be considered.



## 1. Introduction

Advanced pancreatic cancer (APC) is a highly lethal malignancy which has one of the worst treatment outcomes. According to GLOBOCAN data, the incidence and mortality rates were detected as 4.5 and 4.3 per hundred thousand respectively in Turkey in 2012.[1] Nearly half of the patients have metastatic disease at the time of diagnosis; with a 5-year overall survival (OS) rate of only 2.7%.[2] For many years, gemcitabine-based chemotherapy (usually single-agent gemcitabine) has been recommended in the metastatic stage. Nevertheless, more promising results have been reported recently with new combination chemotherapies. In phase 3 PRODIGE study comparing FOLFIRINOX (5-FU, Irinotecan, and Oxaliplatin) combined chemotherapy with gemcitabine monotherapy, overall survival was found to be 11.1 months versus 6.8 months respectively. However, a significant increase in toxicity in combination arm was also reported.[3] In the phase 3 MPACT trial in which the combination therapy of nab-paclitaxel-gemcitabine was compared with single-agent gemcitabine treatment, OS was found to be 8.5 months versus 6.7 months.[4] Nowadays, these new combination treatments have become frequently preferred in routine practice.

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In two recent phase 2 studies, less toxicity was observed with FOLFIRINOX, administered by modifying the doses of chemotherapeutics, with a similar OS to standard-dose treatment.[5,6] In another study with 102 patients with advanced stage pancreatic cancer (APC), similar OS and progression-free survival (PFS) were observed in groups with and without dose modification.[7]

We aimed to show our experience with modified FOLFIRINOX and gemcitabine as first-line therapy in patients with metastatic or unresectable locally advanced pancreatic cancer.

## 2. Material and method

A retrospective analysis of patients who referred to Medical Oncology Clinics of Ankara Oncology Research and Training Hospital with the diagnosis of inoperable locally advanced or metastatic pancreatic cancer and treated with mFOLFIRINOX (Oxaliplatin 65 mg/m$^2$ IV on day 1, Irinotecan 135 mg/m$^2$ IV on day 1, Fluorouracil (FU) 2400 mg/m$^2$ IV infusion over 46 h on day 1, every 2 weeks) or gemcitabine monotherapy (1000 mg/m$^2$ IV on 1. and 8. days, every 21 days) from March 2013 to April 2018 was performed. Hospital registry system data, patient files, laboratory and radiological records were retrospectively screened. Only the patients with pancreatic adenocarcinoma histology were included in the study; other histological types were excluded. Patients who received a treatment regimen other than mFOLFIRINOX or gemcitabine as first-line treatment were not included in the study also. Patients were evaluated for demographic characteristics, the number of chemotherapy cycles, side effects, dose reductions, granulocyte colony-stimulating factor (GCSF) use, presence/absence of neutropenic fever, radiological response, PFS and OS data. IRB approval has not received.

### 2.1. Statistical analysis

SPSS 24.0 (Statistical Package for Social Sciences, Chicago, IL, USA) was used for statistical analysis. Pearson Chi-square test was used for comparison of nonparametric categorical variables. Mann-Whitney test was used for comparison of nonparametric numerical variables. Kaplan-Meier method was used for survival analysis; statistical differences were evaluated by Log-rank test. A value of $p < 0.05$ was considered significant. We did a Cox regression analysis for overall survival.

## 3. Results

### 3.1. General features

General patient characteristics are given in Table 1a. There were 10 (12.5%) patients who had curative surgery before and subsequently advanced to the metastatic stage.

Mean age of patients were 53.74 (95% CI: 33–69) in mFOLFIRINOX group and 65.70 (95% CI: 47–82) in gemcitabine group ($p < 0.001$). Forty-two (97.7%) patients in mFOLFIRINOX group and 28 (75.7%) patients in gemcitabine group had an ECOG PS score of 0 or 1 ($p = 0.003$). Twenty-nine (67.4%) patients in mFOLFIRINOX group and 26 (70.3%) patients in the gemcitabine group had liver metastasis. Liver was the most metastatic site for both groups. Mean basal concentrations of CA 19.9 were 13747 U/mL and 4566 U/mL for mFOLFIRINOX and gemcitabine groups, respectively ($p = 0.040$). Both groups were similar in terms of other patient characteristics (Table 1b).

### 3.2. Efficacy

Findings related to treatment are stated in Table 2.

Median PFS and OS was 5,73 (95% CI: 2,57-8,90) months and 8.77 (95% CI: 6.54–10.99) months with mFOLFIRINOX and 2,77 (95% CI: 2,29-3,24) months and 5.80 (95% CI: 3.08–7.92) months with gemcitabine, respectively (Fig. 1).

In the univariate analysis for OS, the total number of cycles over five affected survival positively ($p < 0.001$, HR:0.30, %95 CI: 0.18–0.50). No significant difference was seen for performance score and age (Table 3).

**Table 1a**
General patient characteristics.

| | n = 80 (%) |
|---|---|
| **Age-year (range)** | 60 (33–82) |
| **Gender** | |
| Male | 57 (71.2%) |
| Female | 23 (28.8%) |
| **Cigarette smoking** | |
| Yes | 38 (47.5%) |
| No | 42 (52.5%) |
| **Alcohol** | |
| Yes | 12 (15%) |
| No | 68 (85%) |
| **Tumor location** | |
| Head | 43 (53.8%) |
| Body | 25 (31.2%) |
| Tail | 12 (15%) |
| **ECOG PS** | |
| 0 | 9 (11.3%) |
| 1 | 61 (76.2%) |
| 2 | 10 (12.5%) |
| **Stage** | |
| Locally advanced | 14 (17.5%) |
| Metastatic | 66 (82.5%) |
| **Previous operation** | |
| No | 70 (87.5%) |
| Yes | 10 (12.5%) |
| **Chemotherapy** | |
| mFOLFIRINOX | 43 (53.7%) |
| Gemcitabine | 37 (46.3%) |

**Table 1b**
General patient characteristics.

| | mFOLFIRINOX (n = 43) | Gemcitabine (n = 37) | p |
|---|---|---|---|
| Age-year (range) | 53.74 (33–69) | 65,70 (47–82) | **<0.001** |
| Gender (male/female) | 33 (76.7%)/10 (23.3%) | 24 (64.9%)/13 (35.1%) | 0.242 |
| ECOG PS (0–1) | 42 (97.7%) | 28 (75.7) | **0.003** |
| Non-Comorbidities | 26 (60.5%) | 15 (40.5%) | 0.153 |
| Cigarette smoking | 24 (55.8%) | 13 (35.1) | 0.125 |
| Alcohol | 8 (18.6%) | 3 (8.1%) | 0.208 |
| Basal CA 19.9 (mean, U/mL) | 13747 | 4566 | **0.040** |
| More than one metastatic site | 18 (41.8%) | 19 (51.9%) | 0.286 |
| Locally Advanced Disease | 8 (18.6%) | 6 (16.2%) | 0.779 |

**Table 2**
Findings related to treatment.

| | MFOLFIRINOX (n = 43) | Gemcitabine (n = 37) | p |
|---|---|---|---|
| Number of cycles | 8 (1–30) | 3 (1–9) | |
| Dose Reduction | 13 [30.2% (10–30)] | 6 [16.2% (10–20)] | 0.098 |
| GCSF usage | 10 (23.3%) | 1 (2.7%) | 0.006 |
| Second-line treatment | 14 (32.6%) | 7 (18.9%) | 0.001 |
| Objective Response (Radiologic PR) | 11 (25.6%) | 6 (16.2%) | 0.512 |
| Clinical Benefit (Radiological PR + SD) | 26 (60.5%) | 14 (37.8%) | 0.094 |

GCSF: Granulocyte Colony Stimulating Factor, PR: Partial Response, SD: Stable Disease, findings except number of cycles is given as the number of patients.

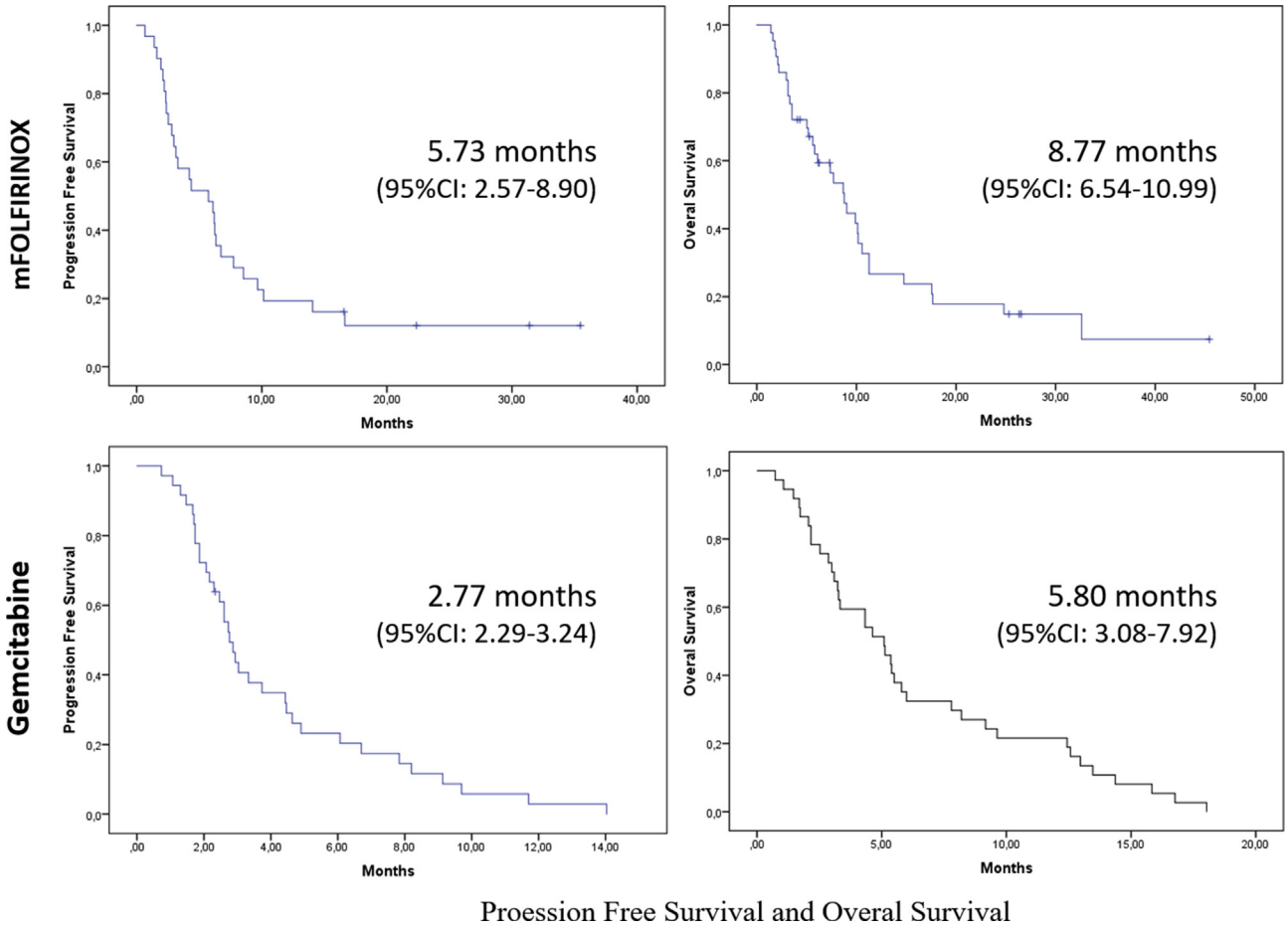


**Fig. 1.** Proession free survival and overal survival.

### 3.3. Side effects

Side effects of anemia, thrombocytopenia, diarrhea, and fatigue were more frequent in the mFOLFIRINOX group, but both groups were similar in terms of statistical significance. Statistical analysis was not performed for grade 3–4 side effects due to the inadequate number of events (Table 4). No treatment-related mortality was observed in both groups.

**Table 3**
Univariate analysis for OS.

| | p | HR | %95 CI |
|---|---|---|---|
| Age (Lowest 60) | 0.35 | 0.34 | 0.49–1.28 |
| Number of Cycle (Lowest 5) | <0.001 | 0.30 | 0.18–0.50 |
| ECOG (0–1) | 0.95 | 0.98 | 0.4–1.9 |

## 4. Discussion

In our study, PFS (5.73 months - 2.77 months) and OS (8.77 months - 5.80 months) were better in the mFOLFIRINOX group than gemcitabine group. In addition, overall survival was only affected by the number of chemotherapy cycles. In a phase 3 trial comparing gemcitabine with 5-fluorouracil in the treatment of advanced pancreatic cancer, OS (5.65 months vs. 4.41 months) was statistically significant in favor of gemcitabine.[8] In addition, two meta-analyses showed that combination therapies of gemcitabine had borderline OS advantage compared to single-agent gemcitabine. Gemcitabine monotherapy had become standard therapy on this issue.[9,10] FOLFIRINOX, one of the current treatment options, was found to be superior to gemcitabine with a fairly long OS of 11.1 months in phase 3 study.[3] In our study, both PFS and OS were found to be better than gemcitabine monotherapy treatment. But,

**Table 4**
Side effects.

| | All Grade Side Effects | | | Grade 3–4 Side Effects | |
|---|---|---|---|---|---|
| | mFOLFIRINOX (n = 43) | Gemcitabine (n = 37) | p | mFOLFIRINOX (n = 43) | Gemcitabine (n = 37) |
| Neutropenia | 22 (51.2%) | 9 (24.3%) | 0.006 | 11 (25.6%) | 4 (10.8%) |
| Neutropenic Fever | | | | 4 (9.3%) | 0 |
| Anemia | 25 (58.1%) | 16 (43.2%) | 0.091 | 1 (2.3%) | 1 (2.7%) |
| Thrombocytopenia | 3 (7.0%) | 3 (8.1%) | 0.92 | 0 | 1 (2.7%) |
| Neuropathy | 5 (11.6%) | 0 | 0.026 | 1 (2.3%) | 0 |
| Nausea | 21 (48.8%) | 7 (18.9%) | 0.002 | 1 (2.3%) | 0 |
| Diarrhea | 10 (23.3%) | 5 (13.5%) | 0.204 | 4(9.3%) | 1 (2.7%) |
| Fatigue | 28 (65.1%) | 23 (62.2%) | 0.467 | 6 (14.0%) | 5 (13.5%) |

survival benefit provided by mFOLFIRINOX was behind the literature and modest. The survival durations we found were better than the literature data of gemcitabine.[8–10]

An inevitable result of combination therapy is the increased toxicity.[3] The higher likelihood of toxicity predicted by mFOLFIRINOX in our study affected patient selection during treatment planning. Therefore, mFOLFIRINOX group was younger and had better ECOG performance score level. In addition, more chemotherapy cycles were applied to this group. These differences might have affected both PFS and OS durations. In our univariate analysis for OS, the total number of cycles over five affected survival positively. Probably because of the small number of patients, we did not see this significance in performance score and age. However, the ratio of objective response (radiological partial response) and the ratio of clinical benefit (radiological partial response and stable disease) were better in the mFOLFIRINOX group but the differences were not statistically significant. This may be due to the inadequate number of patients. But, the better radiological response suggests that the factor that is effective on PFS and OS is not patient selection alone. In addition, in our study PFS and OS were found to be shorter than PRODIGE study.[3] This may be due to patient selection bias and the small number of patients. In a retrospective study, only one in four patients treated with FOLFIRINOX in real life was found to be in accordance with the inclusion criteria of phase 3 FOLFIRINOX study.[11] Similarly, in a retrospective real-life data from Japan, the OS was found to be 8.9 months with FOLFIRINOX. Moreover, in this study, no modification was made to the chemotherapy scheme.[12] In another retrospective Japanese study, OS was reported to be 11.1 months.[13] Retrospective UK study reported PFS 7.2 months, OS 9.3 months and in another US retrospective study, OS was reported as 11.4 months.[14,15] Differences in the literature can be explained by the retrospective nature of the studies, patient selection, and regional-racial differences. In this study, it is obvious that we have obtained PFS and OS benefit in accordance with the literature in the treatment of pancreatic cancer with mFOLFIRINOX treatment.

FOLFIRINOX is a treatment regimen in which intensive toxicity is expected. The basis of toxicity is hematological toxicity and associated neutropenic fever, and it has a wide range of toxicity with toxic deaths.[3,12,13] In our study, when all side effects were taken into account, neutropenia, neuropathy, and nausea were significantly higher in the mFOLFIRINOX group. In addition, anemia, diarrhea, and fatigue were more common but not statistically significant.

In our study, all of the grade 3–4 hematological and non-hematological side effects were less frequent than in the PRODIGE study. In the PRODIGE study, 45.7% grade 3–4 neutropenia was observed. In our study, grade 3–4 neutropenia rate was 25.6%. Despite this, in PRODIGE study, 5.4% of neutropenic fever was observed whereas in our study this rate was 9.3%.[3] In the PRODIGE study, 42.5% of patients were given prophylactic GCSF, whereas in our study this was 23.3%. The reason why neutropenic fever was more frequent in our study could be the lack of use of GCSF. Furthermore, neutropenia and other side effects may be more likely to be determined, depending on the more strict follow-up in phase 3 studies. In the retrospective Japanese study, the neutropenic fever rate was found to be 13% higher than the PRODIGE study.[12] In two recent phase 2 studies, mFOLFIRINOX was used at similar doses to our study and less toxicity was observed with a similar OS to standard-dose treatment.[5,6] It is clear that dose modification is effective in reducing side effects. However, as in the case of neutropenic fever, it should be kept in mind that prospective clinical trial data and daily life data may not coincide exactly. When we compare with the results of a meta-analysis involving 12 studies with modified FOLFIRINOX with our study; grade 3–4 neutropenia, fatigue, nausea, diarrhea, and neuropathy were similar with less anemia and thrombocytopenia in our study. However, the neutropenic fever was seen twice as often compared to the meta-analysis in our study.[16] With the use of more intensive prophylactic G-CSF in daily practice, side effect profile similar to that of the literature can be provided.

The retrospective nature of our study and the low number of patients constitute the main limitations. The difference between the two groups in terms of basic features prevented a healthy comparison between the two groups. Similarly, the statistical evaluation for grade 3–4 side effects could not be made due to the small number of events.

## 5. Conclusion

In advanced pancreatic cancer patients with good ECOG PS, mFOLFIRINOX treatment provided OS and PFS benefit with manageable toxicity profile. Sustainability of treatment due to side effects is a major problem for both the patient and the physician. Dosage modification of the treatment scheme and the use of appropriate prophylactic GCSF may provide a lower side effect profile with similar efficacy and better quality of life in the literature.

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