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Evaluation of the Efficacy and Safety of FOLFOX in First-Line Treatment of Advanced Pancreatic Cancer

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ABSTRACT

Objective: In pancreatic cancer, only 15% to 20% of patients are potentially resectable at diagnosis. Current standard treatment for inoperable and metastatic patients includes: FOLFIRINOX, gemcitabine plus nab-paclitaxel, and NALIRIFOX regimens. Fluorouracil-based treatments can be considered in patient groups with Eastern Cooperative Oncology Group (ECOG) 1-2, advanced age, and multiple comorbidities.

Material and Methods: We aimed to evaluate overall survival (OS), progression-free survival (PFS), safety, and laboratory data in patients with unresectable locally advanced and metastatic pancreatic cancer (ECOG performance score 1) who were treated with FOLFOX as first-line therapy. 46 patients, who were started on FOLFOX in University of Health Sciences Türkiye, Gülhane Training and Research Hospital between June 1, 2016 and May 1, 2024, were evaluated retrospectively.

Results: The median age was 68. 13 patients were locally advanced (28.3%), and 33 patients were in the metastatic stage (71.7%). Partial response was seen in 13 patients (28.2%) and stable response was seen in 19 patients (41.3%) (disease control rate; 69.6%). Median PFS was 5.8 months; median OS was 13.7 months. No patient with locally advanced disease could be operated on during the follow-up. PFS (10 vs. 5 months; p<0.0005) and OS (22 vs. 8 months, p<0.0005) were better for locally advanced disease compared to metastatic disease. Grade 3/4 neutropenia was 21.7%; anemia was 13%, and thrombocytopenia was 13%. Grade 3/4 diarrhea 6.5%.

Conclusion: In locally advanced and metastatic pancreatic cancer, the FOLFOX regimen is considered a good alternative treatment protocol in the low performance status, fragile patient group with efficacy and safety data.

Keywords: Metastatic pancreatic cancer; locally advanced pancreatic cancer; FOLFOX; overall survival; progression-free survival

INTRODUCTION

Pancreatic adenocarcinoma is the sixth leading cause of cancer-related mortality worldwide.[1] The 5-year survival rate is approximately 9%, which highlights its highly aggressive nature.[2] In Türkiye, it ranks as the eighth most common cancer and the fourth most frequent cause of cancer-related death.[1] The median age at diagnosis is 65-69 years in men and 75-79 years in women, and the disease's incidence is reported to be three times higher in women than in men.[3]

Although curative surgery remains the mainstay of treatment, only about 15% of patients are resectable at diagnosis. Approximately 50-60% present with distant metastatic disease, and 25-30% are diagnosed at a locally advanced stage.[3]

According to the National Comprehensive Cancer Network guidelines, a locally advanced or unresectable tumor is defined as tumor contact with the superior mesenteric artery (SMA) or celiac axis greater than 180 degrees, tumor contact with the first jejunal SMA segment, inability to reconstruct the superior mesenteric vein due to invasion or obliteration, or the presence of portal vein thrombosis.[4]

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There is no consensus regarding the optimal approach for locally advanced or unresectable patients with homologous recombination deficiency (HRD)-associated genomic variants or unknown genomic status. For fit patients with adequate performance status and no major comorbidities, modified FOLFIRINOX (mFOLFIRINOX) is preferred. For patients with poor performance status or comorbidities, initiating treatment with the FOLFOX regimen and considering the option of adding irinotecan in subsequent cycles—particularly if HRD-related alterations are identified—may be appropriate, depending on tolerability.[5] In patients without HRD-related genomic variants, either mFOLFIRINOX or gemcitabine plus nab-paclitaxel may be suitable alternatives. Single-agent gemcitabine is generally reserved for patients with a performance status of ≥2 or those with significant comorbidities precluding combination chemotherapy.[4,5] In locally advanced or unresectable disease, resectability should be reassessed after 4-6 cycles of systemic therapy.

For metastatic disease, mFOLFIRINOX is the recommended first-line regimen in patients with good performance status and without significant comorbidities.[6-8] Gemcitabine plus nab-paclitaxel have demonstrated efficacy and safety and may serve as an alternative in patients less fit for intensive triplet therapy, although no head-to-head comparison with mFOLFIRINOX has been conducted. NALIRIFOX represents another option; in the NAPOLI-3 trial, it showed improved overall survival (OS) compared with gemcitabine plus nab-paclitaxel, with a comparable toxicity profile.[9]

For patients with Eastern Cooperative Oncology Group (ECOG) performance status 1 and multiple comorbidities, gemcitabine monotherapy or fluoropyrimidine-based doublet regimens such as FOLFOX,[10] CAPOX,[11] or FOLFIRI[12] may represent reasonable alternatives. The mFOLFOX regimen, in particular, may be considered a first-line treatment option in advanced pancreatic adenocarcinoma patients who are unable to tolerate triplet regimens due to poor performance status or advanced age.

MATERIAL AND METHODS

This retrospective study included 46 patients diagnosed histopathologically with pancreatic adenocarcinoma, who had unresectable locally advanced or metastatic disease, an ECOG performance status of 1, and received first-line FOLFOX chemotherapy between June 1, 2016 and May 1, 2024 at University of Health Sciences Türkiye, Gülhane Training and Research Hospital. All patients were chemotherapy-naïve at baseline.

Inclusion criteria were:

- Histologically confirmed pancreatic adenocarcinoma.
- Measurable disease according to RECIST 1.1 (≥40 mm for locoregional disease, ≥20 mm in the longest dimension for metastatic disease on computed tomography).
- Patients with an ECOG performance status of 1 who are not deemed suitable for triplet therapy by the clinician due to age, comorbidities, clinical condition, etc.
- Adequate hematologic function (hemoglobin ≥9 g/dL; neutrophils ≥1,500/mm^3; platelets ≥150,000/mm^3).
- Adequate renal (creatinine clearance ≥60 mL/min) and hepatic function [bilirubin ≤1.5 × upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase ≤2.5 × ULN, alkaline phosphatase ≤3 × ULN].

Exclusion Criteria Included

Concurrent active malignancy (other than non-melanoma skin cancer or in situ cervical cancer), brain or leptomeningeal metastases, hypersensitivity to 5-fluorouracil (5-FU) or oxaliplatin, pregnancy or breastfeeding, incomplete follow-up, receiving fewer than three cycles of FOLFOX, or undergoing surgical resection at baseline.

Method

Following approval from the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (approval number: 2024-578, date; 10.12.2024), the local/advanced unresectable and metastatic pancreatic cancer patients were scanned via the hospital information system. This patients who were started on FOLFOX in the first line and eligible for participation were accepted into the study.

Age, gender, date of diagnosis and first chemotherapy, pancreatic cancer histopathologic subtype, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19/9), albumin, lymphocyte, C-reactive protein (CRP), CRP/albumin ratio, and response status after 3 months of treatment were evaluated. Progression-free survival (PFS) data were measured after the first treatment until the time of progression and analyzed with the Kaplan-Meier model. OS was measured from the first cure until death. OS data was analyzed by the Kaplan-Meier model. At the end of four courses, the initial outcome assessment was based on RECIST criteria.

Treatment Protocol

The modified FOLFOX-6 (mFOLFOX-6) regimen was administered every 14 days as follows:

• Oxaliplatin 85 mg/m^2 intravenous (IV) over 2 hours on day 1.

• Leucovorin (folinic acid) 400 mg/m^2 IV over 2 hours on day 1, administered concurrently with oxaliplatin.

• 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2,400 mg/m^2 continuous IV infusion over 46 hours via ambulatory pump.

Treatment was continued until disease progression, unacceptable toxicity, or the patient/physician decision.

Tumor response was assessed after 4 cycles using RECIST 1.1 criteria. Toxicity was graded according to National Cancer Institute's common toxicity criteria (NCI-CTCAE) v5.0. Oxaliplatin-related neuropathy was assessed with an oxaliplatin-specific neurotoxicity scale.

NCI-CTC 5.0 was used as the basis for toxicity assessment. An Oxaliplatin-specific scale was used for neurotoxicity assessment. In this assessment: grade 1 is transient paresthesia/dysesthesia that completely regresses until the subsequent cycle, grade 2 is characterized by symptoms that persist for two cycles but do not lead to functional loss, and grade 3 defines neurotoxicity leading to functional loss.

In case of toxicity, dosage, and planning changes were made. Treatment was suspended for 2 weeks if neutrophil count was less than 1,500/mm^3 or platelet count was less than 100,000/mm^3, if there was no improvement during the follow-up period, treatment was discontinued. The Oxaliplatin dose was decreased in the event of grade 3/4 gastrointestinal toxicity (according to the NCI-CTC). In cases of stage 2 and above, hand foot syndrome, the dose of 5-FU was reduced. The oxaliplatin dose was decreased in cases of persistent paresthesia/dysesthesia between cycles.

Studies were conducted in conformity with the institutional and/or national research committee standards and the 1964 Declaration of Helsinki and its subsequent modifications or similar ethical standards.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v25.0. Descriptive statistics were expressed as median (range) for continuous variables and frequencies (%) for categorical variables.

PFS was defined as the time from treatment initiation to documented disease progression or death from any cause. OS was defined as the time from treatment initiation to death from any cause. Survival probabilities were estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test.

Univariate Cox proportional hazards regression was used to identify factors associated with OS and PFS. Variables with $p<0.10$ in univariate analysis were included in the multivariate Cox regression model. The following variables were assessed:

• Age (<70 vs. ≥70 years)

• Gender (male vs. female)

• Disease stage (locally advanced vs metastatic)

• Baseline CEA (<5 vs. ≥5 ng/mL)

• Baseline CA 19-9 (<40 vs. ≥40 U/mL)

• CRP/albumin ratio (<4.2 vs. ≥4.2)

Results from Cox regression were reported as hazard ratios (HR) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

RESULTS

Forty-six patients were involved. Baseline demographic features of the individual patients are presented in Table 1.

Median age was 69.8 years (44-82), female/male ratio was 22/24. 28.3% were diagnosed with locally advanced disease; 71.7% with metastatic disease. All patients had adenocarcinoma morphology.

The median follow-up period was 20 months. In the first response assessment of the patients after chemotherapy, the disease control rate (DCR) was 69.6% (2 complete responses, 11 partial responses, 19 stable responses). The objective response rate (ORR) was 28.3% (Table 2). In the 24-month follow-up period, the median PFS was 5.8 (95% CI: 5.4-9.3), and OS was 13.7 months (95% CI: 11.2-19.1). Kaplan-Meier survival curves are shown in Figures 1 and 2.

In subgroup analysis, as expected, patients with locally advanced disease had significantly better survival than those with metastatic disease.

TABLE 1: Baseline demographic and clinical characteristics of the study population.

Characteristic	n	%
Median age (years, range)	69.8	
Sex (male/female)	22/24	47.8/52.2
ECOG 1	46	100
Stage (IA/M)	13/33	28.3/71.7
CEA (≤5/>5 ng/mL)	18/28	39.1/60.9
CA19-9 (≤40/>40 U/mL)	7/39	15.2/84.8
CRP/Albumin ratio (low/high)	23/23	50.0/50.0

ECOG: Eastern Cooperative Oncology Group; LA: Locally advanced; M: Metastatic; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CRP: C-reactive protein.

• **Median PFS:** 10.4 months vs. 5.4 months; **HR: 0.42**, 95% CI: 0.25-0.71, p<0.0005.

• **Median OS:** 22.0 months vs. 8.0 months; **HR: 0.38**, 95% CI: 0.21-0.68, p<0.0005.

No statistically significant differences in PFS or OS were observed with respect to sex, age (<70 vs. ≥70 years), baseline CEA (<5 vs. ≥5 ng/mL), baseline CA19-9 (<40 vs. ≥40 U/mL), or CRP/albumin ratio (<4.2 vs. ≥4.2).

Laboratory data are summarized in Table 1. In the evaluation using the upper limit of the biochemistry laboratory of University of Health Sciences Türkiye, Gülhane Training and Research Hospital, CEA elevation (>5) was detected in 60.9% of the patients, and CA 19-9 elevation was detected in 74.8% of the patients. The CRP/albumin ratio was found to be within the standard cut-off levels in 50% of the patients. The cut-off value was above 4.2. No statistically significant relationship was found between the elevation of CEA, CA 19/9, and CRP/albumin, PFS and OS.

Safety and Tolerability

Grade 3-4 hematologic toxicities included neutropenia in 21.7%, thrombocytopenia in 13%, and anemia in 13% of patients (Table 3). Among non-hematologic adverse events of grade ≥3, nausea/vomiting was observed in four patients, diarrhea in three patients, and peripheral neuropathy in three patients. Dose modifications due to toxicity were required in 6 patients (13%), while no treatment discontinuations occurred as a result of adverse events.

TABLE 2: Tumor response and disease control rates.

Response	n	%
CR	2	4.3
PR	11	23.9
SD	19	41.3
PD	14	30.4
ORR	13	28.3
DCR	32	69.6

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

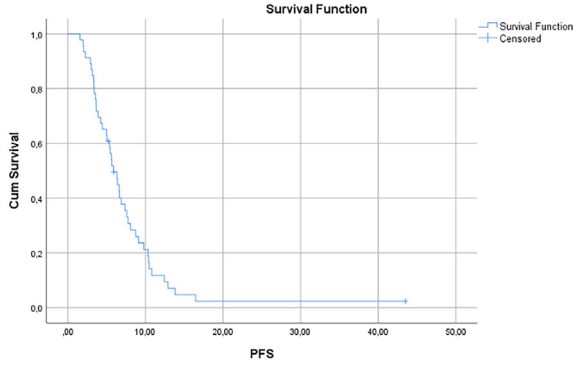

FIGURE 1: The median PFS was 5.8 months (95% CI: 5.4-9.3).

PFS: Progression-free survival; CI: Confidence interval

DISCUSSION

The current standard treatment for pancreatic cancer remains cytotoxic chemotherapy. Although trials investigating RET, BRAF V600E, TRK, KRAS G12C targeted therapies, and PARP inhibitors are ongoing, their efficacy in pancreatic cancer has not yet been conclusively demonstrated. Thus, efforts continue to identify the most effective and tolerable chemotherapy regimens supported by efficacy and safety data.

In metastatic disease, FOLFIRINOX achieved a 32% response rate and 70.2% DCR, with a median PFS of 6.4 months and OS of 11.1 months.[13] Gemcitabine plus nab-paclitaxel demonstrated an ORR of 23%, median PFS of 5.5 months, and OS of 8.5 months.[14] In the NAPOLI-3 trial, NALIRIFOX achieved a DCR rate of 68%, PFS rate of 7.4 months, and OS rate of 11.1 months in metastatic patients.[9] In our study, the median PFS was 5.8 months (95% CI, 5.4-9.3) and OS was 13.7 months

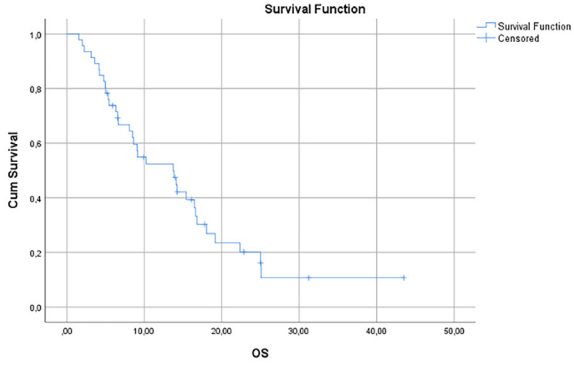

FIGURE 2: The median OS was 13.7 months (95% CI: 11.2-19.1).

OS: Sverall survival; CI: Confidence interval

TABLE 3: Grade 3-4 treatment-related adverse events.

AE	n	%
Hematologic toxicities		
Neutropenia	10	21.7
Thrombocytopenia	6	13
Anemia	6	13
Non-hematologic toxicities		
Neuropathy	3	6.5
Nausea/vomiting	4	8.7
Diarrhea	3	6.5

AE: Adverse event, percentages are based on total number of patients (n=46).

(95% CI: 11.2-19.1), with an ORR of 28.3% and DCR of 69.6%. The inclusion of 28% locally advanced patients in our cohort, compared with exclusively metastatic populations in other trials, may partly explain the relatively improved survival outcomes.

By contrast, a previous study of FOLFOX in locally advanced and metastatic pancreatic cancer reported modest activity, with a PFS of 4 months, OS of 6 months, and a 27% partial response rate.[10] This difference may be related to the inclusion of patients with ECOG 2 status, which was not specified in that report.

The role of FOLFOX in advanced pancreatic cancer remains controversial. In the phase III PANCREOX trial, mFOLFOX-6 in the second-line setting was associated with inferior survival compared with FU/leucovorin alone (median OS, 6.1, vs. 9.9 months).[15] Importantly, however, PANCREOX enrolled heavily pretreated patients in the second-line setting, whereas our study focused on chemotherapy-naïve ECOG 1 patients receiving first-line therapy. These differences in patient selection and treatment context may account for the more favorable outcomes in our study.

To our knowledge, very limited data exist regarding the evaluation of FOLFOX as first-line treatment in advanced pancreatic cancer patients with ECOG ≥1. Despite 28% of our patients presenting with locally advanced disease, none remained unresectable during follow-up. Taken together, our results suggest that FOLFOX may be a reasonable option for ECOG 1 patients deemed unsuitable for triple therapy by clinicians.

Regarding safety, grade 3-4 neutropenia occurred in 21.7%, thrombocytopenia in 12%, and neuropathy in 6% of patients. Dose reduction was performed in 13% of patients, and no treatment discontinuation occurred due to toxicity. By comparison, in the pivotal FOLFIRINOX trial, grade ≥3 neutropenia was reported in 46%, thrombocytopenia in 9%, neuropathy in 9%, nausea in 15%, and diarrhea in 13%.[7] Similarly, gemcitabine plus nab-paclitaxel was associated with grade 3-4 neutropenia in 38%, diarrhea in 6%, and neuropathy in 17%.[14] In the NAPOLI-3 study, diarrhea (20%), neutropenia (14%), and neuropathy (3%) were observed; 56% of patients required dose reduction, and 25% discontinued treatment due to adverse events.[9] Despite all patients in our study having ECOG 1, the toxicity profile appeared more favorable compared to other regimens, supporting the safe use of FOLFOX in clinical practice.

Considering that 37.4% of the patients in the FOLFIRINOX arm in the PRODIGE study[7] had ECOG 0, 42% of the patients with experimental colon cancer in the NAPOLI-3 study[9] had ECOG 0, and 58% of the patients in the gemcitabine plus nab-paclitaxel study[14] had a Karnofsky performance status of 90 and above, it is noteworthy that lower toxicity rates were observed in our study, even though all patients had ECOG 1. Against this background, the toxicity profile in our study appears more favorable, supporting the safe use of FOLFOX in clinical practice.

Biomarker analysis did not reveal significant correlations between baseline CEA, CA19-9, or inflammatory markers and survival outcomes; this may reflect the limited sample size. Nevertheless, prior studies have identified CA19-9 as a prognostic factor in pancreatic cancer and CEA as a marker of poor outcomes in gastrointestinal malignancies.[16-18]

In summary, our study demonstrates that FOLFOX may be a feasible and safe alternative for patients with ECOG 1 advanced pancreatic cancer who are not candidates for intensive regimens such as FOLFIRINOX. While most clinical trials exclude such patients due to concerns about tolerability, our findings suggest that selected ECOG 1 patients may still achieve meaningful benefit from a less intensive regimen. Furthermore, the relatively favorable safety profile compared with standard options reinforces its potential role in real-world practice, particularly in patients with comorbidities or frailty. However, the absence of BRCA/HRD testing, the retrospective design, and the small sample size limit the generalizability of these findings. Larger prospective studies are warranted to validate these observations.

Study Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Second, the sample size was relatively small, which may have reduced the statistical power to detect significant associations. Third, BRCA mutations and other HRD-related genomic alterations were not assessed, although such biomarkers are increasingly recognized as important predictors of treatment response in pancreatic cancer. Finally, heterogeneity in dose modifications and supportive care could have influenced outcomes. Therefore, our results should be interpreted with caution and validated in larger, prospective studies.

CONCLUSION

In advanced pancreatic cancer, the FOLFOX regimen demonstrates an acceptable balance of efficacy and tolerability. It may represent a valuable alternative for elderly or frail patients with impaired performance status who are not candidates for more intensive therapies. Our findings suggest that FOLFOX could be considered a pragmatic option in real-world practice, particularly in patient populations where treatment choices are limited.

Ethics

Ethics Committee Approval: Following approval from the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (approval number: 2024-578, date; 10.12.2024), the local/advanced unresectable and metastatic pancreatic cancer patients were scanned via the hospital information system.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.A., N.M., G.G.G., M.B.A., N.K., Concept: H.A., G.S.Y.K., S.K., B.K., M.B.A., N.K., Design: H.A., G.S.Y.K., S.K., B.K., M.B.A., N.K., Data Collection or Processing: H.A., G.E., G.Y., B.K., Analysis or Interpretation: H.A., G.S.Y.K., N.M., E.K.T., Literature Search: H.A., N.M., G.G.G., Writing: H.A., E.K.T., İ.E., N.K.

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