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Original Article

Second-line nab-paclitaxel and gemcitabine for advanced pancreatic cancer following FOLFIRINOX: outcomes and insights

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Abstract: We aimed to evaluate the efficacy and safety of a combination of nab-paclitaxel and gemcitabine as a second-line treatment, after first-line treatment with FOLFIRINOX regimen, for metastatic or locally advanced unresectable pancreatic cancer. This national multicenter retrospective study included patients with metastatic or unresectable locally advanced pancreatic cancer treated with FOLFIRINOX in the first-line setting. After progression with first-line treatment, all patients were treated with nab-paclitaxel and gemcitabine as second-line treatment. This study included 180 patients across 15 centers with a median age of 60 years. The median overall survival (OS) of all patients was 17.9 months. The median progression-free survival (PFS) following first-line chemotherapy was 8.4 months, whereas the median PFS achieved with nab-paclitaxel plus gemcitabine treatment was 5.5 months. Regarding treatment-related adverse events (TRAEs), all grades of non-hematologic adverse events (AEs) occurred at expected rates. However, the incidence of hematologic TRAEs was lower than anticipated. Grade 5 TRAEs were not observed. Patients who responded well to first-line FOLFIRINOX demonstrated a trend toward better outcomes with NG, although this did not reach statistical significance. The combination of nab-paclitaxel and gemcitabine is safe and effective as second-line treatment for locally advanced unresectable or metastatic pancreatic cancer after FOLFIRINOX.

Keywords: Pancreatic cancer, nab-paclitaxel, second-line therapy

Introduction

Pancreatic cancer mostly originates from the exocrine part of the pancreas [1]. The prognosis of pancreatic cancer remains poor even at early stages, making it a significant challenge in oncology. It is currently the sixth leading cause of cancer-related mortality worldwide [2]. Due to ambiguous symptoms or asymptomatic clinical status, the stage is often locally advanced or metastatic. Almost 80%-85% of pancreatic cancers are unresectable at diagnosis [3, 4].

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Chemotherapy is still the main systemic treatment for locally advanced unresectable and metastatic pancreatic cancers. The standard first-line treatments for metastatic disease are FOLFIRINOX (FFX) regimen and nab-paclitaxel/gemcitabine (NG) combination, since 2011 and 2013, respectively [5, 6]. For the last two years, NALIRIFOX regimen has also taken place among the standard regimens for first-line treatment [7]. There is still no standard treatment for patients whose disease has progression after FFX regimen.

Nab-paclitaxel is an albumin bound paclitaxel and used in the treatment of many types of malignant tumors, such as breast and lung cancers. The combination of nab-paclitaxel and gemcitabine (NG) as a first-line treatment was researched in 2013, and it was found more effective than gemcitabine (G) alone [5]. Numerous retrospective studies and meta-analyses have compared FFX and NG in the first-line setting [8-11]. While some of these studies showed no significant difference in overall survival (OS) between the use of FFX or NG as first-line therapy, others showed that FFX and NALIRIFOX were superior to NG in terms of progression-free survival (PFS) and OS, albeit at the cost of increased toxicity, particularly hematological and gastrointestinal toxicity [11]. Based on these data, NG has begun to be used more freuquently in the second-line treatment of locally advanced unresectable or metastatic pancreatic cancer than in the first-line treatment. Meanwhile, the results of a randomized prospective head-to-head comparison of modified FFX (mFFX) or S-IROX (regimen including S-1, Irinotecan and Oxaliplatin) versus NG in the first-line setting were announced in July 2025 [10]. There was no difference in survival between mFFX and S-IROX versus NG in patients with metastatic or recurrent pancreatic cancer [12]. Numerous studies have explored the effectiveness and safety of gemcitabine-based chemotherapy as first and second-line treatments, including both gemcitabine monotherapy and gemcitabine-based combination regimens. Despite extensive research, no regimen has been conclusively shown to provide a significant survival advantage with consistent supporting data for second-line therapy. Currently, there is no established standard approach for second-line treatment of locally advanced unresectable or metastatic pancreatic cancer [13, 14]. In this study, the efficacy and toxicity of NG as second-line treatment of patients with pancreatic cancer were evaluated.

Materials and methods

This is a national, multicenter, retrospective study designed to evaluate the OS, PFS, response rates (RR) of NG and safety. Patient data from patients diagnosed with metastatic or locally advanced unresectable pancreatic cancer between January 2015 and January 2022 were compiled from 15 centers across seven cities in Türkiye, including prominent metropolitan areas such as Istanbul, Antalya, and Adana. Eligible participants were aged 18 years or older with histologically confirmed pancreatic cancer previously treated with FFX as first-line therapy in locally advanced unresectable and metastatic settings. Patients without pathologically confirmed pancreatic cancer or with pathologically confirmed pancreatic cancer who did not receive FFX as first-line therapy, with locally advanced unresectable disease which became resectable after FFX as first-line therapy were excluded. Additionally, patients with a performance status greater than 2, unevaluable disease for response and any contraindication to receiving nab-paclitaxel were excluded from the study. All patients included in the study experienced disease progression either during or after FFX treatment and subsequently received NG as second-line therapy. Patients received nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2, administered intravenously, on days 1, 8 and 15 of a 28-day cycle. The patients received NG until progression or toxicity. Patients who had never received nab-paclitaxel owing to contraindications were excluded. Demographic data were obtained from hospital databases. Patients' age and gender, disease status (locally advanced unresectable or metastatic), location and size of the primary tumor, location and number of metastases, CA 19-9 levels at diagnosis and after treatment, RAS mutation status and microsatellite instability (MSI) status were also evaluated.

The analysis was conducted using SPSS (statistical package for the social sciences) software version 22.0. OS was defined as the duration from the date of treatment initiation to the date of death or last follow-up for patients with de novo metastatic disease. For patients with

Table 1. Baseline characteristics of patients during first-line treatment

		N (%)
Median ages (years)		60 (28-80)
Sex	Female	74 (41.1)
	Male	106 (58.9)
Localization of tumor	Head	108 (60)
	Body/Tail	72 (40)
Presence of metastasis	No	12 (6.7)
	Yes	168 (93.3)
Site of metastasis	Lymph node	76 (42.2)
	Peritoneum	38 (21.2)
	Liver	112 (62.2)
	Lung	41 (22.9)
	Bone	10 (5.6)
Tumor burden	Locally advanced	14 (7.8)
	Oligometastatic	105 (58.3)
	Metastatic	61 (33.9)
ECOG	0	69 (38.3)
	1	104 (57.8)
	2	7 (3.9)
Baseline CA 19-9 (U/mL)		352 (3-46861)

recurrent metastatic disease, OS was calculated from the date of treatment initiation to the date of death or last follow-up. PFS was measured as the time from treatment initiation until disease progression or the last recorded observation. Patients who were still alive or had not experienced disease progression at the time of the last follow-up were censored as of their last follow-up date. Kaplan-Meier survival estimates and log-rank test were used for survival analyses. Clinical response was evaluated according to Eastern Cooperative Oncology Group Performance Status (ECOG PS) and 3 groups were defined; stable, responsive and unresponsive. The patients with same PS were assessed to have a stable clinical response, with numerically decreasing PS were assessed to have a clinically responsive disease, with numerically increasing PS were assessed to have no clinical response; therefore, they were unresponsive. In addition, laboratory (biochemical) response was evaluated according to changes in tumor marker levels during treatment, three groups were defined; stable, responsive and unresponsive. Patients with negative (within the normal range) tumor marker levels or elevated tumor marker levels at diagnosis and declining levels during treatment were considered responsive. Patients with increased tumor marker levels during treatment, regardless of whether the tumor marker level was low or high at diagnosis, were considered unresponsive. The tumor marker level did not change significantly (± 10%) during treatment and was considered stable.

Categorical variables were presented as numbers (percentages), while continuous variables with normal distribution were presented as mean ± standard deviation (SD); non-normal variables were reported as median (minimum-maximum).

This study was designed and conducted in accordance with Good Clinical Practices and the Declaration of Helsinki and was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Approval Date/No. 30.05.2024/409). In accordance with the guidelines of this journal, we will provide data for the reproducibility of this study in other centers upon request.

Results

A total of 180 patients diagnosed with metastatic or unresetable locally advanced pancreatic cancer and were treated with second-line chemotherapy using NG were included in the study. Of the patients, 106 were male (58.9%) and 74 were female (41.1%), with a median age of 60 years (range: 28-80). The most common ECOG PS at diagnosis was 1 (57.8%) and 0 (38.3%). Most of the tumors were located in the pancreatic head (60%). Metastatic disease was present in 93.3% of the patients at the time of diagnosis, with the liver (62.2%), lymph nodes (42.2%), peritoneum (21.1%), and lungs (22.9%) being the most frequently involved metastatic sites (**Table 1**).

The objective response rate (ORR) to first-line chemotherapy (FFX) was 36.1%, while the disease control rate (DCR) reached 51.1% (**Table 2**).

Table 2. Response rates with FFX (1st line) and NG (2nd line)

		FFX, n (%)	NG, n (%)
Clinical response	Unresponsive	NE	95 (52.8)
	Stable	NE	47 (26.1)
	Responsive	NE	34 (18.9)
	Not available	NE	4 (2.2)
Radiological Response (RECIST v1.1)	CR	5 (2.8)	3 (1.7)
	PR	60 (33.3)	38 (21.1)
	SD	27 (15)	14 (7.8)
	PD	51 (28.3)	60 (33.3)
	NE	37 (20.6)	65 (36.1)
Laboratory response	Unresponsive	NE	80 (44.4)
	Responsive	NE	63 (35)
	Stable	NE	28 (15.6)
	Not available	-	9 (5)

FFX: FOLFİRİNOX, NG: Nab-paclitaxel plus Gemcitabine, NE: Not evaluated, CI: confidence interval, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease.

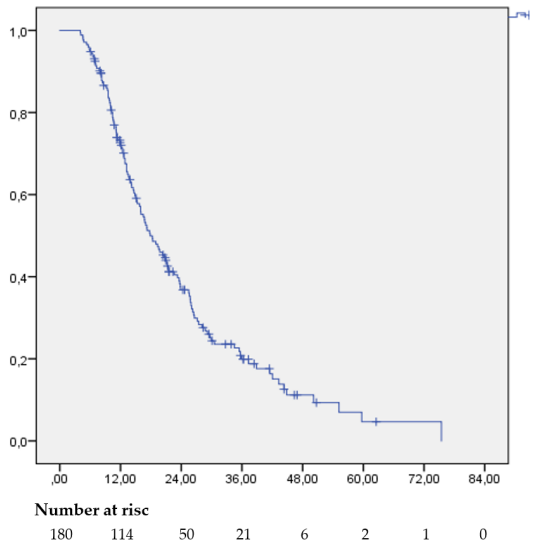

Figure 1. OS of patients treated with 2nd line NG after FFX.

Prior to the initiation of therapy with NG as second-line therapy, the most common ECOG PS was 1, observed in 59.4% of the patients. The clinical response rate to NG treatment was 45% (**Table 2**), with the ORR of 22.8%. Additionally, a decline in CA 19-9 levels was observed in 33.9% of the patients treated with NG, indicating a biochemical response. Across the entire patient population, the median OS (mOS) was 17.9 months. The median PFS (mPFS) with first-line therapy was 8.4 months, while the mPFS with NG as a second-line regimen was 5.5 months (**Figures 1**, **2**). PFS observed with NG was determined to be independent of factors such as the primary tumor site, presence of metastasis, gender or ECOG PS. However, our findings suggest a potential, albeit statistically non-significant, association between PFS and disease classification as locally advanced unresectable or oligometastatic (**Table 3**). We defined oligometastatic disease as having maximum three metastatic sites.

When all grades of treatment-related adverse events (TRAEs) were analyzed, non-hematologic adverse effects were consistent with the literature. Nausea and vomiting were observed in 37.8% of the patients (n=68), loss of appetite in 34.4% (n=62), and diarrhea in 15.6% (n=28). Hematologic adverse events, on the other hand, were less frequent than expected; anemia occurred in 28.3% of patients (n=51), neutropenia in 21.7% (39), and thrombocytopenia in 23.9% (n=43). Importantly, no grade 5 TRAEs were identified during the analysis of TRAEs (**Table 4**).

Discussion

Our findings demonstrate that the combination of NG is an effective and well-tolerated second-line treatment option for patients with locally advanced unresectable or metastatic pancreatic cancer following FFX. The objective response rates for FFX and NG were 36.1% and 22.8%, respectively, while the mPFS durations were 8.4 months and 5.5 months, respectively. The therapeutic benefit of NG was independent of primary tumor location, metastatic site, performance status, age, or gender. Nevertheless, our analysis suggested a potential correlation between the response to NG and disease burden, although this did not reach statistical significance. Specifically, the mPFS for patients with locally advanced unresectable disease, oligometastatic disease, and widespread metastatic disease was 5.7 months, 5.2 months, and 4.1 months, respectively. In terms of safety, adverse events associated with NG were evaluated without grading. Weakness was

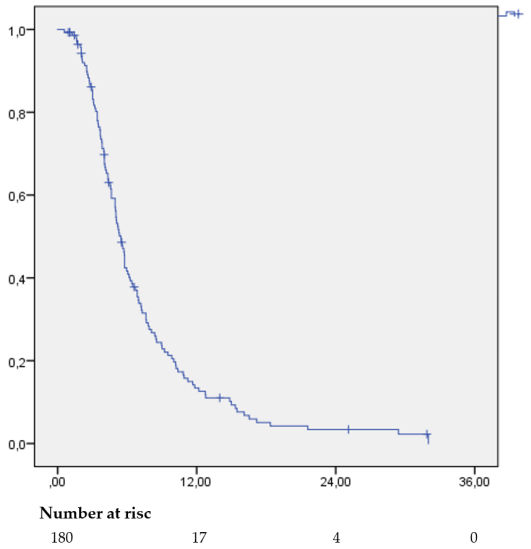

Figure 2. PFS of patients treated with 2nd line NG after FFX.

the most commonly reported adverse event, observed in approximately 58% of patients (n=105).

Currently, there is no standardized approach or regimen recommended in the guidelines for second-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer following FFX [13, 14]. The absence of a clear consensus on second-line therapeutic approaches, combined with the ongoing unmet needs of patients who have failed prior treatments, has motivated the design of this study. The primary objective of this study is to assess the potential efficacy and safety of this combination therapy in patients who have progressed after first-line treatment. Given the scarcity of effective second-line options, exploring novel therapeutic strategies is essential to improve patient outcomes. The findings of this study may offer crucial evidence to support the future inclusion of this combination in clinical practice guidelines and expand the range of viable treatment alternatives for this patient population. Our primary objective was to assess the potency and tolerability of NG as a second-line treatment in patients who experienced progression during or after FFX.

In spite of several studies have been conducted on this topic, the majority are retrospective in nature. In 2015, a prospective multicenter French study published the outcomes of NG as second-line treatment in patients with metastatic pancreatic cancer progressing after FFX [15]. In this study, which included 57 patients, the DCR was 58%, while the ORR was 17.5%. In our study, the DCR with NG is 45%, while the ORR is 22.8%. In the study by Portal et al., the mOS and mPFS with NG were 8.8 months and 5.1 months, respectively. Moreover, the mOS after first-line treatment was 18 months [15]. In our study, the mPFS and mOS values with NG were found to be similar, at 5.5 months and 17.9 months, respectively, when calculated from the initiation of first-line treatment. The fact that the majority of patients in our study were also in the metastatic stage may explain the close similarity of the results.

In 2017, a study from the USA was published with a design almost identical to ours. This multicenter, retrospective study included 30 patients with metastatic or locally advanced unresectable pancreatic cancer who had progressed after first-line FFX treatment. From the initiation of first-line therapy, the mPFS was 7.2 months, and the mOS was 13.7 months. With NG, the reported mPFS and mOS were 3.7 months and 12.4 months, respectively [16]. Although our study and the US study were nearly identical in design and shared many demographic features (e.g., median age, gender distribution, metastatic site distribution), the numerically longer survival times observed in our results may be attributed to the following factors: 1. Patient sample size: Our study included 180 patients, whereas the US study included only 30 patients. 2. Tumor location: In our study, 60% of the patients had tumors located in the pancreatic head, compared with only 40% in the US study. It is widely believed that tumors located in the pancreatic head are diagnosed earlier (due to symptomatic jaundice) and thus may respond better to treatment and achieve longer survival times. The biochemical (CA 19-9) and radiological response rates achieved with second-line NG therapy in the US study were 73% and 57%, respectively. By contrast, the rates in our study were 50.6% and 30.6%, respectively. The lower response rates in our study could potentially be explained by the high proportion of missing data in these evaluations, with 5% and 35% of the data being unavailable, respectively. In this study, the relations-

Table 3. PFS with NG by demographic characteristics

		PFS	HR	P
Sex	Female	5.7	(4.7-6.8)	0.105
	Male	5.1	(4.7-6.8)	
Localization of tumor	Head	5.4	(4.6-6.2)	0.898
	Body/Tail	5.3	(4.0-6.6)	
Presence of metastasis	No	5.9	(0.7-11.1)	0.154
	Yes	5.3	(4.7-5.9)	
Tumor burden	Locally advanced	5.7	(5.4-6.1)	*0.038*
	Oligometastatic	5.2	(3.9-6.4)	
	Metastatic	4.1	(2.8-5.3)	
ECOG	0	5.7	(5.1-6.3)	0.113
	1	5.1	(4.3-5.7)	
	2	4.0	(2.3-5.9)	
Level of CA 19-9 at the diagnosis	Normal	5.9	(4.3-7.6)	0.808
	High	5.3	(4.8-5.8)	
Clinical response	Responsive	9.2	(8.0-14.3)	*<0.001*
	Stable	9.8	(6.4-12.1)	
	Unresponsive	6.4	(4.7-8.1)	
Radiological response	Not available	4.4	(2.7-5.5)	*<0.001*
	Partial	10.2	(7.2-15)	
	Stable	9.0	(5.7-10.4)	
	Progression	4.3	(3.7-6.9)	

CA 19-9: Carbohydrate antigen 19-9, ECOG: Eastern Cooperative Oncology Group.

Table 4. Treatment related adverse events with the NG regimen (any grades)

Adverse events (Non-hematologic)	N (%)
Weakness	105 (58.3)
Nausea-vomiting	68 (37.8)
Loss of appetite	62 (34.4)
Diarrhea	28 (15.6)
Neuropathy	16 (8.9)
Mucositis	14 (7.8)
Alopecia	7 (3.9)
Hand-foot syndrome	2 (1.1)
Hematologic adverse events	
Anemia	51 (28.3)
Thrombocytopenia	43 (23.9)
Neutropenia	39 (21.7)

hip between the best response to FFX according to the RECIST criteria and the response to NG was also evaluated. It was observed that patients whose best response to FFX was progressive disease (PD) showed a trend toward improved survival with NG. This finding was interpreted as potentially being related to the earlier initiation of second-line chemotherapy. However, due to the design of our study and the limitations of our database, we were unable to conduct a similar evaluation. Furthermore, while the US study compared the adverse effects of FFX and NG, we did not record FFX-related adverse effects because this was not among the objectives of our study. Therefore, such a comparison could not be performed in our analysis. However, the adverse effects observed with NG in this study and in our study were similar.

The results of the first multicenter, retrospective French study named AGEO, which comparatively demonstrated the advantage of NG as a second-line treatment for metastatic pancreatic cancer, were published as an abstract in 2020 [17]. This study included 445 patients, with 228 receiving NG and 217 receiving single-agent gemcitabine. After a median follow-up of 22 months, the outcomes achieved with NG versus G were as follows: DCR 56% vs. 31%, PFS 3.3 months vs. 2.1 months (HR (Hazard Ratio) 0.56, P<0.001), and OS 6.8 months vs.

4.3 months (HR 0.64, P<0.0001) [17]. These results demonstrated that NG combination therapy provided a statistically significant improvement compared to G in the second-line treatment of metastatic pancreatic cancer. This benefit was consistent across subgroups, regardless of age, gender, performance status (PS) or the response to first-line FFX. Although NG had a higher incidence of adverse effects compared to G, the adverse effect profile and frequency were consistent with those observed in previous NG studies. In the critique of the study, it was noted that the survival benefit observed with NG might have been influenced by the lower proportion of patients with PS ≥2 in the NG group compared to the G group (26% vs. 39%, respectively). In our study, patients with PS >2 were excluded, and the proportion of patients with PS 2 was relatively low (3.9%). We believe that this difference in PS distribution is a significant factor contributing to the better outcomes observed in our study compared with the AGEO study.

When evaluating the efficacy and safety of the NG regimen, it is essential to highlight two pivotal prospective studies published in recent years: NAPOLI-3 and GENERATE [7, 12]. Both trials directly compared NG with quadruplet regimens (mFFX, S-IROX and NALIRIFOX) as first-line therapy for metastatic pancreatic cancer. Notably, NAPOLI-3 remains the only study to date that has demonstrated the superiority of a quadruplet regimen (NALIRIFOX) over NG in terms of OS and PFS among previously untreated patients.

In contrast, in the landmark study establishing the efficacy of FOLFIRINOX, the comparator arm received single-agent gemcitabine, thereby maintaining NG as a valid first-line treatment option at the time [5]. However, the results of NAPOLI-3 have led to increasing consideration that NG may eventually be relegated to second-line therapy. Still, since these findings are derived from a single trial and have not yet been consistently replicated, NG continues to be included as a first-line option in international guidelines.

Further supporting this guideline stance, the recently published GENERATE trial randomized patients to receive S-IROX, mFFX, or NG. Importantly, neither mFFX nor S-IROX demonstrated a statistically significant advantage over NG, reinforcing their continued role as a standard first-line regimen [12].

Our study has several limitations that warrant acknowledgment. First, as a retrospective and non-randomized analysis, there were no patient cohorts in terms of disease burden, gender, or performance status. This lack of balance may have influenced our findings, and it is possible that some of the observed trends could have reached statistical significance with more evenly distributed and adequately sized groups. Second, missing data posed a challenge, largely due to the use of different recording systems across participating centers and variations in data retention practices determined by individual centers or clinicians. This is an inherent limitation frequently encountered in retrospective, multicenter studies. Consequently, certain parameters - such as adverse events - could not be graded and were instead assessed in a more general manner. Again, dose modifications due to adverse effects were not recorded regularly and therefore could not be used in the statistical analysis.

Had this been a prospective study, predefin ed parameters and systematic data collection throughout the treatment and follow-up period would have ensured more comprehensive and standardized records.

Conclusions

First-line treatment for unresectable locally advanced and metastatic pancreatic cancer currently consists of therapies based on 5-FU, oxaliplatin, and irinotecan (e.g., NALIRIFOX and FOLFIRINOX [13, 14]). However, there is no established standard approach for second-line treatment. Certain clinical, laboratory, and/or radiological markers, that have yet to be identified, may play a role in guiding the selection of treatments following first-line therapy. Although not statistically significant, our study identified findings suggesting that the response to first-line therapy might predict the response to second-line treatment with NG. Further prospective studies with larger patient cohorts and more homogeneous distributions are needed to confirm these observations.

Disclosure of conflict of interest

None.

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