Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX scheme in the treatment of advanced pancreatic cancer: real-life data

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Fecha de recepción: 06/03/2024 - Fecha de aceptación: 23/04/2024

FIRST ONLINE

ABSTRACT

Introduction: Pancreatic cancer (PC) is an unresolved health problem. Therapies such as nab-paclitaxel plus gemcitabine (NabGem) and modified FOLFIRINOX (MFOLFIRINOX) are currently available therapeutic options. However, there are no clinical trials that include both schemes. The objective is to compare the effectiveness and safety of NabGem versus MFOLFIRINOX through real-life data in patients diagnosed with locally advanced and metastatic PC.

Methods: Observational retrospective study was conducted. Efficacy endpoints were overall survival (OS) and progression free survival (PFS). Univariate and multivariate analysis was performed using Cox regression to calculate Hazard Ratios (HR) and 95% confidence intervals (95% CI). Adverse events (AEs), dose reductions associated with toxicity, administration delays, and treatment discontinuations were selected as safety endpoints.

Results: A total of 67 patients were included. No significant differences were found for OS in univariate analysis [HR = 1.80 (95% CI: 0.93-3.49; p=0.08)]. Nevertheless, multivariate analysis found a statistically significant OS differences between NabGem and MFOLFIRINOX [HR = 2.84 (95% CI: 1.03-7.82; p=0.04)]. Regarding to PFS, no significant differences were found in either univariate [HR = 0.85 (95% CI: 0.49-1.49; p=0.57)] or multivariate analysis [HR = 0.91 (95% CI: 0.42-1.99; p=0.82]. AEs of any grade were observed in 84.8% of patients treated with NabGem and of 88.9% population assigned to MFOLFIRINOX. Dose reductions, cycle delays and treatment discontinuations were higher in MFOLFIRINOX group. Conclusion: Multivariate analysis suggested an OS improvement of MFOLFIRINOX versus NabGem. There were no differences in PFS. MFOLFIRINOX presented worse tolerance.

Keywords: **Pancreatic cancer, real-life data, modified FOLFIRINOX, nab-paclitaxel plus gemcitabine**

Nab-paclitaxel más gemcitabina versus FOLFIRINOX modificado en el tratamiento del cáncer pancreático avanzado: resultados en vida real

RESUMEN

Introducción: El cáncer de páncreas (CP) es un problema de salud sin resolver. Las terapias como nab-paclitaxel más gemcitabina (NabGem) y FOLFIRINOX modificado (MFOLFIRINOX) son opciones terapéuticas. No existen ensayos clínicos que incluyan ambos esquemas. El objetivo fue comparar la eficacia y seguridad de NabGem frente a MFOLFIRINOX empleando datos reales de pacientes diagnosticados de CP localmente avanzado y metastásico.

Métodos: Estudio observacional retrospectivo. Como variables de eficacia se empleó la supervivencia global (SG) y la supervivencia sin progresión (SLP). Se realizaron análisis univariantes y multivariantes mediante regresión de Cox para calcular Hazard Ratios (HR) y los intervalos de confianza del 95% (IC95%). Para evaluar la seguridad se seleccionaron los eventos adversos (EA), las reducciones, los retrasos y las interrupciones del tratamiento.

Resultados: Se incluyó a 67 pacientes. No se encontraron diferencias significativas para la SG en el análisis univariante [HR=1,80(IC95%:0,93-3,49; p=0,08)]. Sin embargo, en el análisis multivariante se encontraron diferencias estadísticamente significativas en la SG entre NabGem y MFOLFIRINOX [HR=2,84(IC95%:1,03-7,82; p=0,04)]. En cuanto a la SLP, no se encontraron diferencias significativas ni en el análisis univariante [HR=0,85(IC95%:0,49-1,49; p=0,57)] ni en el multivariante [HR=0,91(IC95%:0,42-1,99; p=0,82]. Se observaron EA de cualquier grado en el 84,8% de los pacientes tratados con NabGem y en el 88,9% de la población asignada a MFOLFIRINOX. Las reducciones, los retrasos y las interrupciones fueron mayores en el grupo de MFOLFIRINOX.

Conclusiones: El análisis multivariante mostró una mejora en SG de MFOLFIRINOX frente a NabGem. No hubo diferencias en SLP. El esquema MFOLFIRINOX presentó peor tolerancia.

Palabras clave: **Cáncer de páncreas, resultados en vida real, FOLFIRINOX modificado, nab-paclitaxel más gemcitabina**

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INTRODUCTION

Pancreatic cancer (PC) is a relevant health problem in society. It represents 3% of all diagnosed neoplasms and generates 7% of deaths attributed to oncological pathologies. For these patients, a 5-year survival rates of approximately 10% have been observed[1]. Likewise, an incidence of 140,000 cases per year has been estimated in Europe[2]. In terms of gender, PC is the eighth most frequent cancer in women and the tenth in men[3].

Most malignant neoplasms of the pancreas are exocrine, of which ductal adenocarcinoma and its variants represent around 90%[4]. The diagnosis in the early stages of the disease is a fundamental element for a better prognosis of patients. Sometimes, tumor detection is complicated since most of the patients remain asymptomatic and no useful tumor markers are available for screening. However, in some cases symptoms include weight loss, jaundice, malabsorption, dyspepsia and nausea[5].

Probability of suffering from the disease could increase due to environmental and hereditary risk factors. These environmental factors include obesity, sedentary lifestyle, poor dietary habits, diabetes, tobacco, alcohol, Helicobacter pylori infection and hepatitis virus infections[6,7]. On the other hand, a small number of cases are related to specific germline genetic mutations. Mutations in BRCA2, p16, ATM, STK11, PRSS1/PRSS2, SPINK1, PALB2 and genes involved in DNA mismatch repair may increase the risk of pancreatic cancer[7].

The initial diagnosis usually occurs at locally advanced or metastatic stage. Surgical resection provides a curative option in patients with potentially resectable tumors. However, in many occasions the disease presents as unresectable due to the involvement of structures adjacent to the tumor or presence of metastases. In these cases, the available therapeutic option is usually chemotherapy. Chemotherapy schemes involving gemcitabine with nab-paclitaxel (NabGem) or regimens based on association of 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) are two of the most widely used therapeutic alternatives[8]. In order to reduce the adverse events (AEs) associated with FOLFIRINOX, a modified FOLFIRINOX scheme (MFOLFIRINOX) based on dose reduction is more frequently used in clinical practice. The existence of efficacy and safety studies directly comparing NabGem and MFOLFIRINOX therapeutic schemes are scarce in the previous literature. Thus, it is necessary to generate evidence with real life results. The aim of this study is to compare the effectiveness and safety of NabGem versus MFOLFIRINOX in patients diagnosed with locally advanced and metastatic PC.

METHODS

Study population and data extraction

Observational retrospective study including patients diagnosed with PC treated with NabGem or MFOLFIRINOX was conducted between January 2016 and November 2022. Patients aged 18 years or older, diagnosed with locally advanced or metastatic PC and performance status measured by Eastern Cooperative Oncology Group (ECOG) ≤ 2 were selected. Cases with resectable tumours and/or neoplasms with histology other than ductal adenocarcinoma were excluded. Patient data extraction was developed through the cytostatic management software (Farmis®) and electronic medical records (Diraya®). The following demographic and clinical data were collected: sex, age, weight, alcohol and tobacco consumption, ECOG, disease stage, tumour histology, previous lines of therapy, treatment duration and number of cycles received.

Treatment regimens

Patients assigned to the NabGem arm received nab-paclitaxel (125 mg/m²) followed by gemcitabine (1000 mg/m2) on days 1, 8 and 15 of each 28-day cycle. Oxaliplatin (85 mg/m2), irinotecan (150 mg/m2), calcium folinate (400 mg/m2) and 5-fluorouracil (5-FU) (2400 g/m²) were administered every 14 days to the population assigned to the MFOLFIRINOX arm. All patients received treatment until progression or unacceptable toxicity, and cross-over to the other treatment regimen was allowed if clinical judgement was deemed appropriate.

Outcomes studied and data analysis

The efficacy endpoints were overall survival (OS) and progression free survival (PFS). OS was defined as the time from treatment initiation to patient death. PFS was defined as the time from the start of treatment to radiological or clinical disease progression. Radiological progression was established according to the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1[9]. Clinical progression was assessed through follow-up in consultation with the physician.

A descriptive analysis was performed for all variables included in the study. Quantitative variables were described as mean ± standard deviation (SD) or median ± interquartile range (IQR) according to the distribution of the variable as verified by graphical (histogram) and statistical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Qualitative variables were described by absolute and relative frequencies. To compare the two treatment groups, Student´s t-test or Mann Whitney U-test were used for quantitative variables, and the $\chi 2$ test or Fisher´s exact test when necessary for qualitative variables. For OS and PFS analysis, Kaplan-Meier method was used and multivariate analysis was also performed using Cox regression to calculate Hazard Ratios (HR) and their 95% confidence intervals (95% CI). All analyses were performed using the SPSS v.18 statistical software and a value of $p<0.05$ was regarded as statistically significant.

The safety endpoints considered were AEs recorded and their grade classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0)[10].

Absolute risk reduction (ARR) and statistical significance of AEs were determined[11]. Dose reductions associated with toxicity, delays, treatment discontinuations and therapies used after discontinuation due to AEs were also recorded.

RESULTS

At data cut-off, 67 patients were registered. Two patients were excluded from the analysis due to presenting resectable pancreatic adenocarcinoma and one due to squamous histology. Finally, a total of 64 patients were included: 46 patients were treated with NabGem and 18 cases received MFOLFIRINOX. Men were more frequent in both groups. Patients included in the NabGem arm were older and had higher ECOG score (statistically significant differences). In

both cohorts, most patients received the drugs evaluated in the study as first-line treatment. Six patients were eligible for cross-over from MFOLFIRINOX to NabGem due to tumor progression. All cross-over patients received NabGem as second line. Demographic and clinical characteristics are shown in Table 1.

Regarding treatment duration, patients received therapy for a median of 4 (range 1-23) months in the NabGem group and 5 (range 1-10) months in the MFOLFIRINOX arm.

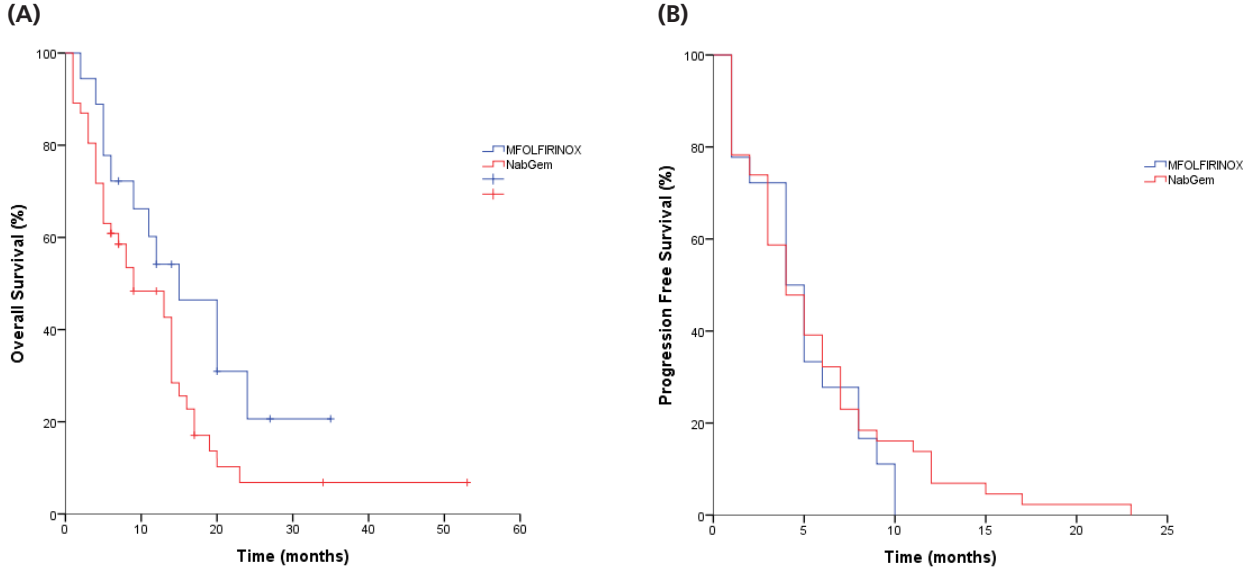
In terms of efficacy endpoints, median OS for NabGem group was 9 months (95% CI: 3.37 to 14.62) vs. 15 months (95% CI: 7.43 to 22.56) for MFOLFIRINOX cohort [Figure 1(A)]. No significant differences were found for OS in univariate analysis [HR =1.80 (95% CI: 0.93-3.49; p = 0.08)]. However, multivariate analysis found a statistically significant OS benefit in favour of MFOLFIRINOX [HR =2.84 (95% CI: 1.03-7.82, p = 0.04)]. Likewise, both univariate and multivariate analysis identified ECOG 2 as a variable with influence on OS results. These data are detailed in Table 2.

Table 1. Demographic and clinical characteristics in the study population

		All population (n = 64)	NabGem n = 46 (71.9%)	MFOLFIRINOX n=18 (28.1%)	p
Sex	Male	44 (68.7%)	29 (63%)	15 (83.3%)	0.12
	Female	20 (31.3%)	17 (37%)	3 (16.7%)	
Age (mean) ± SD* (range)		65.9 ± 9.3 (44 – 79)	68.3 ± 8.3	59.9 ± 9.2	<0.01
Weight (median) Kilograms ± RIC† (range)		60.5 ± 26 (41 – 143)	60 ± 26	64 ± 35.5	0.82
Alcohol	Yes	42 (65.6%)	40 (87%)	2 (11.1%)	>0.99
	No	22 (34.4%)	6 (13%)	16 (88.9%)	
Tobacco	Yes	26 (40.6%)	17 (37%)	9 (50%)	0.34
	No	38 (59.4%)	29 (63%)	9 (50%)	
ECOG (median) ± RIC (range)		1 ± 1 (0 – 2)	1 ± 1	0 ± 1	0.01
ECOG	0	24 (37.5%)	13 (28.2%)	11 (61.1%)	0.03
	1	35 (54.7%)	28 (60.9%)	7 (38.9%)	
	2	5 (7.8%)	5 (10.9%)	0	
Stage	Metastatic	38 (59.4%)	30 (65.2%)	8 (44.4%)	0.13
	Locally advanced	26 (40.6%)	16 (34.8%)	10 (55.6%)	
Previous treatments lines (median) ± RIC (range)		0 ± 0 (0 – 2)	0 ± 0	0 ± 0	0.16
Lines	0	53 (82.7%)	36 (78.2%)	17 (94.4%)	0.36
	1	9 (14.1%)	8 (17.4%)	1 (5.6%)	
	2	1 (1.6%)	1 (2.2%)	0	
	ND‡	1 (1.6%)	1 (2.2%)	-	-
Nº cycles received (median) ± RIC (range)		5.5 ± 7 (1 – 23)	4.5 ± 5.5	7.5 ± 8.2	0.09
Median overall survival time ± RIC (range)		9 ± 10 (1 – 53)	7.5 ± 10	12 ± 14.2	0.07
Median progression free time ± RIC (range)		4 ± 5 (1 – 23)	4 ± 5	4.5 ± 6.2	0.96
Progression	Yes	63 (98.4%)	45 (97.8%)	18 (100%)	>0.99
	No	1 (1.6%)	1 (2.2%)	0	
Deaths	Yes	49 (76.6%)	37 (80.4%)	12 (66.7%)	0.33
	No	15 (23.4%)	9 (19.6%)	6 (33.3%)	

*SD: standard deviation. †RIC: interquartile range. ‡ND: no data.

Figure 1. Kaplan–Meier stimates of overall survival (A) and progression free survival (B).



Median PFS was 4 months (95% CI: 2.52 to 5.48) for NabGem cohort and 4 months (95% CI: 2.22 to 5.78) for MFOLFIRINOX arm [Figure 1(B)]. No statistically significant differences were found for PFS in either univariate [HR = 0.85 (95% CI: 0.49 -1.49; p = 0.57)] or multivariate analysis [HR = 0.91 (95% CI: 0.42 to 1.99; p = 0.82)]. In addition, both univariate and multivariate analysis found ECOG 2 as variable with an impact on PFS results. Only multivariate analysis revealed an influence of age on PFS outcomes. These data are shown in Table 3.

Concerning safety, AEs of any grade were observed in 84.8% of population assigned to NabGem and 88.9% of patients treated with MFOLFIRINOX. The most common AEs associated with NabGem were asthenia (67.4%), neuropathy (30.4%), nausea and vomiting (28.3%). On the other hand, the most frequent AEs related to MFOLFIRINOX were neuropathy (55.6%), diarrhoea (44.4%), and asthenia (38.9). Grade 3 or higher AEs were higher in the MFOLFIRINOX group (27.8%) compared to the NabGem arm (8.7%), with asthenia (11.1% for MFOLFIRINOX vs 4.3% for NabGem) and diarrhea (11.1% in MFOLFIRINOX group vs 2.2% in NabGem cohort) being the most common AEs. Safety results are detailed in Table 4.

Dose reductions were recorded in 50.0% and 61.1% of patients in NabGem and MFOLFIRINOX groups, respectively. Delayed cycle administration occurred in 43.5% of NabGem cohort versus 66.7% of cases in MFOLFIRINOX arm. Finally, treatment was discontinued due to AEs in 30.5% of NabGem arm and 33.4% of MFOLFIRINOX group. Of these cases, 19.6% of patients were treated with gemcitabine monotherapy, 2.2% with the oxaliplatin and capecitabine scheme (XELOX), 2.2 % with capecitabine monotherapy and 6.5% decided not to continue with another treatment. After discontinuing MFOLFIRINOX, 22.2% of patients received the combination of irinotecan, calcium folinate and 5-fluorouracil (FOLFIRI) for AEs to oxaliplatin; 5.6% of patients were treated with the oxaliplatin, calcium folinate and 5-fluorouracil regimen (FOLFOX) for AEs to irinotecan; and 5.6% of cases received gemcitabine.

DISCUSSION

In our study, statistically significant differences favorable to MFOLFIRINOX in OS results were found in the multivariate analysis. However, PFS was similar in both treatments. On the other hand, the influence of ECOG score in

Table 2: Univariate and multivariate analyses in overall survival.

		Univariate		Multivariate	
		HR (CI 95%)*	p	HR (CI 95%)	p
Sex (female vs male)		1.17 (0.64 – 2.16)	0.61	0.86 (0.35 – 2.11)	0.74
Age (years)		1.00 (0.97 – 1.03)	0.96	0.97 (0.93 – 1.01)	0.13
Weight (kilograms)		1.00 (0.99 – 1.02)	0.94	0.99 (0.97 – 1.02)	0.47
Alcohol (yes vs no)		2.22 (1.21 – 4.80)	0.04	1.03 (0.33 – 3.21)	0.96
Tobacco (yes vs no)		1.36 (0.77 – 2.40)	0.29	1.24 (0.65 – 2.38)	0.52
ECOG	0	Ref	-	Ref	-
	1	1.56 (0.85 – 2.86)	0.16	0.97 (0.44 – 2.13)	0.93
	2	12.51 (3.89 – 40.15)	<0.01	5.72 (1.24 – 26.35)	0.03
Stage (locally advanced vs metastatic)		0.87 (0.49 – 1.55)	0.63	0.80 (0.41 – 1.57)	0.52
Lines	0	Ref	-	Ref	-
	1	0.51 (0.21 – 1.20)	0.12	0.31 (0.09 – 1.02)	0.05
	2	0.69 (0.094 – 5.05)	0.71	0.44 (0.04 – 4.56)	0.49
Treatment (NabGem vs MFOLFIRINOX)		1.80 (0.93 – 3.49)	0.08	2.84 (1.03 – 7.82)	0.04

*HR: hazard ratio. CI: confidence interval. Ref: reference

Table 3: Univariate and multivariate analyses in progression free survival.

		Univariate		Multivariate	
		HR (CI 95%)*	p	HR (CI 95%)	p
Sex (female vs male)		0.96 (0.56 – 1.65)	0.96	0.65 (0.30 – 1.40)	0.27
Age (years)		0.98 (0.96 – 1.01)	0.20	0.96 (0.93 – 0.99)	0.04
Weight (kilograms)		1.00 (0.99 – 1.01)	0.95	0.99 (0.98 – 1.01)	0.54
Alcohol (yes vs no)		1.88 (0.88 – 4.01)	0.10	1.02 (0.39 – 2.67)	0.96
Tobacco (yes vs no)		1.03 (0.62 – 1.73)	0.91	0.81 (0.46 – 1.43)	0.46
ECOG	0	Ref	-	Ref	-
	1	1.32 (0.77 – 2.25)	0.31	1.45 (0.73 – 2.89)	0.29
	2	7.79 (2.47 – 24.54)	<0.01	10.89 (2.40 – 49.37)	<0.01
Stage (locally advanced vs metastatic)		0.97 (0.58 – 1.62)	0.89	0.85 (0.48 – 1.50)	0.57
Lines	0	Ref	-	Ref	-
	1	0.60 (0.28 – 1.28)	0.19	0.51 (1.79 – 1.43)	0.20
	2	0.73 (0.10 – 5.35)	0.76	0.68 (0.07 – 6.25)	0.73
Treatment (NabGem vs MFOLFIRINOX)		0.85 (0.49 – 1.49)	0.57	0.91 (0.42 – 1.99)	0.82

*HR: hazard ratio. CI: confidence interval. Ref: reference.

both OS and PFS was observed. Compared with the results obtained in previous randomized clinical trials (RCTs) of FOLFIRINOX such as those of PRODIGE 4/ ACCORD 11[12], the median OS achieved in MFOLFIRINOX arm of our study was higher (15 months vs. 10.8 months) and the median PFS was lower (4 months vs 8 months). For the NabGem regimen, the MPACT trial[13] showed similar medians of OS (9 months vs 8.5 months) and PFS (4 months vs 5.5 months). However, none of the RCTs above mentioned compared a scheme based on oxaliplatin, irinotecan and 5-FU against NabGem. Other descriptive studies showed a median OS of 6-16 months for NabGem and 9-16 months for FOLFIRINOX schemes[14-18]. Our data were within these ranges of values.

A high incidence of AEs was recorded in our population, occurring in more than 80% of the patients of both treatment schemes. Definitive discontinuation of administrations was observed in about one third of patients. Asthenia, neuropathy and gastrointestinal AEs were the most frequent AEs. As mentioned above, there was a cross-over of patients from the MFOLFIRINOX arm to NabGem. This could explain the higher frequency of neurotoxicity related to NabGem in contrast to the safety results reported in the MPACT trial[13]. To date, other retrospective studies have included the classical FOLFIRINOX regimen in routine clinical practice. Our patients received MFOLFIRINOX, a modified regimen that reduces the irinotecan dose to 150mg/m² and suppresses the 5-fluorouracil bolus. This scheme was selected because some non-comparative studies reported more favourable safety profiles of the modified regimen compared to the classical combination, without reducing the efficacy[19-22].

The two therapeutic alternatives included in our comparison have been tested as valid therapeutic options for PC. Some lines of research have focused on analyzing the combination of both therapies. Preliminary results of the SEQUENCE clinical trial have recently been presented. This study evaluated the alternating use of NabGem with oxaliplatin based treatment cycles. A total of 157 patients diagnosed with metastatic PC were randomised to receive either NabGem or NabGem followed by a cycle of FOLFOX (day 29 of every 6-week cycle, referred to as modified FOLFOX6)[23]. Sequential treatment with both regimens was associated with an improvement in median OS (13.2 vs. 9.7 months; HR 0.676; 95% CI [0.438 to 0.937]; p=0.023) in a preliminary analysis[24]. Nevertheless, AEs such as grade ≥3 neutropenia and thrombocytopenia were higher in the alternating regimen of NabGem and modified FOLFOX6.

Currently, prolonging the life of oncological patients with PC is a major challenge. Several years ago, FOLFIRINOX scheme showed greater benefit than gemcitabine monotherapy[25]. A meta-analysis suggested that the superiority of the different combinations with gemcitabine over gemcitabine alone is unclear in global population[26]. Nevertheless, these patients have a poor prognosis. The present study provides real-life data in a scenario where there are no controlled RCTs comparing the two selected therapeutic alternatives. To date, there have been comparative studies on the effectiveness of the classical FOLFIRINOX regimen versus other alternatives[25]. Previous single arm publications evaluated the safety profile of MFOLFIRINOX. Our comparative effectiveness and safety data of NabGem versus MFOLFIRINOX in a single study represent an added value in patients with unresectable or metastatic locally advanced PC. Some limitations of our study are the retrospective design and the limited number of patients. In addition, some EAs may not be notified due to their low frequency. These limitations are similar to those found in the available bibliography[14]. However, our real-life comparison developed a rigorous methodology (multivariate analysis) to minimize bias.

Table 4: Adverse events in the study population.

	NabGem (n=46)	MFOLFIRINOX (n=18)		
	N (%)	N (%)	ARR (CI 95%)*	P
Any grade				
Alopecia	4 (8.7%)	0 (0%)	8.7% (CI95%: 0.6% to 16.8%)	P≤ 0.05
Anaemia	3 (6.5%)	0 (0%)	6.5% (CI95%: -0.6% to 13.6%)	NSS
Asthenia	31 (67.4%)	7 (38.9%)	28.5% (CI95%: 2.2% to 54.8%)	P≤ 0.05
Diarrhoea	11 (23.9%)	8 (44.4%)	-20.5% (CI95%: -46.6% to 5.6%)	NSS
Dysaesthesia	0 (0%)	1 (5.6%)	-5.6% (CI95%: -16.2% to 5.0%)	NSS
Edema	3 (6.5%)	0 (0%)	6.5% (CI95%: -0.6% to 13.6%)	NSS
Skin disorder	3 (6.5%)	0 (0%)	6.5% (CI95%: -0.6% to 13.6%)	NSS
Constipation	3 (6.5%)	0 (0%)	6.5% (CI95%: -0.6% to 13.6%)	NSS
Myalgia	1 (2.2%)	0 (0%)	2.2% (CI95%: -2.0% to 6.4%)	NSS
Mucositis	5 (10.9%)	2 (11.1%)	0.2% (CI95%: -17.3% to 16.9%)	NSS
Nausea and vomiting	13 (28.3%)	4 (22.2%)	6.1% (CI95%: -17.1% to 29.3%)	NSS
Neuropathy	14 (30.4%)	10 (55.6)	-25.2% (CI95%: -51.7% to 1.3%)	NSS
Neutropenia	6 (13.0%)	6 (33.3%)	-20.3% (CI95%: -44.1% to 3.5%)	NSS
Onychopathy	3 (6.5%)	0 (0%)	6.5% (CI95%: -0.6% to 13.6%)	NSS
Thrombocytopenia	3 (6.5%)	2 (11.1%)	-4.6% (CI95%: -20.8% to 11.6%)	NSS
Rash	1 (2.2%)	0 (0%)	2.2% (CI95%: -2.0% to 6.4%)	NSS
Grade ≥3				
Asthenia	2 (4.3%)	2 (11.1%)	-6.8% (CI95%: -22.5% to 8.9%)	NSS
Diarrhoea	1 (2.2%)	2 (11.1%)	-8.9% (CI95%: -24.0% to 6.2%)	NSS
Neuropathy	1 (2.2%)	0 (0%)	2.2% (CI95%: -2.0% to 6.4%)	NSS
Neutropenia	0 (0%)	1 (5.6%)	-5.6% (CI95%: -16.2% to 5.0%)	NSS

*ARR: absolute risk reduction calculated over a confidence interval at 95%. CI: confidence interval. NSS: no statistical significance.

Our study found an improvement in OS associated with MFOLFIRINOX over NabGem in locally advanced and metastatic PC. Dose reductions and delays in cycle administrations were more frequent in the MFOLFIRINOX scheme. Nevertheless, definitive treatment discontinuations were similar in both regimens. These results should be interpreted with caution, in the absence of RCTs comparing both treatments.

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