

FOLFIRINOX or Gemcitabine Plus Nab-paclitaxel as First Line Treatment in Pancreatic Cancer: A Real-World Comparison

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Abstract. *Background/Aim:* Advanced pancreatic cancer has a poor prognosis and a 5-year survival rate <5%; thus, treatment of patients with advanced unresectable or metastatic disease is challenging. Current guidelines recommend either gemcitabine plus nab-paclitaxel (GnP) or FOLFIRINOX (FOL) as first-line treatment. Data on both efficacy and toxicity of FOL versus GnP in metastatic cancer are limited. This study aimed to compare the two chemotherapy regimens in terms of efficacy and toxicity in a real-world setting. *Patients and Methods:* This retrospective propensity score matching study reviewed the medical records of 123 consecutive patients with advanced or metastatic pancreatic cancer who received either GnP or FOL between March 2013 and January 2019 in Guglielmo da Saliceto Hospital, Piacenza. *Results:* Fifty patients (40.65%) received FOL, administered in an attenuated dose, and seventy-three patients (59.35%) received GnP. After a propensity matching score, 100 patients were retrospectively evaluated. In the final matched cohort, there was no difference in neoadjuvant therapy, radiotherapy, and surgery performed before the first-line therapy between the two groups. Progression-free survival and overall survival were comparable between the two groups and no difference was found in the percentage of toxicity. *Conclusion:* There was no difference in outcomes between patients who received FOL and those who received

GnP. Unexpectedly, no greater FOL-related toxicity was found, probably due to the dose reduction.

The incidence of pancreatic ductal adenocarcinoma (PDAC) is increasing; it is the fourth leading cause of cancer-related death across the world (1, 2). The majority of patients with PDAC are diagnosed with advanced or metastatic disease, and less than 20% of these patients are diagnosed with early stage and undergo surgical resection with curative intent; however, the relapse rate in resected patients remains high in the range of 50-70% (3).

Advanced-metastatic patients show a poor prognosis with a 5-year survival rate <5% (4). The treatment of patients with advanced disease is unfortunately unsatisfying, although there are some hopeful studies that are considering target therapies using nano delivery systems (5). In 1997, a randomized trial comparing gemcitabine (GEM) with bolus of 5-fluorouracil (5-FU) demonstrated an improvement in median overall survival (OS) with GEM treatment, which became the standard of care in first-line treatment of metastatic pancreatic cancer (6). However, the efficacy of single-agent GEM is marginal, with a median OS of 5.65 months and a 1-year OS rate of 18% (5). In 2011, the combination of 5-FU, leucovorin, irinotecan, and oxaliplatin, known as FOLFIRINOX (FOL), significantly improved the response rate (RR) and OS in comparison to GEM monotherapy as a first-line chemotherapy treatment in patients with metastatic pancreatic cancer (7). In 2013, a phase III trial showed a significant OS benefit with the combination of nano-particle albumin-bound (nab)-paclitaxel plus GEM (GnP) in comparison to GEM monotherapy with an overall toxicity lower than the toxicity showed in the FOL study (8). This regimen showed feasibility and safety also with the alternative biweekly regimen in routine clinical practice in retrospective studies and case series (9, 10) even for patients with recurrent PC after pancreatectomy (11).

Current guidelines recommend GnP or FOL as the choice for first-line treatment; however, no randomized trials have directly compared these two first-line regimens; furthermore, in the absence of a direct comparison in a head-to-head clinical trial

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of first-line therapy, the choice of first-line therapy is up to the treating physician. Data on the comparison of the efficacy and toxicity of FOL and GnP in metastatic cancer are predominantly based on retrospective data (12-21). The objective of our retrospective study was to compare the survival outcomes and toxicity of FOL and GnP, in a real-world setting, for the first-line treatment of advanced or metastatic PDAC. The study included 123 consecutive patients, 50 of them (40.65%) treated with FOL and 73 (59.35%) treated with GnP.

Patients and Methods

Study population and data collection. In this study, we retrospectively reviewed the medical records of 123 consecutive patients with a histologically confirmed diagnosis of PDAC who received either GnP or FOL as their first-line chemotherapy between March 2013 and January 2019 at the Oncology Unit, Piacenza General Hospital. Its objective was to evaluate the efficacy and safety of FOL in comparison to GnP in consecutive patients with PDAC in a general hospital. The study was approved by the Institutional Review Board of Piacenza Hospital (code 569/2020/OSS/AUSLPC) and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each patient. Patient characteristics, toxicities (all grades), RR, progression-free survival (PFS), and OS were evaluated.

Treatment. All patients were treated with either FOL or GnP. FOL consisted of 85 mg of oxaliplatin per square meter given as a 2-h intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, delivered as a 2-h intravenous infusion, with the addition, after 30 min, of irinotecan at a dose of 180 mg per square meter, given as a 90-min intravenous infusion. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter administered by intravenous bolus, followed by a continuous intravenous infusion of 2,400 mg per square meter over a 46-h period every 2 weeks. FOL was used with a dose reduction: bolus-fluorouracil was reduced by 20% and irinotecan was reduced by 25% (22, 23). GnP consisted of a 30-min intravenous infusion of nab-paclitaxel at a dose of 125 mg per square meter followed by gemcitabine at a dose of 1000 mg per square meter on days 1, 8, and 15, every 4 weeks (12).

Statistical analysis. Data were collected using Microsoft Excel (Microsoft Office version 2010). Information recorded included each patient's sex, age, Eastern Cooperative Oncology Group-performance status (ECOG PS), diagnosis date, stage, number of metastatic sites, presence of metastases in the liver, lung, or elsewhere, neoadjuvant therapy, surgery, radiation therapy, adjuvant therapy, first-line therapy, subsequent lines of therapy, tumor progression, and survival. Toxicities related to the first-line therapy were also documented. The statistical review of the study was performed by a biomedical Statistician. A propensity score matching (PSM) was used to reduce differences in baseline characteristics between the two study groups. To estimate the propensity score, we used logistic regression, including the following covariates: sex, age, diagnosis date, stage, number of metastatic sites, presence of metastases in the liver, lung, or elsewhere, neoadjuvant therapy, surgery, radiation therapy, adjuvant therapy, toxicity, first-line

therapy, and subsequent lines of therapy. A one-to-one nearest-neighbor matching protocol without replacement was used to match the two groups of patients (24).

Median and interquartile range (IQR) values were used to describe quantitative variables; qualitative variables were described with absolute and percentage frequencies. Normality was checked for all continuous variables. Comparisons of the covariates were conducted using Pearson's χ^2 test or Fisher's exact test for categorical variables and a *t*-test or Mann–Whitney *U*-test for continuous variables.

PFS was defined as the time from the first dose of chemotherapy until documentation of disease progression or death from any cause; OS as the time from the first dose of chemotherapy until death from any cause. PFS and OS were estimated by the Kaplan–Meier method and compared using the log-rank test. A *p*-value <0.05 for a two-sided test was considered statistically significant. Statistical analyses were performed with RStudio 3.6.0.

Results

Patient characteristics in the whole population and the matched population. We evaluated 123 consecutive patients with advanced or metastatic pancreatic cancer: 50 (40.65%) patients received first-line FOL therapy and 73 (59.35%) received first-line GnP therapy. The baseline characteristics of the patients are presented in Table I. There were more male patients in the GnP group than the FOL group ($p=0.04$). The final matched cohort consisted of 50 patients in the FOL group and 50 patients in the GnP group. After PSM, there were no significant differences in the baseline characteristics between the two groups (Table I). The percentage of female patients was higher in the group treated with FOL than the group treated with GnP (62% vs. 56%). Fewer patients in the GnP group had stage III disease (40% vs. 42%), and fewer patients in the GnP group had more than two sites for metastases (20% vs. 26%). While more patients in the GnP group had liver metastases (48% vs. 48%), fewer experienced any grade of toxicity (40% vs. 46%). In particular, in the FOL arm, four patients discontinued treatment for G4 toxicity, whereas in the GnP group, one patient discontinued therapy permanently for G4 toxicity. However, none of the differences between the two groups were statistically significant.

Survival analysis. The Kaplan–Meier curves revealed that there were no significant differences in the OS and PFS rates between the patients treated with GnP and those treated with FOL (Figure 1, all log-rank tests $p>0.05$) in the one-year follow-up. The Kaplan–Meier curves of the other covariates on OS and PFS demonstrated that patients with stage IV pancreatic cancer had a significantly worse OS and PFS relative to those with stage III pancreatic cancer (log-rank tests $p<0.01$), male patients have a worse PFS than female patients (log-rank tests $p<0.05$), patients with liver metastases had a significantly worse OS and PFS relative to those without liver metastases (log-rank tests $p<0.001$), OS and PFS significantly worsen with increasing ECOG (log-rank

Table I. Characteristics of the study population before and after propensity score matching.

	Whole study population			Matched population		
	FOL (n=50)	GnP (n=73)	<i>p</i> -Value	FOL (n=50)	GnP (n=50)	<i>p</i> -Value
Sex, n (%)						
M	19 (38)	43 (58.9)	0.04	19 (38)	22 (44)	0.68
F	31 (62)	30 (41.1)		31 (62)	28 (56)	
Median age [IQR], (years)	69.5 [62.25-75]	69 [62-73]	0.38	69.5 [62.25-75]	70 [63-73]	0.71
Stage, n (%)						
III	21 (42)	29 (39.7)	0.95	21 (42)	20 (40)	1
IV	29 (58)	44 (60.3)		29 (58)	30 (60)	
Metastatic site, n (%)						
<2	37 (74)	61 (83.6)	0.29	37 (74)	40 (80)	0.64
≥2	13 (26)	12 (16.4)		13 (26)	10 (20)	
Liver metastases, n (%)						
No	28 (56)	40 (54.8)	1	28 (56)	26 (52)	0.84
Yes	22 (44)	33 (45.2)		22 (44)	24 (48)	
Lung metastases, n (%)						
No	45 (90)	68 (93.2)	0.77	45 (90)	46 (92)	1
Yes	5 (10)	5 (6.8)		5 (10)	4 (8)	
Other metastases, n (%)						
No	37 (74)	58 (79.5)	0.63	37 (74)	40 (80)	0.64
Yes	13 (26)	15 (20.5)		13 (26)	10 (20)	
Neoadjuvant, n (%)						
Yes	49 (98)	70 (95.9)	0.90	49 (98)	49 (98)	1
No	1 (2)	3 (4.1)		1 (2)	1 (2)	
Adjuvant, n (%)						
No	44 (88)	64 (87.7)	1	44 (88)	44 (88)	1
Yes	6 (12)	9 (12.3)		6 (12)	6 (12)	
Surgery, n (%)						
No	44 (88)	63 (86.3)	1	44 (88)	44 (88)	1
Yes	6 (12)	10 (13.7)		6 (12)	6 (12)	
Toxicity, n (%)						
No	27 (54)	43 (58.9)	0.72	27 (54)	30 (60)	0.69
Yes	23 (46)	30 (41.1)		23 (46)	20 (40)	
Radiation therapy, n (%)						
No	39 (78)	65 (89)	0.16	39 (78)	42 (81)	0.61
Yes	11 (22)	8 (11)		11 (22)	8 (16)	
ECOG, n (%)						
0	27 (54)	40 (54.8)	0.79	27 (54)	27 (54)	1
1	22 (44)	30 (41.1)		22 (44)	22 (44)	
2	1 (2)	3 (4.1)		1 (2)	1 (2)	
Subsequent lines, n (%)						
No	20 (40)	35 (47.9)	0.49	20 (40)	19 (38)	1
Yes	30 (60)	38 (52.1)		30 (60)	31 (62)	

ECOG: Eastern Cooperative Oncology Group-performance status; GnP: gemcitabine plus nab-paclitaxel; IQR: interquartile range; FOL: FOLFIRINOX.

tests $p < 0.05$), and patients with first-line toxicity (all grades) had worse OS than those without severe toxicities (log-rank tests $p < 0.01$). A total of 61 (61%) patients underwent second-line therapy within one year after beginning first-line therapy; no difference was found between the GnP and FOL groups. Table II reports the second-line therapy based on the patient's first-line therapy (GnP or FOL). Only 14 (14%) patients underwent third-line therapy; of those, 22.95% had undergone second-line chemotherapy due to progression of the disease

after undergoing first-line therapy (Table III); eight (57.14%) of those patients were in the GnP group and six (42.86%) were in the FOL group.

Discussion

PDAC has a 5-year survival rate $< 5\%$ with few options available for chemotherapy regimens. GEM monotherapy has been the best option of first-line treatment for more than 15

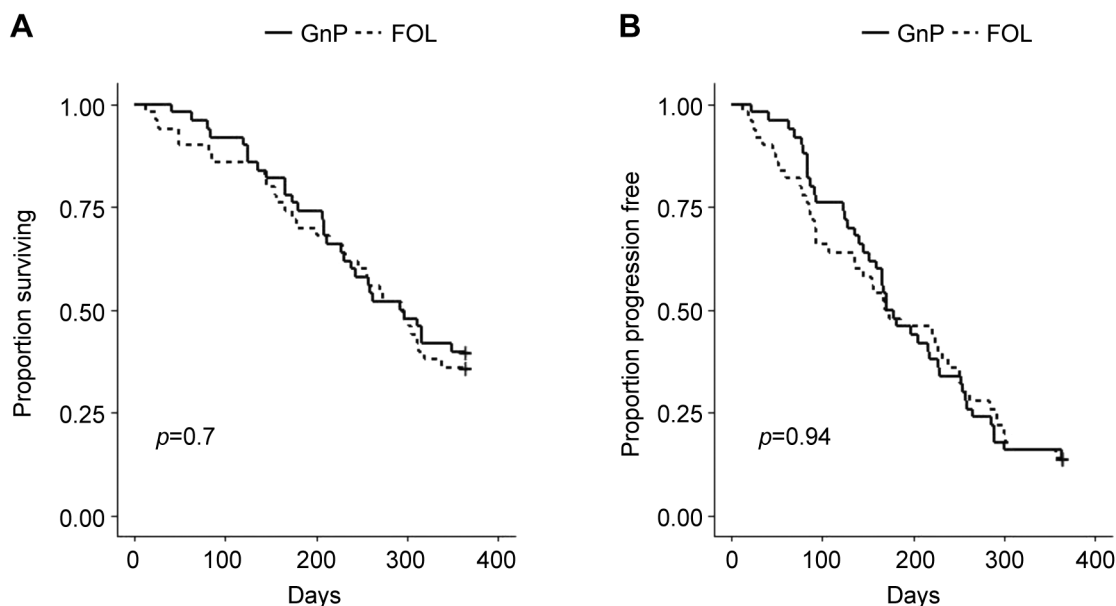


Figure 1. Kaplan–Meier curves for patients treated with gemcitabine plus nab-paclitaxel (GnP) or FOLFIRINOX (FOL). (A) Overall survival after one year; (B) Progression-free survival after one year. *p*-Value was evaluated with a log-rank test.

years; the new first-line formulation GnP showed a greater PFS (5.5 months vs. 3.7 months) with an OS of 8.5 months vs. 6.7 months (25). The most relevant study (PRODIGE 4/ACCORD 11) of FOL first-line therapy suggests that this treatment option has a significant impact on OS (11.1 months vs. 6.8 months with the GEM regimen) with the limitation of the adverse events in the experimental arm compared to the control arm (neutropenia, febrile neutropenia, and diarrhea grades 3-4) (7). Only observational study data are available directly comparing these two first-line regimens. Thus, the choice of regimen is up to the treating physician (12, 13). According to guidelines, monotherapy is recommended in patients with limited performance status (ECOG PS 2-3) (6). In that study, treatment selection was mainly driven by clinician preference, PS, and availability.

This study presents a statistical propensity score matching analysis that allowed us to better balance the populations, as one of the major biases of retrospective observational studies is the comparison between two nonrandomized cohorts.

Our data indicate no difference in 1-year PFS and 1-year OS in a retrospective cohort of 100 patients, in a variety of clinical settings. FOL and GnP exhibited comparable efficacy as first-line therapies, with no difference in survival outcomes (OS, PFS) (12, 21). Notably, the tumor burden was the same with no difference in outcome with either type of therapy relative to the number of metastases or the specific metastatic sites (lung vs. liver). There were no differences in terms of age or ECOG PS for the patients treated with FOL and the patients treated with GnP. Regarding covariates, the

statistically significant differences observed on OS and PFS are in line with literature data. Both regimens were well-tolerated; it must be emphasized that there was no statistically significant difference in toxicity between the two regimens. Toxicities were managed according to drug data sheet for both regimens. This is relevant if we consider that every grade of toxicity doubles the 1-year mortality risk and significantly reduces the 1-year PFS. It is important to acknowledge that our study is based on an observational real-world population characterized by a high median age (in the matched population 69.5 for the FOL arm and 70 for the GnP arm). Additionally, some patients in our cohort were pre-treated with neoadjuvant or adjuvant regimens.

The unexpected, relatively low toxicity rate for any grade in the first line treatment in the FOL arm (46%) is probably strictly associated with the dose reduction that we implemented, as we demonstrated in a previous study (26). These reductions do not have an effect on tumor progression and/or the patients' outcome.

The data suggest that the choice of first-line treatment did not significantly impact the decision to continue treatment, as evidenced by the comparable percentages of patients undergoing second-line therapy in both the GnP (62%) and FOL (60%) groups. Moreover, the second-line therapy varied widely, encompassing combinations and mono-chemotherapy with diverse protocols; 16 patients (53%) treated with first-line GnP were treated with second-line FOL and 11 patients (35.5%) who received first-line FOL were treated with second-line GnP, with no differences in outcomes between the two groups.

Table II. Second-line therapy based on the patients' first-line therapy.

Second-line therapy	GnP n=31	FOL n=30
GnP, n (%)	1 (3.23)	16 (53.33)
Capecitabine, n (%)	4 (12.90)	3 (10)
Carboplatinum-Etoposide, n (%)	1 (3.23)	0 (0)
Degramont, n (%)	1 (3.23)	0 (0)
FOLFIRI, n (%)	4 (12.90)	1 (3.33)
FOLFIRINOX, n (%)	11 (35.48)	1 (3.33)
FOLFOX, n (%)	5 (16.13)	0 (0)
Gemcitabine, n (%)	1 (3.23)	8 (26.67)
Gemcitabine-Capecitabine, n (%)	2 (6.45)	1 (3.33)
Irinotecan, n (%)	1 (3.23)	0 (0)

FOL: FOLFIRINOX; GnP: Gemcitabine plus nab-paclitaxel.

Table III. Third-line therapy based on the patients' first-line therapy.

Third-line therapy	GnP n=8	FOL n=6
GnP, n (%)	0 (0)	4 (66.7)
Degramont, n (%)	1 (12.5)	0 (0)
FOLFIRI, n (%)	1 (12.5)	0 (0)
FOLFIRINOX, n (%)	4 (50)	0 (0)
FOLFOX, n (%)	1 (12.5)	0 (0)
Gemcitabine, n (%)	0 (0)	2 (33.3)
Gemcitabine-Capecitabine, n (%)	1 (12.5)	0 (0)

FOL: FOLFIRINOX; GnP: Gemcitabine plus nab-paclitaxel.

Our study, in line with other retrospective data (14), demonstrated that second-line treatment FOL after GnP is feasible in a specific cohort of patients (in our study the percentage was 35.5%) with good PS and younger age. In fact, the median age was approximately 70. Unexpectedly, 13% of patients underwent third-line therapy and 6% underwent fourth-line therapy. Apparently, OS is high if we consider inoperable conditions; however, this is only the case for non-metastatic patients at the beginning of treatment.

The role of FOL as first-line treatment is now reconsidered according to a recent study on the use of the poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor Olaparib (27). This benefit was seen in a subset of germline BRCA1/2 mutated population, particularly as maintenance therapy in cases where the disease had not progressed during first-line platinum-based chemotherapy. This emphasizes the importance of selecting patients for platinum-based therapy in the first-line setting to ensure that individuals who could potentially benefit from PARP inhibitors, particularly with first-line GnP chemotherapy, are not inadvertently excluded.

NAPOLI-3 (28) is a randomized, open-label, phase 3 trial exploring the efficacy and safety of NALIRIFOX (liposomal

irinotecan + oxaliplatin + 5-fluorouracil + leucovorin) versus GnP treatment in a previously untreated PDAC metastatic setting. The results recently published showed a statistically significant median OS of 11.1 months in the NALIRIFOX arm compared with 9.2 months in the GnP arm ($p=0.036$); the median follow-up was 16.1 months. In both arms, about 50 percent of patients received a subsequent line of chemotherapy (51% of patients previously treated with NALIRIFOX and 54% of patients with GnP). High rate of grade 3/4 treatment-emergent adverse events occurred in patients receiving NALIRIFOX (322 of 370). The study highlights modest advantages in favor of the NALIRIFOX regimen; however, direct comparisons between NALIRIFOX and FOLFIRINOX are lacking. The PRODIGE 4 study had a different population based on enrollment criteria and the comparison arm (7). In addition, the median survival of patients receiving GnP in this study differs from that reported in the registrational study (12).

Conclusion

The literature suggests that the choice of first-line FOL therapy is mainly based on the patient's condition, because toxicity is worse for third-line FOL therapy in comparison to GnP therapy. Our study found no difference in survival outcomes between the two treatments. Moreover, no difference in toxicity was found between the two regimens. In fact, there was no greater FOL-related toxicity, probably also due to the use of a safe and effective FOL dose reduction (20% of bolus-fluorouracil and 25% on irinotecan) (22, 23).

While our study has some limitations due to the retrospective study design and the treatment selection that was based on the clinicians' choice and the patients' preference and characteristics, it included a large number of patients with characteristics more similar to real-world data. Furthermore, recent data on PARP inhibitors in subpopulations responding to first-line platinum-based chemotherapy suggest that FOL can be used as a first-line chemotherapy for advanced metastatic pancreatic cancer. This complexity in first-line treatment choices underscores the importance of developing a treatment strategy as the primary therapeutic goal in advanced pancreatic cancer. The fixed-dose reduction in FOL, as reported in previous studies (22, 23) and seen in the patients presented in this study, could be an important option. Moreover, the study's findings in patients with poorer OS and older age are more representative of a real-world setting.

Conflicts of Interest

Luigi Cavanna: consulting or advisory role for AstraZeneca, Merck. Travel, accommodations, expenses: Celgene, Pfizer, Ipsen. The other Authors have no financial support or relationships that may pose a conflict of interest.

Authors' Contributions

Orlandi E was the guarantor and designed the study; Citterio C and Vecchia S participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Anselmi E and Cavanna L revised the article critically for important intellectual content.

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