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ORIGINAL ARTICLE

Three fluoropyrimidine-based regimens in routine clinical practice after nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: An AGEO multicenter study

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KEYWORDS
Metastatic pancreatic cancer;
Nab-paclitaxel plus gemcitabine;
Second-line chemotherapy;
FOLFIRINOX;
FOLFIRI;
FOLFOX

Summary
Background: A combination of nab-paclitaxel plus gemcitabine (N + G) has recently become a standard first-line treatment in patients with metastatic pancreatic adenocarcinoma (MPA), but there are currently no published data concerning second-line treatment after N + G. The aim of this study was to evaluate the survival outcomes and tolerability of three usual fluoropyrimidine-based regimens FOLFOX, FOLFIRI and FOLFIRINOX after N + G failure in MPA patients.
Methods: Patients receiving N + G as first-line regimen were prospectively identified in 11 French centers between January 2014 and January 2017. After disease progression or unacceptable toxicity, patients eligible for second-line therapy were enrolled in the study. The primary endpoint was overall survival following the second-line regimen. Secondary endpoints were objective response, progression-free survival and safety.
Results: Out of 137 patients treated with N + G as first-line regimen, 61 (44.5%) received second-line chemotherapy, including FOLFOX (39.4%), FOLFIRI (34.4%) or FOLFIRINOX (26.2%). Baseline characteristics were not different between the 3 groups. In particular, median age was 71.7 years, sex ratio was 1/1, and performance status (PS) was 0 in 11.5% of case. Main grade 3 toxicities were neutropenia (4.9%) and nausea (3.3%), without major differences between the groups. No toxic death was observed. Median second-line progression-free survival (PFS) and overall survival (OS) were 2.95 (95% CI: 2.3—5.4) and 5.97 months (95% CI: 4.0—8.0), respectively, with no difference between the 3 groups. Median OS from the start of first-line chemotherapy was 12.7 months (10.4—15.1) and was significantly better in patients receiving FOLFIRI after N + G failure, 18.4 months (95% CI: 11.7-24.1, $P < 0.05$), as compared with FOLFOX or FOLFIRINOX (10.4 and 12.3 months, respectively).
Conclusion: This study suggests that second-line fluoropyrimidine-based regimens after N + G failure are feasible, have a manageable toxicity profile in selected patients with MPA, and are associated with promising clinical outcomes, in particular when combined with irinotecan. Randomized phase 3 trials are needed to confirm this trend.

Background

Pancreatic adenocarcinoma is a frequent malignancy with a poor prognosis. The five-year overall survival (OS) rate is around 6% [1]. Its incidence has gradually increased over the past 10 years and there were an estimated 458 918 new cases worldwide in 2018 [2]. About 80% of patients have disease that is unresectable, because of metastases or locally advanced disease. Without chemotherapy the median OS of patients with metastatic pancreatic adenocarcinoma (MPA) is consistently less than 6 months [3].

The standard treatment for MPA since 2011 has been FOLFIRINOX, for which median OS is 11.1 months, compared to 6.8 months with gemcitabine [4]. A combination of nab-paclitaxel plus gemcitabine (N + G) also increased survival in a phase 3 trial, as compared with gemcitabine alone. Median OS was 8.5 months compared to 6.7 months with gemcitabine, and median progression-free survival (PFS) was 5.5 months versus 3.7 months with gemcitabine [5]. Given the availability of these two first-line standard treatments, questions arise about the choice of first-line treatment choice and treatment sequencing. Historically, few studies have assessed second-line chemotherapy in MPA. The increased survival offered by new first-line treatments has made second-line chemotherapy possible for more patients.

We therefore conducted a multicenter, prospective cohort study to assess the efficacy and tolerability of 5-FU-based second-line regimens, including FOLFIRINOX, after failure of first-line treatment with nab-paclitaxel plus gemcitabine in patients with MPA.

Patients and methods

Patients and baseline characteristics

Clinical data from each consecutive patient receiving first-line N + G for metastatic pancreatic adenocarcinoma, in 11 gastrointestinal oncology units, were prospectively reviewed. Patients had to be at least 18 years old, have an ECOG-PS (Eastern Cooperative Oncology Group performance status) score of 0, 1 or 2, and have histologically or cytologically proven PA. After disease progression or unacceptable toxicity, all patients receiving a fluoropyrimidine-based second-line chemotherapy were identified. Treatment regimens were FOLFOX, FOLFIRI 1 or 3 regimens (FOLFIRI 1/3), and FOLFIRINOX. FOLFIRI.3 is a regimen in which irinotecan is administered before and after a 46-h infusion of fluorouracil and leucovorin [6]. Patients not treated with a fluoropyrimidine-based second-line regimen, patients with a locally advanced cancer, or who underwent secondary resection or chemoradiotherapy (CRT), were excluded. The administration and choice of second-line chemotherapy were decided locally in each center at a multidisciplinary meeting.

The following tumor-related information was collected: date of diagnosis, location of the primary tumor (head, body or tail of the pancreas), number and location of metastatic sites. Initial evaluation included carbohydrate antigen 19-9 (CA 19-9) assay.

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Treatment and outcomes

The modalities of first-line N + G were collected: number of cycles, reasons for treatment discontinuation, and best response using RECIST version 1.1 criteria [7] (RECIST v1.1).

The second-line regimen was administered until disease progression, unacceptable toxicity or patient refusal. The date of the first infusion of second-line chemotherapy and the number of cycles administered were recorded. Tolerability was assessed by recording all chemotherapy-related adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V4. Serious adverse events, including treatment-related deaths, grade 3 or 4 toxicities, withdrawals for toxicity, and dose reductions for adverse events were recorded.

Treatment efficacy was assessed every 2 to 3 months by chest-abdomen-pelvis computed tomography (CT) scans using RECIST v1.1, and by CA 19—9 monitoring [8].

Statistical analysis

Quantitative data were expressed as medians (range), and qualitative data as percentages.

The objective response rate (OR) was calculated as the sum of complete and partial responses. The disease control rate (DCR) was defined as the sum of complete and partial responses and stable disease. First-line PFS (PFS1) was defined as the time from the start date of nab-paclitaxel plus gemcitabine to the date of first progression or death for any reason. Patients alive without progression in first-line therapy and who started a second line were censured at the end of first-line treatment. First-line OS (OS1) was defined as the time from the start date of nab-paclitaxel plus gemcitabine to the date of death for any reason; patients alive were censured at the last follow-up date. PFS2 was defined as the time from the start date of the second line to the date of first progression in second-line treatment or death for any reason; patients alive without progression in the second line and who started a third line were censured at the end of second-line treatment. OS2 was defined as the time from the start date of the second line to the date of death for any reason; patients alive were censured at the last follow-up date. Survival curves were generated with the Kaplan—Meier method. Median follow-up was calculated with the reverse Kaplan—Meier method. All analyses were performed with a two-sided type 1 error of 5%.

Results

Patient and tumor characteristics

Between January 2014 and January 2017, 137 patients from 11 French centers treated with N + G for unresectable pancreatic cancer were identified. Of these 137 patients, 75 (54.7%) received second-line therapy, which was fluoropyrimidine-based second-line therapy for metastatic disease in 61 (44.5%) patients (Fig. 1). Twenty-four patients received a FOLFOX regimen, 21 FOLFIRI, and 16 FOLFIRINOX.

Most patients had an ECOG-PS score of 0 or 1 (61%). Median age was 71.7 years [41—83.5]. Most tumors were located in the head of the pancreas (50.8%) and most patients had only one metastatic site (57%). The mean number of cycles of first-line chemotherapy received was 15 for gemcitabine and 12 for nab-paclitaxel (Table 1). Second-line therapy was almost always (95%) started because of disease progression.

Median L1 duration, number of metastatic sites, PS, CA 19-9, and neuropathy were statistically comparable between the 3 groups.

Tolerability

Grade 3 adverse events occurred in 6 patients (9.8%), mainly neutropenia (4.9%) and nausea (3.3%) (Table 2). No grade 4

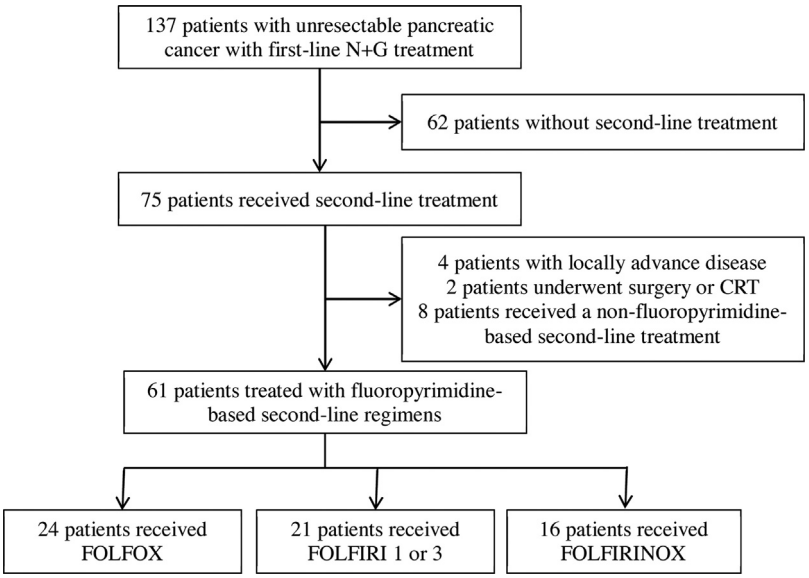

Figure 1 Flowchart.

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Table 1 Patient and tumor characteristics at second-line start.

n (%)	Overall population *n* = 61	FOLFOX *n* = 24	FOLFIRI 1/3 *n* = 21	FOLFIRINOX *n* = 16	*P*
Age	71.7	73.7	71.7	64.5	0.005
(years; median (range))	(41.2-83.5)	(42.8-83.5)	(41.2-81.4)	(41.4-77.7)	
ECOG - PS					0.24
0	7 (11.5)	2 (8.3)	4 (19.1)	1 (6.3)	
1	30 (49.2)	11 (45.8)	7 (33.3)	12 (75.0)	
2	22 (36.1)	10 (41.7)	9 (42.9)	3 (18.8)	
Metastatic sites					
Liver	46 (75.4)	20 (83.3)	13 (61.9)	13 (81.3)	0.20
Peritoneum	23 (37.7)	9 (37.5)	8 (38.1)	6 (37.5)	0.99
Lung	12 (19.7)	6 (25.0)	2 (9.5)	4 (25.0)	0.35
Other	13 (21.2)	5 (20.8)	5 (23.8)	3 (18.8)	0.79
Number of metastatic sites					0.55
1	35 (57.4)	13 (54.2)	15 (71.4)	7 (43.8)	
2	20 (32.8)	8 (33.3)	5 (23.8)	7 (43.8)	
>2	6 (9.8)	3 (12.5)	1 (4.8)	2 (12.4)	
CA 19.9 level	740	370	1150	370	0.88
(U/mL; median (range))	(0-45000)	(0-37700)	(3-21000)	(12-45000)	
First line duration	23.6	14.7	25.6	16.9	0.10
(weeks; median (range))	(1.7-69.7)	(1.7-38.7)	(5.4-69.7)	(4.0-42.9)	
Persistent neuropathy (grade 1, 2 or 3)					
No	43 (70)	18 (75)	16 (76)	9 (56)	0.48
Yes	15 (24.6)	5 (21)	5 (24)	5 (31)	
Third-line chemotherapy	21 (34.4)	7 (33.3)	8 (38.1)	6 (28.6)	

ECOG—PS: Eastern Cooperative Oncology Group performance status.

Table 2 Safety evaluated according to the NCI-CTCAE V4.

n (%)	Overall population *n* = 61	FOLFOX *n* = 24	FOLFIRI 1/3 *n* = 21	FOLFIRINOX *n* = 16	*P*
Neutropenia					0.54
Grade 2	4 (6.6)	0	1 (4.8)	3 (18.8)	
Grade 3	3 (4.9)	1 (4.2)	1 (4.8)	1 (6.3)	
Grade 4	0	0	0	0	
Anemia					0.47
Grade 2	2 (3.3)	2 (8.3)	0	0	
Grade 3	1 (1.6)	0	0	1 (6.3)	
Grade 4	0	0	0	0	
Thrombocytopenia					0.30
Grade 2	1 (1.6)	0	1 (4.8)	0	
Grade 3	1 (1.6)	0	0	1 (6.3)	
Grade 4	0	0	0	0	
Diarrhea					0.35
Grade 2	10 (29.5)	1 (4.2)	6 (28.6)	3 (18.8)	
Grade 3	0	0	0	0	
Grade 4	0	0	0	0	
Nausea					0.09
Grade 2	11 (18.0)	2 (8.3)	8 (38.1)	1 (6.3)	
Grade 3	2 (3.2)	0	1 (4.8)	1 (6.3)	
Grade 4	0	0	0	0	
Max toxicity					0.03
Grade 2	22 (36.1)	4 (16.7)	13 (61.9)	5 (31.3)	
Grade 3	6 (9.8)	1 (4.2)	2 (9.5)	3 (18.8)	
Grade 4	0	0	0	0	

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Table 3 Patient survival and tumor response rate.

	Overall population $n=61$	FOLFOX $n=24$	FOLFIRI 1/3 $n=21$	FOLFIRINOX $n=16$	P
Best Response (RECIST v1.1 criteria) (n, %)					
Complete response	0	0	0	0	0.17
Partial response	3 (4.9)	0	2 (9.5)	1 (6.3)	
Stable disease	25 (40.9)	7 (29.2)	11 (52.4)	7 (43.8)	
Progressive disease	30 (49.2)	16 (66.7)	8 (38.1)	6 (37.5)	
Not assessable	3 (4.9)	1 (4.2)	0	2 (12.5)	
Disease control rate	28 (45.9)	7 (29.2)	13 (61.9)	8 (50.0)	
Survival (median, 95% CI) (months)					
PFS 1	6.0 (4.1-6.8)	5.5 (2.8-6.6)	6.8 (6.0-9.0)	4.2 (2.9-8)	0.10
OS 1	12.7 (10.4-15.1)	10.4 (7.6-14.5)	18.4 (11.7-24.1)	12.3 (6.8-15.7)	0.02
PFS 2	2.95 (2.3-5.4)	2 (1.5-2.3)	6.6 (2.5-9.4)	3.4 (2-6.9)	0.08
OS 2	5.97 (4.0-8.0)	3.5 (2.3-6)	9.7 (4.5-11.2)	6.1 (2.8-8.8)	0.13

toxicity was observed and no toxic death occurred. Treatment was stopped in 56 patients (92%), mostly because of disease progression ($n=50$). No statistical difference was observed between the treatment regimens.

Forty-one patients (67.2%) had a transient or permanent dose reduction without significant differences between the 3 groups (FOLFOX 58%, FOLFIRI 1/3 67%, FOLFIRINOX 81%, $P>0.05$), because of asthenia (51.2%), peripheral neurotoxicity (17.1%), advanced age (12.2%) or hematological toxicity (7.3%). Prophylactic use of G-CSF was decided in 10 patients and of erythropoietin in 10 patients, with no difference between the three groups. Dose reductions for asthenia were more frequent in patients treated with FOLFIRINOX (76.9%, $P=0.04$) compared with FOLFOX (50.0%) and FOLFIRI 1/3 (28.6%). Dose reduction for neuropathy was more frequent with FOLFOX (28.6%) and FOLFIRINOX (23.1%) than with FOLFIRI (0%, $P=0.04$). Persistent neuropathy was observed in 24.6% of all patients after N + G.

Efficacy

The best response for the overall population was partial response (PR) in 4.9%, stable disease (SD) in 41% and progressive disease (PD) in 49.2% of patients, with no difference between the 3 groups (Table 3). DCR was respectively 29.2%, 61.9%, and 50.0% for the FOLFOX, FOLFIRI and FOLFIRINOX groups, with no significant difference ($P=0.17$).

Median OS1 was 12.7 months [95% CI: 10.4—15.1]. Median OS1 was significantly higher in the FOLFIRI group (18.4 months [95% CI: 11.7—24.1]) as compared with the FOLFOX (10.4 months [95% CI: 7.6—14.5]) and FOLFIRINOX groups (12.3 months [95%CI: 6.8—15.7]) ($P<0.05$). Median PFS1 was 6.0 months [4.1—6.8], with no difference between the 3 groups. Median OS2 was 5.97 months [95% CI: 4.0—8.0] and median PFS2 was 2.95 months [95% CI: 2.3—5.4], with no difference between the 3 groups.

The median duration of second-line treatment was significantly longer with FOLFIRI 1/3, with a median of 14.3 weeks (0—47.4) and, respectively, 6.0 weeks (0-58.1) and 12.5 weeks (0.3—56) in the FOLFOX and FOLFIRINOX groups ($P=0.04$). Response rates to the second-line regimen were not influenced by the prior response to N + G during first-line treatment. No difference in first-line duration between the 3 groups was observed ($P=0.10$).

A third-line regimen was possible in 34.4% (21 patients) of patients, without statistical significance between the 3 groups.

Discussion

Trials in metastatic pancreatic cancer over the past decade have mostly focused on first-line treatment [9], because of the aggressive characteristics of this cancer, the physical deterioration of patients, and the lack of effective treatment options. In fact, only 48%—61% of patients can receive second-line treatment [4,10,11]. FOLFIRINOX [4] and nab-paclitaxel plus gemcitabine [5] are currently the two standard regimens recommended in a first-line setting; the sequential FIRGEM schedule, which alternates gemcitabine and FOLFIRI.3 [12], is an option for unfit patients. However, the optimal second-line chemotherapy after progression during these two standard regimens is still not clearly defined [13]. Indeed, considering the two recent options for first-line chemotherapy, it seemed logical to test the second regimen after failure of the first one in patients able to receive second-line treatment.

For instance, in a prospective multicenter cohort Portal et al. [14] showed significant efficacy and good tolerability of N + G after FOLFIRINOX, with a median OS of 8.8 months. By contrast, there are few data concerning the reverse sequence, FOLFIRINOX after N + G. The use of aggressive triplet chemotherapy such as FOLFIRINOX after N + G is limited to patients with good PS, normal bilirubin level and good hematologic function, and is consequently more limited in a second-line setting. An Italian retrospective study [15] reported the outcome of 122 patients receiving N + G followed by: FOLFOX/XELOX (45%), FOLFIRI (22%), FOLFIRINOX (18%) and other single-agent therapies (15%), and observed a median OS of 13.5 months [12.7—14.3], with no significant difference between these groups, compared with 6.8 months for 99 patients receiving best supportive care alone [5.6—8.0].

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The exploratory analysis evaluating second-line therapy after N + G in the MPACT phase 3 trial [16] demonstrated that second-line treatment containing a fluoropyrimidine (77% of second-line regimens) was feasible, with an increases OS as compared with patients with no second-line treatment. The longest median OS was observed in patients receiving fluoropyrimidine-based combinations such as FOLFIRINOX ($n = 18$) and FOLFOX ($n = 36$), with a median OS of 15.7 months and 13.7 months, respectively. It is worth noting that only two patients received FOLFIRI in this study.

The efficacy of second-line oxaliplatin after gemcitabine failure was the subject of two contradictory randomized studies. Pelzer et al. [17] observed that the OFF regimen prolonged survival time compared to best supportive care alone, whereas the recently published PANCREOX trial [18] showed a detrimental effect of FOLFOX in terms of median OS compared to 5FU monotherapy (6.1 months vs. 9.9 months; $P = 0.02$). It is worth noting in these trials that patients had gemcitabine alone as first-line treatment and few data are available concerning second-line treatment after N + G.

Our study shows that 55% of patients treated with N + G are eligible for second-line treatment. FOLFOX, FOLFIRI 1/3 and FOLFIRINOX were the most used protocols after progression, and offered clinical benefit with an acceptable toxicity profile after N + G failure.

Median PFS1 was numerically better (but not statistically) for FOLFIRI 1/3 group (6.8 months) as compared to other regimens, which may have impacted OS1 that is also numerically better in this group and confirmed that this regimen should be at least equivalent to FOLFOX, as previously reported in a randomized phase 2 study after gemcitabine failure [19], with median OS of 16.6 and 14.9 weeks for modified FOLFIRI and modified FOLFOX, respectively. The recent phase 3 NAPOLI study [20] supports the efficacy of irinotecan in the second-line setting, showing increased OS of liposomal irinotecan (Nal-IRI) plus 5FU in a population of patients pretreated with gemcitabine, compared with 5FU monotherapy (median OS of 6.2 months vs. 4.2 months; $P = 0.012$). Once again, these results were recorded after gemcitabine alone and not after N + G.

In our study, no toxic deaths occurred and the safety profile of the three regimens appeared acceptable, especially in terms of neuropathy after Nab-paclitaxel use, which was comparable in the three groups. The different mechanisms involved in oxaliplatin and nab-paclitaxel neurotoxicity probably explain the absence of significant cumulative neuropathy with this therapeutic sequence [21].

One hypothesis to explain the better PFS2 in FOLFIRI 1/3 group (6.6 months) is that the persistent neuropathy could influence the dose intensity prescribed for the oxaliplatin-based second-line chemotherapy.

One of the limitations of our study is its non-randomized design, even though it corresponds to the data of a real-life study: the proportion of patients able to receive a second line is low, and corresponds to the data of previous studies. There is a potential selection bias in patients able to receive second-line treatment and the number of patients in each second-line therapy group is limited. Nevertheless, it is a prospective study with strict monitoring. Moreover, it is the first large study comparing three chemotherapy regimens after N + G failure. Another limitation is the lack of multivariate analysis because of limited number of patients included.

Although caution is required, our findings support the use of second-line therapy for patients with metastatic pancreatic cancer and show that a fluoropyrimidine-based combination after nab-paclitaxel plus gemcitabine has significant clinical effect and acceptable tolerability. Modified FOLFIRINOX remains an attractive option in selected patients. The encouraging results observed with FOLFIRI 1 or 3 now need to be confirmed in a comparative randomized trial. Whatever the regimen used in this study, the PFS remained low, around 3 months, and new drugs need to be tested in a second-line setting in metastatic pancreatic cancer.

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Disclosure of interest

The authors declare that they have no competing interest.

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