Use of gemcitabine as a second-line treatment following chemotherapy with folfirinox for metastatic pancreatic adenocarcinoma

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Abstract. There is a lack of prospective data about second-line treatments for metastatic pancreatic ductal adenocarcinoma patients. This is partially due to recent changes in first-line chemotherapy treatments. Despite this dearth of information, 50.0% of the patients who experience failure with first-line folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (folfirinox) treatment are eligible for additional chemotherapy. In this setting, gemcitabine is widely used without any standard recommendations available. The present study evaluated 42 patients who received gemcitabine subsequent to a first-line treatment of folfirinox between January 2008 and December 2012 at the Centre Léon Bérard (Lyon, France). Clinical data, biological data and tumor characteristics were retrospectively analyzed to identify prognostic factors for successful treatment with gemcitabine. In total, 11 patients (26.2%) experienced control of their cancer with gemcitabine treatment. However, there was no predictive marker for their response to the drug. The median overall survival was 3.6 months from gemcitabine initiation [95% confidence interval (CI), 2.1-5.1]. The median length of gemcitabine treatment was 1.5 months (95% CI, 0.3-13.3). Among the 11 patients who were successfully treated with gemcitabine, 6 were resistant to first-line folfirinox treatment. Patients who were non responsive to folfirinox had a higher probability of success with gemcitabine compared with patients that responded to folfirinox (54.5 vs. 21.4%, respectively; P=0.061). The present study did not identify any clinical or biological marker with a predictive value for successful gemcitabine treatment. Furthermore, successful gemcitabine treatment was not correlated with patients' response to first-line folfirinox treatment. This suggests an absence of cross-resistance in the chemotherapy protocols and provides evidence for effective cancer treatment with the second-line gemcitabine therapy.

Introduction

Pancreatic adenocarcinoma is the sixth cause of cancer-associated mortalities worldwide (1). The majority of patients with pancreatic adenocarcinoma present with an unresectable tumor or with metastatic disease, which lead to a 5-year survival rate of ~5%. Since the mortality rate remains close to the incidence rate, this is a particularly dreaded form of cancer (1). For years, gemcitabine was the front-line chemotherapy for the advanced disease due to its effects on quality of life and overall survival (OS) (2,3). In 2011, folinic acid, fluorouracil (5-FU), irinotecan and oxaliplatin (folfirinox) was observed to produce better outcomes compared with those of the standard gemcitabine chemotherapy (median OS, 11.1 vs. 6.8 months, respectively; P<0.001) (4). Henceforth, folfirinox became the first-line treatment for patients with advanced pancreatic adenocarcinoma who had a good Eastern Cooperative Oncology Group (ECOG) performance status (5). More recently, Von Hoff et al reported an improved outcome when nanoparticle albumin-bound (nab)-paclitaxel was combined with gemcitabine (GemBrax) compared with that of gemcitabine treatment alone (6).

When gemcitabine was the standard first-line treatment, an oxaliplatin-based chemotherapy was usually proposed as the second-line chemotherapy (7). Indeed, based on promising results from phase II studies (8-10), a randomized-phase III study demonstrated that the median survival time upon failure of first-line gemcitabine treatment increased to 21 weeks with oxaliplatin/folinic acid/5-fluorouracil treatment and best supportive care (BSC) compared with only 10 weeks in patients receiving BSC alone (7). Other studies have reported different experiences with second-line treatments subsequent to gemcitabine, with modest efficacy for patients who still have a good ECOG performance status (Table I).

In the phase III study by Conroy et al (4), 47% of patients who experienced treatment failure with folfirinox received a

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second-line therapy. In the phase III study by Von Hoff *et al* (6), 38% of the nab-paclitaxel and gemcitabine treatment group, and 42% of the gemcitabine alone group received second-line chemotherapy. Notably, 6% of the gemcitabine group received second-line treatments of nab-paclitaxel and gemcitabine, and these patients had a longer survival rate than the patients receiving gemcitabine treatment alone (median survival, 9.4 vs. 6.8 months, respectively; P<0.001).

Several scenarios could account for these data. First, patients usually experience a decline in their ECOG performance status, which may limit the therapeutic options for second-line treatment (11). Second, the survival benefit of second-line treatments is clinically questionable. Certain data are in favor of second-line therapy (12), whereas others do not encourage its use (13). Based on phase II data, a median survival of 4-6 months after the initiation of second-line treatment may be achieved with salvage chemotherapy in selected patients (14-16).

Folfirinox is currently the first-line treatment for metastatic pancreatic cancer in our center (Centre Léon Bérard, Lyon, France). For second-line therapy, patients are usually treated with gemcitabine alone when clinical trials are unavailable. The present study aimed to retrospectively analyze this treatment approach, which has not been validated in a phase III randomized study, in order to evaluate the clinical benefit of this strategy and to identify any clinical or biological characteristics that could predict the treatment outcome.

Patients and methods

Patients. The present study retrospectively reviewed 42 consecutive cases of advanced-stage pancreatic adenocarcinoma in patients who were treated with gemcitabine as the second-line chemotherapy (following initial treatment with folfirinox) between January 2008 and December 2012 at the Centre Léon Bérard (Lyon, France). Folfirinox was administered in accordance with the study regimen reported by Conroy *et al* (4): Treatment was provided for 6 months (12 cycles) or until disease progression or unmanageable toxicity occurred. When 6 months of folfirinox was achieved, discontinuation was proposed. At the point of disease progression, folfirinox reintroduction was considered for first-line continuation and this treatment was included in the total number of folfirinox cycles that were received. Clinical (age, sex, history of recent diabetes, thromboembolic events, and body mass index and its variation during chemotherapy) and biological [hemoglobin, total bilirubin, lymphocyte levels, carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels, and their variation during chemotherapy] data, as well as tumor characteristics [pancreas localization, Union for International Cancer Control staging (17) at diagnosis, number of metastatic sites, presence of skip metastasis and computed tomography (CT)-scan evaluation every 2 months] were collected prior to or during gemcitabine treatment to elucidate any parameter with a predictive value on survival. Patients who had previous surgery and adjuvant chemotherapy were excluded. All patients provided their informed consent for inclusion in the study and an external Ethics Committee (Comité de Protection des Personnes LYON SUD-EST IV) gave its approval for the project on 16th December 2015.

The side effects of gemcitabine were graded using the Common Toxicity Criteria defined (Common Terminology Criteria for Adverse Events scale developed by Eastern Cooperative Oncology Group and the National Cancer Institute with last version 4.03 released in 2010; http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Tumor objective response was monitored every 2 months with a CT-scan using the Response Evaluation Criteria in Solid Tumors (18), physical examination and assessment of blood tumor markers. Control of the disease was defined as achieving a complete response, partial response or disease stabilization while on chemotherapy. OS was measured from the initiation of treatment to the date of mortality for any reason or to the last follow-up assessment.

Statistical analysis. Descriptive statistics are presented as medians and ranges for the quantitative data, and as proportions for the qualitative data. Survival data are presented as Kaplan-Meier curves. OS was defined as the time from the initiation of gemcitabine chemotherapy to mortality (whatever the cause). Patients alive at the last date of follow-up were censored.

Patients were defined as 'responders' [responders group (RG)] to gemcitabine chemotherapy if the disease was under control (complete or partial response, or tumor stability) during the first evaluation of treatment efficacy (2 months after initiation). Patients were defined as 'non-responders' if disease progression or mortality was experienced prior to the first evaluation [non-responders group (NRG)]. The association between response (yes/no) and potential predictive factors was studied using the χ^2 or Fisher's exact tests for qualitative variables, and the nonparametric Wilcoxon test for quantitative variables. Due to the small sample size, a multivariate analysis was not performed. In all cases, P<0.05 was considered to indicate a statistically significant difference, and a P-value between 0.05 and 0.1 was considered to indicate a trend. All statistical analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA). The statistical methods used in the present study were reviewed by Miss Nadia Oussaid (a biomedical statistician at the Centre Léon Bérard).

Results

Patient characteristics. Among the 42 patients enrolled in the present study, 22 (52.4%) were males (Table II). The majority of patients (90.5%) had a good performance status (PS) (0 or 1) at diagnosis. In total, 50.0% of the tumors were localized in the pancreatic head, 26.2% in the body and the remaining tumors in the tail. In total, 5 patients (12.0%) had a recent diagnosis of diabetes (<2 years), while 8 patients (19.1%) had jaundice at their first consultation; the obstruction was relieved through an endoscopic retrograde cholangiopancreatography with stent insertion (14.3%) or biliodigestive surgical derivation (4.8%). At diagnosis, 95.2% of patients had metastatic cancer (stage 4): 28 patients (70.0%) had 1 metastatic site; 11 patients (27.5%) had 2 metastatic sites; and 1 patient had 3 metastatic sites. In addition, 5 patients (12.0%) had lung metastasis without any liver localization.

Treatments

First-line folfirinox treatment. On average, 9.4 cycles of folfirinox were administered as the first-line treatment

Table I. Studies available about second-line therapies after a first-line treatment of gemcitabine for pancreatic cancer.

Author, year	Trial	First-line chemotherapy	Second-line chemotherapy	Patients, n	Response rate, %	Median PFS, months (range)	Median OS, months (range)	PFS at 6 months, %	OS at 6 months, %	OS at 1 year, %	Ref.
Pelzer et al, 2011	Phase III CONKO-003	GEM	OFF vs. FF	46			4.82 vs. 2.3		23 vs. 10	10 vs. 0	(7)
Tsavaris et al, 2005	Phase II	GEM	5-FU/AF/OX	30	23.3 (PR) 30 (SD)	5.3 (3-4.7)	5.8 (4.7-7.7)				(8)
Cantore et al, 2004	Phase II	GEM-containing treatment	IRI plus OX	30	10	4.1 (0.7-13.1)	5.9			23.3	(9)
Demols et al, 2006	Phase II	GEM	GEMOX	33	22.6 (PR)	4.2	6 (0.5-21)				(10)
Boeck et al, 2006	Phase II	GEM	Pemetrexed	52	3.8 19.2 (SD)	1.6 (0.25-14.5)	4.7 (0.25-19.6)				(14)
Kulke et al, 2007	Phase II	GEM	CAP plus erlotinib	30	10 (PR)	3.4	6.5			26	(15)
Xiong et al, 2008	Phase II	GEM	CAP plus OX	41	2.6 (PR) 26 (SD)	2.3	5.7		44	21	(37)
Reni et al, 2008	Retrospective study	GEM	PEFG	46	24 (PR)	5	8.3	34		26	(38)
Boeck et al, 2007	Phase II	GEM	CAP	39	0 (PR) 15 (SD)	2.3 (0.5-45.1)	7.6 (0.7-45.1)				(39)
Reni et al, 2006	Phase II	GEM	Raltitrexed plus OX	41	24 (PR) 11 (SD)	1.8	5.2	14.6		12	(40)
Burris et al, 2005	Phase II	Any prior treatment	Rubitecan	58	7		3		17	9	(41)
Jacobs et al, 2004	Phase III	Any prior treatment	Rubitecan	196	11 (PR) 38 (SD)	1.9	3.5				(42)
Ulrich-pur et al, 2003	Phase II	GEM	IRI plus raltitrexed vs. raltitrexed	38	16 vs. 0	4 vs. 2.5	6.5 vs. 4.3				(43)
Kozuch et al, 2001	Retrospective study	Any prior treatment	G-FLIP	34	24 (PR) 21 (SD)	3.9	10.3				(44)
Altwegg, 2012	Retrospective study	GEM	All second-line therapies	80	40 (PR+SD)	3.4	5.8			13.6	(45)
Wang-Gillam et al, 2016	Phase III NAPOLI-1	GEM-containing treatment	Nanoliposomal IRI plus FF vs. FF	417	16 (PR) v. 1 (PR)	3.1 vs. 1.5	6.1 vs. 4.2				(46)

OFF, oxaliplatin, 5-fluorouracil and folinic acid; 5-FU/FA or FF, 5-fluorouracil and folinic acid; CAP, capecitabine; OX, oxaliplatin; IRI, irinotecan; PEFG, cisplatin, epirubicin, gemcitabine and 5-fluorouracil; G-FLIP, gemcitabin, folinic acid, 5-flurorouracil and irinotecan; GEM, gemcitabin; GEMOX, gemcitabine and oxaliplatin; 5-FU, 5-fluorouracil; OS, overall survival; PR, partial response; SD, stable disease.

Table II. Clinical characteristics of patients with pancreatic adenocarcinoma (n=42).

Characteristic	Patients, n (%)
Median age (range), years	63.5 (47-76)
Sex ratio, male/female	22/20
TNM stage at diagnosis, n (%)	
4	40 (95.2)
3	0 (0.0)
2	2 (4.8)
Metastatic sites at diagnosis, n (%)	
0	2 (4.8)
1	28 (66.6)
2	11 (26.2)
3	1 (2.4)
TNM stage at the start of second-line gemcitabine, n (%)	
4	41 (97.6)
3	0 (0.0)
2	1 (2.4)

TNM, tumor-node-metastasis.

Table III. Treatment characteristics in pancreatic adeno-carcinoma patients (n=42).

Treatment	Patients, n (%)
Folfirinox followed by GEM, total number of chemotherapy regimens received	
2	42 (100.0)
3	17 (40.5)
4	3 (7.0)
Folfirinox response at 2 months	
Disease controlled (disease stabilization or partial response)	28 (66.6)
Disease progression	12 (28.6)
NA	2 (4.8)
Treatment interruption following first-line therapy	
Patients, n (%)	12 (28.6)
Time to second-line therapy, months	3.4
GEM response at 2 months	
Disease controlled (disease stabilization or partial response)	11 (26.0)
Disease progression	31 (74.0)
GEM toxicity, maximum grade observed	
1	5 (11.9)
2	6 (14.3)
3	6 (14.3)
Treatment interruption	1 (2.4)

GEM, gemcitabine; NA, not available.

(range, 2-36 cycles). A total of 21 patients received 6 months of folfirinox and discontinued chemotherapy for 3.2 months (range, 0-20 months) before disease progression occurred. Overall, folfirinox treatment induced disease stability or a partial response in 27 patients (69.2%). During the first-line treatment, 16 patients (38.1%) had progressed prior to receiving 6 months of folfirinox, and 7 patients (16.7%) had tumor progression at the 6-month evaluation. Second-line chemotherapy was introduced for patients whose disease had progressed (83.3%) or who experienced toxicity (14.3%); a single patient (2.4%) requested early treatment discontinuation following 8 cycles (without limiting toxicity and despite partial response). In total, 5 patients (12.5%) received >6 months of folfirinox: 2 did not have discontinuation and experienced progressive disease following 16 and 17 cycles of treatment, respectively (oxaliplatin was interrupted due to neurotoxicity following 14 cycles and 10 cycles, respectively), while 3 patients had a therapeutic interruptions. Of these 3 patients, 1 patient received folfirinox again following an interruption of 4 months, with long disease control; the other 2 patients had a 6-month and a 20-month interruption, respectively, prior to reintroduction of first-line chemotherapy with folfiri (folinic acid, 5-fluorouracil, irinotecan) only (due to residual neurotoxicity to oxaliplatin), resulting in no benefit on disease control. The disease control offered by folfirinox reintroduction led to another 4-month therapeutic interruption following 12 additional cycles. The disease was controlled again at the third time of folfirinox treatment, but progression occurred following 9 cycles.

Second-line gemcitabine treatment. Gemcitabine treatment was initiated with a median time of 1.75 months (range, 0-20 months) upon termination of folfirinox treatment. Overall, gemcitabine treatment was well tolerated (Table III). A single

grade 4 thrombocytopenia was recorded. In total, 6 patients experienced a maximum of grade 2 toxicity (4 had thrombo-cytopenia, 1 had arthromyalgia and 2 had anemia). In addition, 4 other patients had a maximum of grade 3 neutropenia, and 1 patient discontinued gemcitabine treatment due to asthenia.

The median follow-up for the second-line treatment was 5.8 months (range, 0.3-25.5 months). From the 42 patients, 39 (92.9%) succumbed at the cut-off analysis time. The median OS was 3.6 months [95% confidence interval (CI), 2.1-5.1] after starting the second-line chemotherapy (Fig. 1). The median OS from the diagnosis was 13.4 months (range, 3.3-30.7 months).

A median of 4.5 gemcitabine infusions were administered (range, 1-40 infusions); the median length of the treatment was 1.5 months (range, 0.3-13.3 months). After 2 months of gemcitabine chemotherapy, only 11 patients (26.2%) had the disease under control (mainly stable disease) and continued with treatment. Disease control at the first evaluation was the only identified significant prognostic factor for OS (P=0.0012) (Fig. 2). A total of 31 patients (74.0%) experienced disease progression at the first evaluation.

Clinical, biological and tumor data analyses. The present study attempted to identify predictive biological or clinical
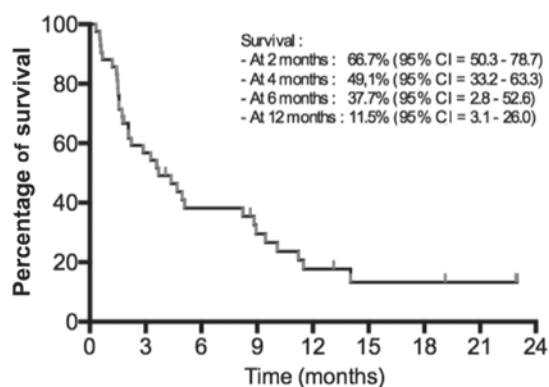
Figure 1. Overall survival following second-line chemotherapy initiation.
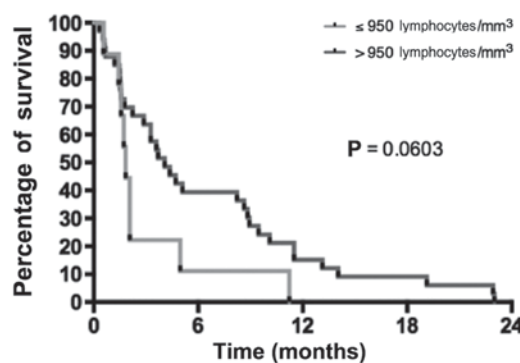

Figure 3. Survival as a function of the lymphocyte levels prior to second-line therapy.
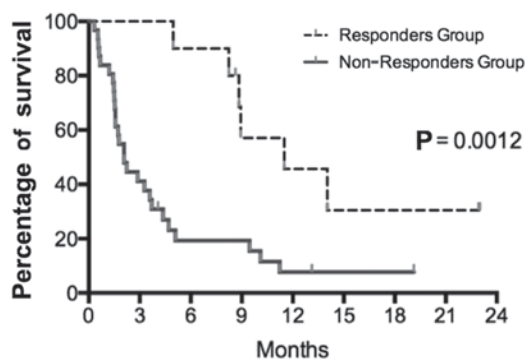

Figure 2. Survival following gemcitabine initiation in the responders and non-responders groups. Log-rank analyses identified the first evaluation as a surrogate marker for survival.
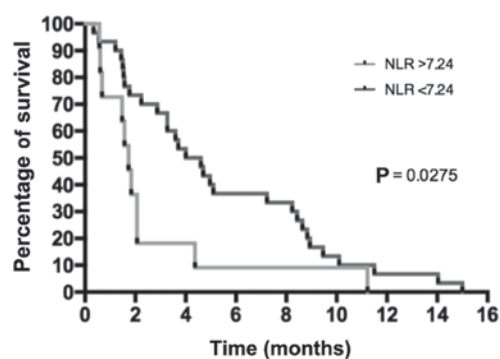

Figure 4. Survival as a function of NLR prior to second-line therapy. NLR, neutrophile/lymphocyte ratio.

characteristics explaining gemcitabine's efficacy. General characteristics such as PS were evaluated. This parameter was not different between the two groups; all the patients had a PS of 0-1 in the RG, and 27/31 patients (87.0%) had the same score in the NRG (P=0.350). The body mass index prior to the second-line treatment or its variation during therapy did not differ between the RG and NRG. The overall median body mass index preceding the second-line chemotherapy was 23.34 kg/m^2 (range, 17.20-36.20 kg/m^2). Similarly, the age at diagnosis and sex were not different between the two groups.

Various biological parameters were also compared between the two groups. The albumin level at diagnosis tended to be higher in the RG than in the NRG (median, 41 g/l in RG vs. 35 g/l in NRG; P=0.063). The lymphocyte levels prior to the second-line chemotherapy were not different between the NRG and RG (the mean lymphocyte levels were 1,349.5 and 1,593.8 lymphocytes/mm^3, respectively; P=0.640). A value of 950 lymphocytes/mm^3 was used as the cut-off to separate RG and NRG patients, and it was observed that patients with lymphocyte levels <950 lymphocytes/mm^3 had poorer survival than patients with lymphocyte levels above this cut-off (Fig. 3). The neutrophil/lymphocyte ratio (NLR) preceding the second-line chemotherapy was 7.24 and 3.56 in RG and NRG, respectively, suggesting a trend between lower NLR and RG (P=0.200), while a significant higher survival percentage was observed in patients with a NLR <7.24 (P=0.030) (Fig. 4). The tumor burden was also analyzed. The number of metastatic sites prior to initiating the second-line treatment tended to be

higher in the NRG than in the RG, although the difference was not significant (90.0% of RG patients had 1 metastatic site vs. 63.3% of patients in the NRG; P=0.420). There was also a trend for higher average CEA levels in the NRG than in the RG (156.3x10^{-6} vs. 44.3x10^{-6} g/l, respectively; P=0.330). The mean CA19-9 levels did not differ between the two groups (24,311.6 kU/l in the RG vs. 17,109 kU/l in the NRG; P=0.250).

Patients with primary resistance to folfirinox. Of the 11 patients in the RG, 6 exhibited primary resistance to folfirinox and had early disease progression. Patients whose disease progressed during folfirinox treatment had a higher probability of responding to gemcitabine (54.5 vs. 21.4%, respectively; P=0.061; Table IV). By contrast, only 3/15 patients whose disease was well controlled with folfirinox (20.0%) experienced any disease control with second-line gemcitabine treatment. In the RG, of the 6 patients who exhibited primary resistance to folfirinox, 2 received a prolonged benefit under gemcitabine treatment, and their cancer remained under control for 6 months.

Third-line treatments. Of the patients whose disease progressed while receiving gemcitabine, 19 patients (45.0%) were administered a third-line chemotherapy regimen and 3 patients received a fourth-line chemotherapy treatment (Table III). Among these patients, 15 received >1 cycle of therapy, while 8 patients received >3 cycles. During the third-line treatment, only 2 patients experienced prolonged disease control with

Table IV. Correlation between folfirinox and gemcitabine responses in pancreatic adenocarcinoma patients (n=42).

Folfirinox	Gemcitabine		Total, n (%)	Fisher's exact test
	Controlled disease, n (%)	Resistant disease, n (%)		
Controlled disease	5 (45.5)	22 (78.6)	27 (69.2)	P=0.061
Resistant disease	6 (54.5)	6 (21.4)	12 (30.8)	

gemcitabine-oxaliplatin (15 cycles prior to disease progression) and with folinic acid, 5-FU and oxaliplatin (14 cycles prior to discontinuation and surveillance). The latter patients experienced disease progression after 6 months of treatment, but were able to control the cancer with 5-FU and folinic acid combination prior to discontinuation and surveillance.

Discussion

There is a lack of prospective data about second-line treatments for metastatic pancreatic ductal adenocarcinoma (PDAC) patients. This is partially due to the recent changes in first-line chemotherapy treatments (4,19). Despite this dearth of information, a significant proportion of PDAC patients are eligible for second-line therapy. In the Action to Control Cardiovascular Risk in Diabetes 11 study, 47% of patients who received folfirinox were eligible for second-line chemotherapy, and the majority of them received gemcitabine (4). In the Metastatic Pancreatic Adenocarcinoma Clinical Trial, 38% of patients received second-line chemotherapy (19). The published data that suggest that second-line chemotherapy is beneficial are mainly derived from studies on gemcitabine-refractory patients (20,21).

When folfirinox treatment fails to improve a patient's cancer, gemcitabine monotherapy appears to be a convenient treatment option due to its safety profile (3); however, there are no prospective data available or studies planned to address its efficacy according to the website (https://clinicaltrials.gov/). The present study reports the findings on a single center cohort of patients who received second-line gemcitabine treatment for advanced-stage pancreatic adenocarcinoma. A survival of 3.6 months with second-line chemotherapy was observed, which is in agreement with previous published data (Table I) (7-10,14,15,22-31). Response to gemcitabine therapy at the first follow-up evaluation (at 2 months) impacted significantly the OS of the patients.

Notably, the present study demonstrated that gemcitabine was able to control cancer in patients who were resistant to folfirinox treatment, suggesting that there is no cross-resistance between folfirinox and gemcitabine regimens. Indeed, it was observed that patients who were resistant to first-line folfirinox treatment tended to respond well to gemcitabine treatment (54.5 vs. 21.4%, respectively). These data strengthen the argument for gemcitabine treatment, particularly if the patient displays primary resistance to folfirinox, and also support the requirement for more effective drug combinations.

Predictive factors of successful gemcitabine treatment were also analyzed; however, no predictive biological markers were identified, which may be due to the small cohort size. CA19-9 level did not display a predictive value

during second-line treatment, whereas it does have a predictive value for first-line treatment (11). Other biomarkers were not evaluated, including the Glasgow prognostic score or its modified version, which is an inflammation-based prognostic score using standard laboratory measurements of albumin and C-reactive protein (32,33). This score is able to identify systemic inflammatory responses responsible for poor survival due to tumor growth stimulation and catabolic effects on the host's metabolism at every stage of the disease for resectable, unresectable and metastatic pancreatic cancer (33-35). The measurement of pre-treatment plasma circulating DNA KRAS mutation load and CA19-9 level has also been recently shown to be a strong prognostic factor for PDAC patients who receive gemcitabine or folfirinox (36). It has also been suggested that human equilibrative nucleoside transporter 1 (hENT1) expression may select patients for gemcitabine treatment (37). However, there are issues regarding the evaluation of its expression by immunohistochemistry, since two different antibodies are usually employed: 10D7G2 monoclonal murine antibody (not commercialized) and SP120 rabbit monoclonal antibody (commercialized by Ventana Medical Systems, Inc., Tucson, AZ, USA). All studies using the above murine antibody demonstrated a significant predictive value in response to gemcitabine in an adjuvant setting only (38-40) whereas those using the aforementioned rabbit monoclonal antibody did not (41). Data on advanced pancreatic cancer are scarce, with only two studies published to date, both of which used the SP120 rabbit monoclonal antibody to measure hENT1 expression, and no evidence of predictive value was identified (42,43). Thus, the role of hENT1 as a predictive marker of gemcitabine efficacy remains unclear, particularly in a metastatic pancreatic cancer setting.

The main limitations of the present study are its retrospective design and the small sample size. Another limitation is the use of a monotherapy treatment. Various clinicians use a dual-therapy regimen such as gemcitabine and cisplatin or GemBrax subsequent to first-line folfirinox treatment, despite the lack of evidence regarding its efficacy from prospective studies (31-33). In France, reimbursement for nab-paclitaxel is not yet available, thus limiting its prescription. Bertocchi *et al* (44), Portal *et al* (45) and Palacio *et al* (46) recently reported the results of a GemBrax regimen for second-line therapy following a gemcitabine- or pyrimidine-based treatment (including folfirinox). However, definitive conclusions could not be drawn due to the retrospective design of the studies and the lack of a control arm. New drug combinations with gemcitabine are currently under study in phase II trials as mentioned in https://clinicaltrials.gov/, but the choice of the control arm in future phase III studies remains open. Furthermore, second-line chemotherapy may

have a significant effect on the OS results in phase III trials. Therefore, it appears to be essential to report these second-line treatments in phase III trials that evaluate first-line therapies in order to analyze any differences in the OS results.

In conclusion, the use of gemcitabine as a second-line treatment is well tolerated in PDAC patients, and may offer a small benefit to their OS (median, 3.6 months; 95% CI, 2.1-5.1), particularly in patients whose disease progressed during first-line folfirinox treatment. The management of metastatic PDAC patients has recently evolved, as the results of new chemotherapy regimens (folfirinox and GemBrax) have shown significant benefits over gemcitabine alone for first-line treatments (4,19). These therapeutic advances provide an opportunity for clinicians to explore new strategic approaches. Therefore, second-line treatments must be prospectively evaluated in order to draw formal conclusions about their efficacy.

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