ANTICANCER RESEARCH *40*: 4011-4015 (2020)
doi:10.21873/anticanres.14395

Safety and Efficacy of Gemcitabine, Docetaxel, Capecitabine, Cisplatin as Second-line Therapy for Advanced Pancreatic Cancer After FOLFIRINOX

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Abstract. *Background/Aim: The aim of this monocentric study was to evaluate the efficacy and tolerability of a polychemotherapy regimen based on gemcitabine, docetaxel, capecitabine, cisplatin (PDGX) as second-line for advanced pancreatic cancer after FOLFIRINOX. Patients and Methods: Patients received FOLFIRINOX as first-line regimen were retrospectively identified between January 2016 and January 2019. After disease progression or unacceptable toxicity, patients eligible for second-line therapy were treated in our center by PDGX. Results: During this period, 18 patients received PDGX regimen as second-line therapy. Main grade 3 toxicities were hematologic, which required dose adaptation in 14/18 patients. No toxic death was observed. Median second-line progression-free survival (PFS) and overall survival (OS) were 2,91 and 5,3 months, respectively. Total OS from the initiation of first-line was and 11,9 months. Conclusion: Second-line PDGX regimen after FOLFIRINOX failure is feasible, with notable toxicity profile and is associated with poor clinical outcomes.*

Pancreatic cancer is a frequent adenocarcinoma with poor prognosis and an increased incidence over the past ten years. It is the seventh leading cause of cancer-related death, with more than 330,000 deaths worldwide annually (1). The five-year overall survival (OS) rate is around 5% with. More than 75% of patients have unresectable locally advanced or metastatic disease. Therefore, the development of an effective and tolerable therapeutic strategy is crucial to improve the prognosis in this situation.

Since 2011, the first-line standard treatment for advanced pancreatic adenocarcinoma is FOLFIRINOX. In a French phase III trial, FOLFIRINOX have shown an improvement of median OS (11.1 months, compared to 6.8 months with gemcitabine) (2). More recently, a doublet regimen with nab-paclitaxel and gemcitabine also improved survival in a phase III trial compared to gemcitabine. 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 (3). In France, nab-paclitaxel is not financed by the health care authorities and most patients received FOLFIRINOX as a first-line therapy. Very few studies have assessed second-line chemotherapy after failure of FOLFIRINOX. In Italy, polychemotherapies are frequently tested in first-line for pancreatic cancer. PAXG regimen (4) (cisplatin, nab-paclitaxel, gemcitabine and capecitabine) was compared to biotherapy gemcitabine -nab-paclitaxel and gave an impressive response rate. Some alternative regimens like PEXG (5) (cisplatin, epirubicin, gemcitabine and capecitabine) or PDXG (cisplatin, docetaxel, gemcitabine and capecitabine) were also tested in first-line or second-line with similar efficacy profile.

These studies were the basis of our proposal of PDXG (cisplatin, docetaxel, capecitabin and gemcitabine) as second-line after failure of FOLFIRINOX. We report here the safety and the efficacy of such protocol used in our center.

Patients and Methods

Patients. Patients diagnosed with advanced pancreatic adenocarcinoma and treated with PDGX as second-line therapy after progression during first-line therapy with FOLFIRINOX at Georges Francois Leclerc center (Dijon, France) from January 2016 to

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Key Words: Pancreatic cancer, chemotherapy, cisplatin, capecitabine, gemcitabine, docetaxel.

January 2019 were eligible for analysis. Patients who received at least one cycle of PDXG were included. Medical records were retrospectively reviewed after approval by the hospital Ethics Committee.

Eligibility criteria for this retrospective review included histologic diagnosis of locally advanced or metastatic pancreatic adenocarcinoma, who experienced progression of disease after FOLFIRINOX as first-line therapy or intolerance to this regimen and used of at least once cycle of PDGX as second-line therapy. Data collection was concluded in September 2019. Toxicity of the regimen was graded retrospectively by 2 physicians. Imaging evaluation was performed with computed tomography (CT). CT scans were also reviewed by 2 physicians to improve diagnostic accuracy.

Treatment. Chemotherapy cycles were repeated every 28 days, until there was evidence of either unacceptable side effects or progression of disease (PD). Capecitabine was administered at 1,250 mg/m^2/day on days 1-28 continuously. Cisplatin was infused at 30 mg/m^2 and gemcitabine at 800 mg/m^2, docetaxel at 25 mg/m^2 on days 1 and 15. Dose reductions and treatment discontinuations were performed according to physician's decision, based on toxicity.

Safety. Toxicity was evaluated before each cycle according to the NCI-CTC-AE v5.

Statistical analysis. Demographic and clinical characteristics are summarized in Table I. The objective response rate (OR) was defined as complete and partial response. The disease control rate (DCR) was defined as objectives responses and stable disease. First-line PFS (PFS1) was defined as the time from the start date of FOLFIRINOX to the date of first progression or death for any reason. First-line OS (OS1) was defined as the time from the start date of FOLFIRINOX to the date of death for any reason; patients alive were censured at the last follow-up date. 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%. Statistical analysis was performed using Prism.

Results

Patient characteristics. Between January 2016 and January 2019, 89 patients received FOLFIRINOX as first-line regimen for advanced pancreatic cancer. Among 66 patients that received a second-line, 18 patients received at least one cycle of PDXG polychemotherapy regimen. These 18 patients were enrolled in this retrospective study. The median age was 68,2 years with an equal sex ratio. The majority of patients had a WHO performance status of 1. Patient characteristics at the initiation of PDXG are shown in Table I. The median number of FOLFIRINOX regimen per patient was 9 cycles (range=3-43 cycles). Partial response (PR) was observed in 3 patients (16.6%), stable disease (SD) in 10 patients (55.6%), and progressive disease (PD) in 5 patients (27.8%). Median PFS1 was 5.4 months.

There was no treatment-related death. Toxicities of PDXG regimen chemotherapy are described in Table II. Three (16.6%) patients developed grade 3-4 toxicities. The most common grade 3-4 toxicities were haematological toxicity and diarrhoea. Febrile neutropenia occurred in one patient (5%). Dose reduction occurred in 14 patients because of side effects with reduction of docetaxel dose in 5 patients and/or capecitabine in 9 patients. Discontinuation of therapy occurred in 11 patients due to significant side effects. Granulocyte colony-stimulating factors (G-CSF) were prophylactically given to all patients.

Efficacy outcomes. Median follow-up of surviving patients was 18 months. We observed that 3 patients had partial response and 4 patients stable disease at 2 months; ORR and DCR were 17% and 39%, respectively. We observed a decrease in CA.19.9 levels at 2 months in 11 patients. Median PFS was 2.91 months (Figure 1A). OS2 was 5.3 months (95%CI=0.52-36.9) (Figure 1B). OS1 was 11.9 months (95%CI=5.7-43) (Figure 1C). There was no influence of response to first-line FOLFIRINOX on PDXG response.

Discussion

In this single-center retrospective study, we show that PDXG as a second-line after FOLFIRINOX was effective. Our population corresponded to usual second-line patients with a median PFS under FOLFIRINOX as a first-line of 5.4 months. With PDXG regimen as a second-line, median PFS was 2.91 months, DCR was 39%, ORR was 17% and median OS was 5.3 months. Main toxicities were hematological.

Since the last decade, chemotherapeutic combinations like FOLFIRINOX and nab-paclitaxel plus gemcitabine have shown a survival benefit *versus* gemcitabine monotherapy. They are the most commonly used first-line therapies in patients with good performance status (6). Therefore, gemcitabine monotherapy is now more frequently administered in first-line as an option for "unfit" patients with advanced pancreatic cancer who have poor performance status. Quadritherapies have already been tested as first-line. In 2005, PEFG (cisplatin, epirubicin, 5-Fluorouracil, gemcitabine), based on four agents that were known to be active in pancreatic cancer, showed promising activity (7). The same team evaluated PDXG in 2012, changing epirubicin by docetaxel. They showed similar survival results but a better ORR with PDXG (60% vs. 37%) (5). More recently, in 2018, a phase II study tested PAXG as a first-line therapy. Median PFS was 8.3 months and OS was 14.4 months (4). In these studies, hematological toxicity was the main limiting dose factor. More recently, a combination of cisplatin, nab-paclitaxel and gemcitabine have shown substantial result in first-line with ORR of 71% (8).

After progression under first-line chemotherapy, approximately only about 50% of patients with advanced

Table I. *Clinical characteristics of patients*.

Characteristics	n=18	
	n	%
Age		
Median (range)	68.2 (51-79)	
Gender		
Male/Female	9/9	
ECOG-PS		
0	2	
1	10	
2	5	
3	1	
CA19-9		
Median (range)	2,628 (3.7-133,400)	
Disease extent		
Locally advanced	3	
Metastasis	15	
Site of primary tumor		
Head/Others	9/9	
Site of metastasis		
Liver/Lung/Others	13/3/5	72/17/28
PFS mFX		
Median	5.4 months	
Response of mFX		
CR	0	0
PR	3	16.6
SD	10	55.6
PD	5	27.8

Table II. *PDGX adverse events*.

Maximal toxicity	All	Grade 3/4
Neutropenia	5 (28%)	1 (5.5%)
Febrile neutropenia	1 (5.5%)	1 (5.5%)
Anaemia	15 (83%)	1 (5.5%)
Thrombocytopenia	11 (61%)	4 (22%)
Neurotoxicity	7 (39%)	1 (5.5%)
Nausea/vomiting	10 (55%)	0%
Asthenia	15 (83%)	0%
Kydney	1 (5.5%)	0%
Hand-foot syndrome	1 (5.5%)	0%
Diarrhoea	8 (44%)	1 (5.5%)

pancreatic cancer are still physically fit enough to receive second-line chemotherapy or subsequent lines (9). Historically, most of second-line therapies were evaluated after gemcitabine as a first-line. Following the results of the CONKO-003 study, FOLFOX (5-fluorouracil plus oxaliplatin) regimen is recommended by the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines as second-line therapy after previous treatment

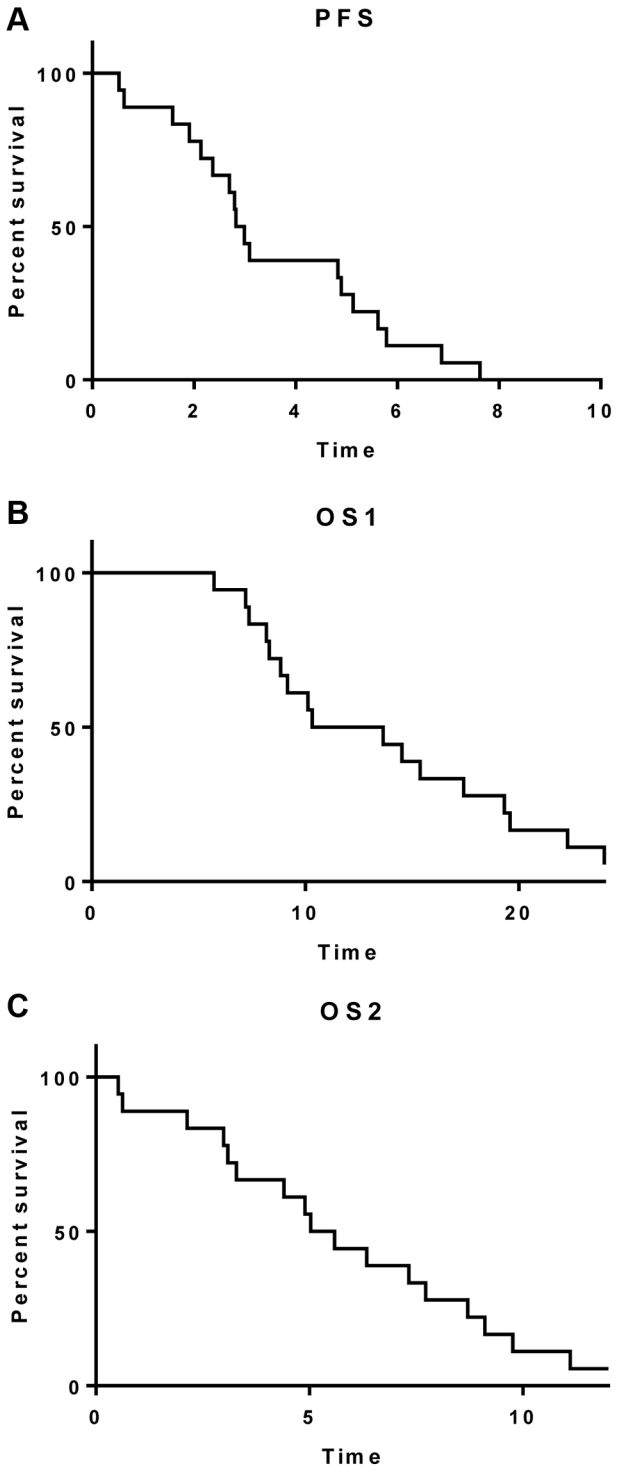

Figure 1. *Progression-free survival and overall-free survival. A: Kaplan–Meier estimates for progression-free survival. B: Kaplan–Meier estimates for overall survival 1 (OS1 was defined as the time from the start date of FOLFIRINOX to the date of death for any reason; patients alive were censured at the last follow-up date). C: Kaplan–Meier estimates for overall survival 2 (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).*

by gemcitabine (10, 11). Their results cannot be extrapolated to patients which are frequently treated with FOLFIRINOX or nab-paclitaxel–gemcitabine as first-line therapy. The benefit of gemcitabine second-line is weak with a DCR of only 26% and a mean OS of 3,6 months (12). Patient survival observed with combination therapies was higher than that of single agent therapies. In particular, the pooled response rate and OS of taxane-based combinations has been reported to be higher than that of other regimens at 48% and 5.4 months, respectively (13). Gemcitabine and nab-paclitaxel, after failure of FOLFIRINOX as first-line, have shown median PFS and OS of 3,8 months and 7,6 months, respectively, with no influence of response to first-line FOLFIRINOX on further response to nab-paclitaxel–gemcitabine (14). In the phase III MPACT trial (15), patients treated by FOLFIRINOX as second-line therapy after nab-paclitaxel–gemcitabine had a median overall survival of 15.7 months. The FOLFIRINOX followed by nab-paclitaxel and Gemcitabine or vice versa gave similar OS outcomes (16).

Quadritherapy (PEGF regimen), which showed impressive results as first-line therapy, was examined as second-line. After failure of gemcitabine, PEGF regimen showed some evidence of efficacy with an acceptable toxicity profile (17). Single agent as second-line chemotherapy is poorly effective. Doublet or quadritherapies have shown a promise of efficacy. Based on this observation we decided to administer PDXG regimen in patients after failure of FOLFIRINOX. However, in this study, efficacy did not differ from previous report of gemcitabine monotherapy as second-line. Toxicity and treatment discontinuation were a major difficulty in its management.

Our retrospective analysis has limitations in interpretation of survival because of small patient numbers in a single center. Our findings show that PDGX appears as a feasible regimen in second-line. However, this regimen did not bring more impressive results than the doublet therapy and had a major toxicity profile and should not be recommended.

Conflicts of Interest

Authors declare no conflicts of interest related to this study.

Authors' Contributions

JDF and FG designed the study. JV, LB, LG, RP and FG will include and follow patients. JDF performed statistical analyses and figures. FG supervised the study. JDF and FG wrote the manuscript. All co-Authors read and approved the final manuscript.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin *65*: 87-108, 2015. PMID: 25651787. DOI: 10.3322/caac.21262

2 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul J-L, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet J-B, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C and Ducreux M: FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. N Engl J Med *364(19)*: 1817-1825, 2011. PMID: 21561347. DOI: 10.1056/NEJMoa1011923

3 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J and Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med *369(18)*: 1691-1703, 2013. PMID: 24131140. DOI: 10.1056/NEJMoa1304369

4 Reni M, Zanon S, Balzano G, Passoni P, Pircher C, Chiaravalli M, Fugazza C, Ceraulo D, Nicoletti R, Arcidiacono PG, Macchini M, Peretti U, Castoldi R, Doglioni C, Falconi M, Partelli S and Gianni L: A randomised phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma. Eur J Cancer *102*: 95-102, 2018. DOI: 10.1016/j.ejca.2018.07.007

5 Reni M, Cereda S, Rognone A, Belli C, Ghidini M, Longoni S, Fugazza C, Rezzonico S, Passoni P, Slim N, Balzano G, Nicoletti R, Cappio S, Doglioni C and Villa E: A randomized phase II trial of two different 4-drug combinations in advanced pancreatic adenocarcinoma: cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel (PEXG or PDXG regimen). Cancer Chemother Pharmacol *69*: 115-123, 2012. PMID: 21626049. DOI: 10.1007/s00280-011-1680-2

6 Taieb J, Prager GW, Melisi D, Westphalen CB, D'Esquermes N, Ferreras A, Carrato A and Macarulla T: First-line and second-line treatment of patients with metastatic pancreatic adenocarcinoma in routine clinical practice across Europe: a retrospective, observational chart review study. ESMO Open *5*: e000587, 2020. PMID: 31958291. DOI: 10.1136/esmoopen-2019-000587

7 Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E and Carlo VD: Gemcitabine *versus* cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol *6*: 369-376, 2005. PMID: 15925814. DOI: 10.1016/S1470-2045(05)70175-3

8 Jameson GS, Borazanci E, Babiker HM, Poplin E, Niewiarowska AA, Gordon MS, Barrett MT, Rosenthal A, Stoll-D'Astice A, Crowley J, Shemanski L, Korn RL, Ansaldo K, Lebron L, Ramanathan RK and Hoff DDV: Response rate following albumin-bound Paclitaxel plus gemcitabine plus cisplatin treatment among patients with advanced pancreatic cancer: A Phase 1b/2 pilot clinical trial. JAMA Oncol *6*: 125-132, 2020. PMID: 31580386. DOI: 10.1001/jamaoncol.2019.3394

9 Hua J, Shi S, Liang D, Liang C, Meng Q, Zhang B, Ni Q, Xu J and Yu X: Current status and dilemma of second-line treatment in advanced pancreatic cancer: is there a silver lining? OncoTargets Ther *11*: 4591-4608, 2018. PMID: 30122951. DOI: 10.2147/OTT.S166405

10 Pelzer U, Kubica K, Stieler J, Schwaner I, Heil G, Görner M, Mölle M, Hilbig A, Dörken B, Riess H and Oettle H: A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol *26*: 4508-4508, 2008. DOI: 10.1200/jco.2008.26.15_suppl.4508

11 Ducreux M, Cuhna ASa, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T and Arnold D: Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol *26*: v56-v68, 2015. PMID: 26314780. DOI: 10.1093/annonc/mdv295

12 Sarabi M, Mais L, Oussaid N, Desseigne F, Guibert P and De La Fouchardiere C: Use of gemcitabine as a second-line treatment following chemotherapy with folfirinox for metastatic pancreatic adenocarcinoma. Oncol Lett *13*: 4917-4924, 2017. PMID: 28599496. DOI: 10.3892/ol.2017.6061

13 Nagrial AM, Chin VT, Sjoquist KM, Pajic M, Horvath LG, Biankin AV and Yip D: Second-line treatment in inoperable pancreatic adenocarcinoma: A systematic review and synthesis of all clinical trials. Crit Rev Oncol Hematol *96*: 483-497, 2015. DOI: 10.1016/j.critrevonc.2015.07.007

14 Mita N, Iwashita T, Uemura S, Yoshida K, Iwasa Y, Ando N, Iwata K, Okuno M, Mukai T and Shimizu M: Second-line gemcitabine plus nab-paclitaxel for patients with unresectable advanced pancreatic cancer after first-line FOLFIRINOX failure. J Clin Med *8*, 2019. PMID: 31146420. DOI: 10.3390/jcm8060761

15 Chiorean EG, Wan Y, Whiting S and Botteman M: 2346 Impact of nab-paclitaxel (nab-P) plus gemcitabine (G) *vs* gemcitabine alone on Karnofsky performance status (KPS) in metastatic pancreatic cancer patients with good or poor performance status at baseline: A post-hoc analysis of the MPACT trial. Eur J Cancer *51*: S450, 2015. DOI: 10.1016/S0959-8049(16)31262-X

16 Vogl UM, Andalibi H, Klaus A, Vormittag L, Schima W, Heinrich B, Kafka A, Winkler T and Öhler L: Nab-paclitaxel and gemcitabine or FOLFIRINOX as first-line treatment in patients with unresectable adenocarcinoma of the pancreas: does sequence matter? BMC Cancer *19*: 28, 2019. PMID: 30621630. DOI: 10.1186/s12885-018-5240-6

17 Reni M, Cereda S, Mazza E, Passoni P, Nicoletti R, Balzano G, Zerbi A, Arcidiacono PG, Staudacher C and Di Carlo V: PEFG (Cisplatin, Epirubicin, 5-Fluorouracil, Gemcitabine) regimen as second-line therapy in patients with progressive or recurrent pancreatic cancer after gemcitabine-containing chemotherapy. Am J Clin Oncol *31*: 145-150, 2008. PMID: 18391598. DOI: 10.1097/COC.0b013e31814688f7

Received May 25, 2020
Revised June 15, 2020
Accepted June 16, 2020