XELIRINOX Regimen a Triple Combination of XELoda, IRINotecan and OXaliplatin in First-line Treatment of Metastatic Pancreatic Adenocarcinoma

Haider Y. Shukur

Najaf Cancer Clinic (NCC), Department of Oncology, Jabir ibn Hayyan Medical University, Iraq

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Abstract FOLFIRINOX CT has shown notable responses in patients with metastatic PAC and has significantly improved prognosis. However, FOLFIRINOX is currently not frequently applied to all patients because of its high incidence of adverse events. Alternated XELIRINOX may be better for its acceptance in more patients' population. In this study, we evaluated the efficacy and safety of XELIRINOX in metastatic PAC. A total of 40 metastatic PAC patients were treated with XELIRINOX (Capecitabine substitute 5-FU, 75% Irinotecan dose and 100% Oxaliplatin dose) between January 2014 and January 2018 in our NCC. All 40 patients were evaluated with CR occur only in 2.5% (1/40) with an OAR of 35% (14/40). The frequent grade 3/4 adverse events are neutropenia (30%) and diarrhea (30%). No treatment-related death was observed. The median OS and median PFS is 10.5 months and 7.5 months, respectively. In conclusion, XELIRINOX had significantly improved tolerance with near similar efficacy to FOLFIRINOX. These findings may provide evidence for the use of XELIRINOX in more patient population with metastatic pancreatic adenocarcinoma.

Keywords XELIRINOX, CT, Pancreatic Cancer, Capecitabine, Irinotecan, Oxaliplatin, Triplet Regimen

1. Introduction

During the year 2018 in the United State, an estimated 55,440 people will be diagnosed with exocrine PC, where the majority of these tumors (85%) are adenocarcinomas arising from the ductal epithelium, and approximately 43,330 people will be dying of the disease as demonstrated by Islami et al.[1] Furthermore, the 5-year relative survival rate was only 8%, and that of the distant stage was only 3%

as stated by Siegel et al.[2]

Siegel et al., because of its aggressive character and the fact that most patients present with relatively advanced disease, most die from the disease, So it considers the fourth most common cause of cancer –related death among U.S. men (after lung, prostate & colorectal cancer) and women (after lung, breast & colorectal cancer).[1]

Simard et al. notice that, although incidence is roughly equal in both sexes, an African American has a higher incidence of pancreatic cancer than white Americans. [3]

Furthermore, the incidence of PC in the US increased from 1999 to 2008, possibly because of the increasing prevalence of obesity, an aging population & other unknown factors as notified by Ehemann et al. [4]. But Worni et al. saw mortality rates have remained largely unchanged. [5]

Fogel et al. stated that, the surgical resection offers the only chance of cure. However, only 15 to 20 % of patients have resectable disease at initial diagnosis; the majority has either locally advanced or metastatic cancer as mentioned by Warsame et al. [6, 7]

Other than surgical resection, systemic CT is the only major treatment that can improve survival in patients with locally advanced or metastatic PC. Twenty years ago, gemcitabine (GEM) replaced an IV bolus 5-fluorouracil (5-FU) as the main chemotherapeutic drug for treating advanced PC because a modest survival increase (5.65 versus 4.41 months) and more clinical benefits were found in a Phase III clinical trial as confirmed by Burris et al. [8]

Di Marco et al. said that, although the GEM monotherapy had been the gold standard for pancreatic cancer, but the response rate of GEM monotherapy remains low (approximately 10%), and an improved strategy is desperately needed [9].

Therefore, numerous clinical trials combined GEM with other anti-tumour agents to increase the anti-tumour effects, but most such studies were unable to demonstrate the

superiority of or a significant improvement in OS for GEM combination therapy; only GEM combined with capecitabine and erlotinib have shown promise as confirmed by Warsame et al. [7]

Recently, Conroy et al. in the PRODIGE 4/ACCORD 11 randomized trials, a four-drug regimen called FOLFIRINOX, consisting of folinic acid, 5-fluorouracil, irinotecan and oxaliplatin, was demonstrated to prolong OS compared to GEM monotherapy (11.1 months versus 6.8 months). These results suggested that this combined regimen should be used in clinical practice as a first-line option for advanced PC patients. [10]

Shortly thereafter, Von Hoff et al. explored that a regimen of GEM and albumin-bound paclitaxel was shown to have statistically significant survival benefits in OS and PFS, thus providing another choice for treating advanced PC. [11]

However, FOLFIRINOX appears to be more effective than GEM/NAB-P as documented by Chan et al. [12]

Although FOLFIRINOX is a first-line option for patients with metastatic PAC, there is a controversy about whether the survival benefits of the four-drug combination regimen outweigh the associated toxicities as stated by Gresham et al. [13]

However, the survival gain comes at a cost. Compared to GEM, FOLFIRINOX is reported with a higher rate of grade 3/4 adverse events, including neutropenia (45.7% versus 21%), fatigue (23.6% versus 17.8%), vomiting (14.5% versus 8.3%), diarrhea (12.7% versus 1.8%), and sensory neuropathy (9% versus 0%). For this reason, FOLFIRINOX was only used in patients ≤ 76 years old who have a good performance status (ECOG 0 or 1) at full dose, and the tolerability still remains a main concern as revealed by Conroy et al. [10,14].

As a result, an increasing number of studies have aimed to improve chemotherapeutic or targeted therapy regimens to reduce toxicity without compromising efficacy. Using dose attenuation, Mahaseth et al. reported a significantly reduced incidence of adverse events with a similar median OS (9.0 versus 11.1 months compared to full dose) [15]. Similarly, Stein et al. demonstrated that reduction of irinotecan and bolus 5-fluorouracil by 25% resulted in significantly decreased neutropenia, vomiting, and fatigue, with a relatively high response rate of 35.1% [16].

To decrease the side effects of FOLFIRINOX and increase its tolerability, we planned this study to assess the effectiveness and toxicities of this alternated XELIRINOX regimen in patients with metastatic PAC. We hope more patients can benefit from this alternated XELIRINOX regimen.

Capecitabine is an oral fluoropyrimidine carbamate prodrug designed to generate 5-FU preferentially in tumor cells due to the high concentration level of thymidine phosphorylase enzyme. This allows to mimic continuous 5-FU infusion at the tumor site and to reduce exposure of adjacent healthy tissues without causing discomfort and

complications related to IV administration. It has been widely used for the treatment of colorectal cancers and breast cancer as noticed by Mazard et al. [17]

Cassidy et al. there are different phase III trials have shown that capecitabine is at least as active and effective as 5-FU in the first-line treatment of mCRC, with a superior safety profile. [18]

Moreover, Machen et al. the use of capecitabine instead of 5-FU, either with irinotecan or oxaliplatin, confirmed the activity and efficacy of the drug. [19]

Mazard et al. there is a phase I trial showed promising results of the combination of capecitabine, oxaliplatin and irinotecan in mCRC subjects and suggested that this tri-therapy may provide valuable therapeutic alternative, especially in patients with GI cancer. [17]

Based on these results, the triple combination of capecitabine with oxaliplatin and irinotecan appears to be an interesting regimen. Therefore, it is of interest to explore the possibility to replace IV 5-FU and leucovorin in the FOLFIRINOX regimen with capecitabine and to assess the efficacy and tolerability of this modified regimen in the treatment of metastatic PAC, that could simplify the treatment delivery and reduce the complications related to the central venous catheter compared to infusional 5-FU, as used in the FOLFIRINOX regimen.

Machen et al. stated that there are different schedules of capecitabine emerged from phase I trials. [20] It is worth noting that mathematical methods applied to the definition of the ideal treatment schedule suggested that the optimal duration of treatment with capecitabine is 7 days and predicted that drug delivery beyond 7 days could contribute to toxicity, with diminishing anticancer benefit as noticed by Traina et al. [21]

Moreover, a randomised phase II trial conducted by Scheithauer et al. demonstrated that a dose intensified bimonthly combination of oxaliplatin plus capecitabine administered for 7 days followed by 7 days rest is as safe and feasible as the combination of oxaliplatin on day 1 with capecitabine administered from day 1 to day 14 every 3 weeks, with higher RR and PFS for the bimonthly regimen. [22]

2. Patients and Methods

2.1. Patient Eligibility

This was a prospective study involving metastatic PAC receiving XELIRINOX from January 2014 to January 2018 at the Najaf Cancer Clinic (NCC), Affiliated clinic, Jaber Ibn Hayyan Medical University. Patients, who were histologically diagnosed with metastatic PAC and were prescribed XELIRINOX as first line treatment, were eligible for inclusion. In all cases, metastatic PC was diagnosed by a multidisciplinary team, according to the National Comprehensive Cancer Network definitions.

2.2. Inclusion Criteria

- 1) WHO-PS of 0-2
- 2) Age 40 to 75 years
- 3) GFR ≥ 30 ml/min
- 4) Patient with solitary kidney was included
- 5) Written informed consent had to be given.

2.3. Exclusion Criteria

- 1) WHO-PS ≥ 3
- 2) Abnormal biochemistry (i.e., bilirubin 1.3-ULN, alkaline phosphatase 5-ULN, AST/ALT 5-ULN).
- 3) Inadequate bone marrow, liver or renal functions;
- 4) Double malignancies
- 5) Older than 75 years.

2.4. Pretreatment Evaluation Included

All patients were evaluated every four cycles of XELIRINOX (every two months) using high-resolution computed tomography (HRCT) scan chest- abdomen and enhanced MRI of the liver. The serum tumor markers CA19-9 & CEA levels were examined pretreatment as baseline and at each time of tumor response assessment.

Physical examination and laboratory tests (CBC, and chemistry) were performed every time before CT. Tumor response was categorized in CR, PR, SD, and PD according to the Response Evaluation Criteria in Solid Tumors (version 1.1) mentioned by Eisenhauer et al. [23]

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The OS was defined as the duration from the beginning of CT till the date of death of any cause. PFS was defined as the duration from the beginning of CT till the date of disease progression or death. Patients without event were censored at the last follow-up date (February 1st, 2018). For patients with XELIRINOX, information was collected at the moment of admission. While patients who had discharged were followed up every 3 months in a clinic by physical examination, laboratory tests, chest-abdomen HRCT, enhanced MRI of the liver & markers.

2.5. Treatment Schedule

The XELIRINOX regimen consisted of irinotecan 135 mg/m² i.v. in 250 ml of NaCl, 0.9% over 1 h, followed immediately by oxaliplatin 85 mg/m² i.v. in 250 ml dextrose 5% . Capecitabine was administered at the dose of 2000 mg/m² per day orally in two divided doses from day 1 to day 7. Treatment was repeated every 2 weeks and administered until evidence of disease progression, unacceptable toxicity, patient refusal or for a maximum of 12 cycles.

For all patients, this treatment was preceded by premedication as antiemetic (dexamethasone 16 mg and

5-HT₃ receptor antagonists 8 mg ondansetron), Ranitidine 150 mg and diphenhydramine maleate ampoule all are administered intravenously in 100 ccs normal saline solution over 15 min. just before chemotherapy , also vitamin B6 ampoule 50 mg/ml given to reduce neurotoxicity induced by oxaliplatin. Furthermore B6 tablets 50 mg BID & celecoxib 200 mg capsule once daily during capecitabine uses to reduce incidence of hand foot syndrome & peripheral neuropathy. Atropine 0.25 mg subcutaneously was given to treat the cholinergic syndrome, and repeated as prophylaxis of future events in the following cycles. All these premedication were used to enhance the tolerance against XELIRINOX-related adverse events. All patients in the cohort were offered alternated XELIRINOX (2-weekly schedule) and evaluated every 4 cycles.

CBS and other necessary blood tests were regularly performed every two weeks prior to each cycle. Biliary stenting and drainage procedures were performed in patients with jaundice and tapping ascitic fluid were performed if present prior to starting treatment.

Toxicities were graded according to the NCI CTC version 4.0. Treatment was delayed until recovery in case of neutrophils < 1.000 per mm³, platelets < 100.000 per mm³ or diarrhoea or stomatitis grade > 1 on the planned day of treatment. In the case of peripheral neurotoxicity grade > 2 , oxaliplatin was interrupted.

In the case of previous dose-limiting toxic effects, treatment delayed was permitted until recovery, then continued after resolution of the event with same doses of oxaliplatin, irinotecan and capecitabine dose reduced by 25%, except in the case of grade 3–4 diarrhoea, when only irinotecan and capecitabine doses were reduced by 25%. Loperamide 2 mg, orally every 2 h, and oral rehydration were prescribed in case of delayed diarrhoea. In the case of life-threatening toxic effects, treatment was definitively interrupted or continued at doses reduced by 50%. Prophylactic treatment with G-CSF for neutropenia was recommended.

Patients discontinued the study in the event of unacceptable toxic effects or evidence of progressive disease, or at their request. For those patients with CR, PR or SD, the duration of XELIRINOX will be as long as 12 cycles and then keep patient on close follow up. When disease, recurrent, XELIRINOX is still the first choice for patients with a good performance score.

2.6. Treatment Assessments

During treatment, the assessment, including toxicity and response evaluation:

At the end of fourth cycles, patients were assessed with physical examination, blood chemistry, blood count and creatinine were performed every 2 weeks. Evaluation of tumour response was performed with a CT scan of the chest-abdomen every 8 weeks according to the standard RECIST criteria .The best OAR for each patient was

reported as mentioned by Eisenhauer et al.[23]

Then, responding patients complete further four cycles then re-evaluate completely and planned to received last four cycles then re-evaluate completely and keep on follow up every 3 months. In other hand, patients with disease progression after fourth cycles shift to BSC.

3. Statistical Analysis

Data were analyzed using SPSS software (version 22). Numerical data were expressed as median and range as appropriate. Qualitative data were expressed as a percentage. The survival curves were estimated using the Kaplan–Meier technique.

4. Results

Table 1. Patient Clinicopathological Characteristics

Characteristic	No. of patients N=40
Age -Mean(Range)	61.3 (40-75)
Age > 65No. (%)	14 (35)
Sex No.(%)	
Female	12 (30)
Male	28 (70)
Smoke-No.(%)	
No	8 (20)
Yes	32 (80)
Alcohol-No.(%)	
No	36 (90)
Yes	4 (10)
WHO-Performance state- No.(%)	
0	18 (45)
1	12 (30)
2	10 (25)
Sites of metastasis- No.(%)	
Peritoneal with ascites	12 (30)
Liver	16 (40)
Lung	8 (20)
Bone	3 (7.5)
Distant LN (supraclavicular)	1 (2.5)
No. of metastatic sites- No.(%)	
Solitary	27 (67.5)
Multiple	13 (32.5)
Presenting symptoms-No.(%)	
Jaundice	5 (12.5)
Ascites	12 (30)
Pain	34 (85)
Weight loss	30 (75)
Intervention needed-No. (%)	
Biliary stent	5(12.5)
Tapping ascetic fluid	12 (30)

Between January 2014 and January 2018, 40 patients were enrolled in our clinic (NCC) and received the XELIRINOX treatment with the median follow-up was 15 months (range 2–48 months). The baseline characteristics are listed in Table 1. The range of age was 40-75, with a mean age of 61.3 years old .Twenty-six (65%) patients were 65 years old and below, but 14 (35 %) were 66 years age or older. Twelve (30%) patients were female, while 28

(70%) were male. Thirty two (80%) patients were smoky, while 8(20%) were nonsmoker. Thirty six (90%) patients were non-alcoholic, while only 4 (10%) were drink alcohol. The majority of the patients 18(45%) demonstrated a WHO-PS of 0 while 12 (30%) had WHO-PS of 1 and remaining 10(25%) had WHO-PS of 2. Two-third had a solitary metastatic site while remaining 13(32.5%) had multiple metastatic sites. The most common metastatic site was the liver, which diagnosed in 16(40%) patients while bone & distant LN found with lowest percentage 3(7.5%) & 1(2.5%) respectively, and 12(30%) had peritoneal metastasis with malignant ascites and remaining 8(20%) had lung metastasis. Twenty-eight (70%) patients presented with abdominal pain when diagnosed, and five patients (12.5%) placed biliary stent or catheter because of jaundice and 12 (30%) underwent tapping of ascetic fluid before chemotherapy start.

Baseline tumor marker results, including CA19-9, CEA, are also listed in Table 2. Thirty-six - patients (90%) were found with elevated CA19-9 levels prior to start CT, but only four patients (10%) had normal CA19-9. On the other hand, only eleven patients (27.5%) found with elevated CEA, but remaining twenty-nine patients (72.5%) had normal baseline CEA. The detailed patient characteristics are listed in Table 2.

Table 2. Objective Response rate, No. = 36

Response	No. of patients (%)
CR	1 (2.5%)
PR	13 (32.5%)
SD	12 (30%)
PD	14 (35%)
ORR	14 (35%)
CBR	26 (65%)
Median PFS in months (CI)	7.5(7.05-7.94)
Median OS in months(CI)	10.5(9.19-11.80)

4.1. Treatment Delivery

The median overall treatment period was 5.5 months and ranged from 1-6 months. The number of CT cycles ranged from 2-12 cycles with a median of 11 cycles. Treatment delay was present in 40 (100%) patients. The duration of treatment delay ranged from 1 to 10 weeks with a median of 5 weeks.

All 40(100%) patients needed hospitalization due to toxicity during the treatment course .The duration of hospitalization ranged from 3 to 14 days with a median of 9 days. It looks interesting that thirty-six (90 %) patients can tolerate and completed the full course of 12 cycles CT regimen ,but unfortunately four (10 %) of patients received only up to four cycles.

4.2. Efficacy

Four patients (10%) were dying in the early treatment

period within the first two months with four cycles chemotherapy and cannot restaged. Thirty-six patients (90%) were restaged after XELIRINOX treatment. The response of these patients was evaluated and is shown in Table 2. We found CR was observed, only in one patient out of 40 (2.5%) and 13(32.5%) patients achieved a PR. Twelve (30%) patients persisted stable disease. Unfortunately, 14 out of 40 (35%) had progressive disease.

Objective response rate (ORR) was (35%) and clinical benefit rate (CBR) was (65%). The response to therapy is summarized in Table 2. Ten patients had to be taken off treatment due to disease progression and best supportive care was administered to him, then later on died. Four (10%) patients were early dead, so the final total number of deaths were 14 (35%) patients.

4.3. Toxicity

In general, the incidence of adverse events was 100% (No.= 40). Regarding hematological toxicity, anemia was the most frequent one, with an incidence of 60%. Followed

by thrombocytopenia occur in 40 % of patients, but both of them of grade 1. For neutropenia, we observed 12 patients (30%) with grade 3/4 toxicities, but neutropenic fever occurs in only four (10%) patients. On the other hand, the most frequent non-hematological toxicity was nausea occurs in 26 patients (65%) with grade 1/2, also vomiting occurs in 18 patients (45%) with grade 1/2, with very low percentage of grade 3/4 nausea& vomiting occurs in two patients (5%) probably due to the combination therapy of ondansetron, dexamethasone during the CT and oral fluorouracil content in this regimen. Diarrhea occurs in 18 patients (65%) with grade 1/2 and occurs in 12 patients (30%) with grade 3/4. Other adverse events occur more frequently in most patients, but of grade 1/2 as, fatigue, anorexia, poor appetite & Stomatitis. The incidence of weight loss $\geq 5\%$ occur in half of our patients. The incidence of sensory neuropathy was high and occurs in 30 patients (75%) but of grade 1/2. Lastly hand and foot syndrome occurs in only 6 patients (15%) of grade 1/2 with no patients with grade 3/4. Totally, 12 patients (30%) received G-CSF treatment before or after chemotherapy.

Table 3. Adverse events during treatment, No. = 40

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicity No.-(%)				
Anemia	24(60%)	8(20%)	2(5%)	0
Neutropenia	4 (10%)	12(30%)	6(15%)	6(15%)
Thrombocytopenia	16(40%)	2(5%)	2(5%)	0
Neutropenic fever	4(10%)			
Non Hematological toxicity No.-(%)				
Nausea	20(50%)	6(15%)	2(5%)	0
Vomiting	12(30%)	6(15%)	2(5%)	0
Stomatitis	8(20%)	8(20%)	0	0
Diarrhea	14(35%)	12(30%)	8(20%)	4(10%)
Poor appetite	12(30%)	8(20%)	0	0
Anorexia	8(20%)	12(30%)	2(5%)	0
Weight loss $\geq 5\%$	20(50%)			
Sensory Neuropathy	20(50%)	10(25%)	2(5%)	0
Fatigue	8(20%)	14(35%)	2(5%)	0
Hand and Foot Syndrome	4(10%)	2(5%)	0	0

4.4. Survival

Median follow-up was 15 months (range 2–48). 4(10%) patients died in the early treatment period and completed up to four chemotherapy cycles and can't restage. Thirty six (90%) patients continue and completed all CT cycles. The median PFS was 7.5 months (95% CI: 7.059- 7.941), figure (1). Regarding OS, median OS was 10.5 months (95% CI: 9.193-11.807), figure (2)

Figure 1. Kaplan-Meier curve of Progression free survival

Figure 2. Kaplan-Meier curve of Overall survival.

4.5. Correlation

There is none significant correlation between PFS and age, ($r = 0.028$), and $P = 0.866$ as showing in the table (4). There is significant negative correlation between PFS and WHO-PS, ($r = -0.365$) and $P = 0.020$. There is significantly negative correlation between PFS and number of metastatic sites, ($r = -0.309$) and $P = 0.050$. There is highly significantly negative correlation between PFS and normal baseline tumor marker, ($r = -0.471$) and $P = 0.002$. Also there is highly significantly positive correlation between PFS and tumor marker reduction during treatment, ($r = 0.525$) and $P = 0.001$. There is none significant correlation between PFS and weight loss $\geq 5\%$ during treatment, ($r = 0.212$) and $P = 0.188$. Finally, there is highly significantly strong positive correlation between PFS and any treatment response ($r = 0.507$) and $P = 0.001$.

Table 4. Correlation of PFS and OS to patient's characteristics

Characteristic	PFS in months		OS in months	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age in years	0.028	0.866 NS	0.431	0.005 HS
WHO-Performance State	-0.365	0.020 S	-0.536	<0.001 HS
Number of metastatic sites	-0.309	0.050 S	-0.535	<0.001 HS
Normal baseline tumor Marker	-0.471	0.002 HS	0.261	0.103 NS
Decrease tumor marker	0.525	0.001 HS	0.724	<0.001 HS
Weight loss $> 5\%$ during treatment	0.212	0.188 NS	0.769	<0.001 HS
Clinical benefit rate	0.507	0.001 HS	0.796	<0.001 HS

r: Spearman correlation coefficient; NS: not significant at $P \leq 0.05$; S: significant at $P \leq 0.05$; HS: highly significant at $P \leq 0.01$

On the other hand, regarding OS correlation, there is strong positive correlation between OS and age, ($r = 0.431$), and $P = 0.005$ as showing in the Table 4. There is highly significant negative correlation between OS and WHO-PS, ($r = -0.536$) and $P = <0.001$. There is highly significantly negative correlation between OS and number of metastatic sites, ($r = -0.535$) and $P = <0.001$. There is none significantly correlation between OS and normal baseline tumor marker, ($r = 0.261$) and $P = 0.103$. Also there is highly significantly positive correlation between OS and tumor marker reduction during treatment, ($r = 0.724$) and $P = <0.001$. There is highly significant positive correlation between OS and weight loss $\geq 5\%$ during treatment, ($r = 0.769$) and $P = <0.001$. Finally, there is highly significantly strong negative correlation between OS and any treatment response ($r = 0.796$) and $P = <0.001$.

5. Discussion

Metastatic PAC patients have extremely short survival, and few treatment modalities have been established in such clinical scenario. FOLFIRINOX chemotherapy can

produce remarkable efficacy in metastatic PAC patients with significantly increased survival, compared to gemcitabine monotherapy and is a promising strategy for these unfortunates. However, the application of FOLFIRINOX is largely limited by its considerable toxicity, as well as 5-FU had to be administered as a 48-h continuous infusion by a central venous catheter to make the combination feasible as noticed by Conroy et al. [10]

As a consequent, many oncologists are hesitating to prescribe FOLFIRINOX for metastatic PAC patients, although it may have better efficacy to combat tumor therefore very limited metastatic PAC patients have tried the FOLFIRINOX regimen in some institutions.

To make FOLFIRINOX more practicable, many investigators have made their efforts to enhance patients' tolerance to this CT through various ways as stated by Guntur et al. [24]. Mahaseth et al. significantly reduced the incidence of grade 3/4 neutropenia and diarrhea without compromising the efficiency of FOLFIRINOX simply by removing fluorouracil bolus and using G-CSF at the same time [15]. Stein et al. reduced the doses of both irinotecan and 5-FU bolus by 25%, and found that the incidences of neutropenia, vomiting and fatigue were significantly decreased [25]. Other modification strategy for advanced PC includes avoiding the use of irinotecan and it may be referenced in metastatic PAC patients as mentioned by El-Hadaad et al. [26]

Our study is the first trial to evaluating the activity of a first-line triplet combination of alternated XELIRINOX by giving same the oxaliplatin dose, but reducing irinotecan to 75 % of the full dose and substituted capecitabine instead of 5-FU (that used in FOLFIRINOX) for the purpose of improving tolerability.

Meanwhile, our modification maintained considerable efficacy of XELIRINOX, with an ORR of 35% and CBR of 65% & prolonged survival with acceptable toxicity.

In the current study, we enrolled 40 metastatic PAC patients and provided a novel alternative strategy for FOLFIRINOX according to our experience. In our cohort, the median OS and PFS were 10.5 and 7.5 months, respectively, comparable to the previous studies.

Alternated XELIRINOX is also supposed to reduce adverse events. Conroy et al. reported that grade 3/4 adverse events with FOLFIRINOX treatment are neutropenia (45.7%), fatigue (17.8%), vomiting (14.5%), and diarrhea (12.7%) [27]. We showed that only 30% of patients receiving XELIRINOX suffered grade 3/4 neutropenia, which was usually short lasting and rarely complicated, and only 5% grade 3 fatigue without grade 4, vomiting occurs in 50% grade 1-3 without grade 4. Furthermore sensory neuropathy occurs much lower in our study with only (5%) grade 3 without grade 4 compared to (9%) occur grade 3-4 in FOLFIRINOX. But the incidence of hand and foot syndrome occurs in (15%) of our patients, which only of grade 1-2.

The major concern with the XELIRINOX regimen is the gastrointestinal toxicity, in particular in terms of grade 3/4

(30%) was observed more frequently and higher than FOLFIRINOX, but it is manageable and acceptable. We believe that the lowering Irinotecan dose to 75% and use one week capecitabine in addition to the use of G-CSF contributed to the reduction of grade 3/4 neutropenia and diarrhea.

The relatively low risk of grade 3/4 (5%) hematological adverse events (anemia, thrombocytopenia and neutropenic fever) and none CT-related treatment cessation or death suggested a good tolerability of our XELIRINOX regimen.

6. Summary

We showed that the substitution of capecitabine for infusional 5-FU, in combination with lowering irinotecan dose to 75% and constant oxaliplatin dose, retained an interesting activity in the first-line treatment of metastatic PAC and well tolerated & could replace the need for an implanted central venous catheter with an ORR of 35 %, median OS of 10.5 months, and PFS of 7.5 months. However, the incidence of grade 3–4 diarrhoea experienced with the XELIRINOX regimen seems higher than that with FOLFIRINOX, but it was manageable and acceptable in addition to that, the regimen with the oral fluoropyrimidine seemed less manageable than that with infusional 5-FU. Therefore, a triple-drug combination of CPT-11 and L-OHP with capecitabine instead of infusional 5-FU as we used is a preferable alternative to FOLFIRINOX, and can be considered for patients with metastatic PAC. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire may be needed to obtain a better evaluation of the quality of life of patients receiving XELIRINOX treatment. To our knowledge, this is the first prospective study aiming to evaluate the efficacy of XELIRINOX in metastatic PAC patients. More studies involving well-designed randomized controlled trials are required to validate these results and to display whether XELIRINOX regimen used as an alternative to FOLFIRINOX in advanced PAC.

7. Abbreviations

BSC: best supportive care
 CT: Chemotherapy
 G-CSF: Colony stimulating factor
 GI: Gastrointestinal
 IV: Intravenous
 PAC: Pancreatic adenocarcinoma
 PC: Pancreatic cancer
 RECIST: Response evaluation criteria in solid tumors
 WHO-PS: World Health Organization-Performance state.

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Conflict of Interest

There is no any potential conflict of interest.

Ethical Clearance

Taken from our scientific university committee (Jaber Bin Hayyan Medical University)

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