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Treatment of Pancreatic Adenocarcinoma with FOLFIRINOX-A Study of Efficacy and Safety in a Saudi Population

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Abstract

Background: FOLFIRINOX is emerging as the standard of care for fit patients with metastatic pancreatic cancer (MPC). However, use FOLFIRINOX associated with high toxicity rates reported in earlier studies; some physicians are reluctant to use it. We reviewed our experience with FOLFIRINOX in pancreatic adenocarcinoma, focusing on dose adjustments, toxicity, and efficacy. This study aims to evaluate FOLFIRINOX in the treatment of locally advance or metastatic pancreatic adenocarcinoma adult patients at King Fahd Medical City, Riyadh from January 2012 to December 2017.

Methods: We were review data for all locally advanced, or metastatic pancreatic adenocarcinoma adult patients treated with FOLFIRINOX in King Fahd Medical City between January 2012 to December 2017. Eficacy, toxicity and tolerability were evaluated.

Results: Twenty-five patient with locally advance pancreatic cancer and twenty-four patients with metastatic pancreatic cancer were treated with FOLFIRINOX. The overall median survival time 9.27 month, the overall median progression-free survival was 7.44 month. Patient with LAPC had median PFS and OS of 9.7 and 12.7 months, respectively, and patient with MPC median PFS 5.3 month and OS 6.7 months. Forty-seven patients (96%) received FOLFIRINOX in the first line with median PFS 7.4 month and OS 9.27 month. In the whole cohort (LAPC and MPC), ten patients (20%) had partial response to chemotherapy. Further, 18 patients (36%) have stable disease. Twenty-One patients (42%) had no response as they progressed on FOLFORIRNOX. The most frequent grade ¾ toxicity was neutropenia (42%) renal toxicity (4%) and liver toxicity (6%), required emergency admission (51%) of patients.

Conclusion: The efficacy of FOLFIRINOX for pancreatic cancer was less than reported in the clinical trial while toxicity was similar to that report, selected patient and careful monitored toxicity can help the patient.

Keywords: Chemotherapy treatment; Metastatic; Pancreatic adenocarcinoma; Efficacy and Safety; Saudi population; Folfirinox; Cancer patients

Introduction

Pancreatic adenocarcinoma carries a poor prognosis with a 5-year survival of 6% [1]. Majority of the patients present with metastatic or unresectable disease, and only around 10 to 20% of the patients are potentially resectable [2]. Historically chemotherapy had not been known to have a significant impact in terms of improvement in survival. In 1997, Burris [3] showed improved survival from 4.4 to 5.6 months with gemcitabine compared to Flurouracil, and it became the standard of care. Since then, combinations of different agents including, Cetuximab and bevacizumab failed to show any substantial survival benefit [4-6]. but the combination with erlotinib was improved survival of 2 weeks [7].

In 2011, results of phase II/III partenariat de Recherche en oncology digestive(PRODIGE) 4/ Actions concertees dans les cancers colo-Rectaux et digestifs (ACCORD)11 trial, were published by Conroy et al. that showed a meaningful improvement in the median survival of patients with metastatic disease with FOLFIRINOX (5-flurouracil, irinotecan, and oxaliplatin) when compared with gemcitabine in the first line setting [8]. The trial randomized metastatic pancreatic cancer patients <75 years of age, ECOG (Eastern Cooperative group) Performance Status 0 or 1 and bilirubin of <1.5 times the upper limit of normal to either receive gemcitabine or FOLFIRINOX. With 171 patients in each arm, the median survival was 11.1 months in the FOLFIRINOX arm compared to 6.8 months in the gemcitabine arm (p-value <0.001, HR 0.57, 95% CI = 0.45 -0.73). Although the FOLFIRINOX group reported a higher quality of life, it also showed significant toxicities including 45.7% grade 3 or 4 neutropenia, 5.4% febrile neutropenia, 12.7% diarrhea, 9.1% thrombocytopenia and 9% sensory neuropathy. Because the trial enrolled younger patients with a good PS and 62% had either body or tail adenocarcinoma (32% had pancreatic head lesions with 14.3% requiring biliary stents), concerns were raised as to the application of the trial results to the general population. In 2013, Von Doff DD published the results of MPACT(Metastatic pancreatic adenocarcinoma clinical trial [9] which compared nab-paclitaxel in combination with gemcitabine to gemcitabine alone. It showed a survival benefit of 8.5 vs. 6.7 months in the nab-paclitaxel arm (p <0.001). The toxicities of this regime are different from FOLFIRINOX, and the regime is now widely accepted as an option for many patients.

In our center at King Fahad Medical City, we have been using FOLFIRINOX as the first line treatment for metastatic pancreatic cancer in the eligible patients. We herein aim to describe the efficacy, toxicity, and analysis of potential prognostic factors in patients treated with FOLFIRINOX as first-line treatment in metastatic and locally advanced pancreatic adenocarcinoma at King Fahad Medical City, Riyadh.

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Materials and Methods

A retrospective chart review was conducted from electronic hospital records of all cancer patients who had FOLFIRINOX in the treatment of locally advance or metastatic pancreatic adenocarcinoma at the Adult Medical Oncology Ward, King Fahad Medical City, Riyadh, Saudi Arabia from January 2012 to December 2017.

Patients who received FOLFIRINOX will be included regardless of prior treatment such as other chemotherapies, radiotherapy, surgery, or local ablative therapies. The multidisciplinary team determined the unresectability (stage III and IV). LAPC will be defined as arterial involvement of >90 degrees or venous involvement of >270 degrees.

Inclusion criteria

1) Patients who at least received one cycle of FOLFIRINOX and had histological confirmation of either.
    a) Locally advanced pancreatic adenocarcinoma including borderline resectable disease and unresectable disease.
    b) Metastatic pancreatic adenocarcinoma.
2) Patients with a prior history of chemotherapy for pancreatic cancer are also eligible.

Exclusion criteria

1) Patients with endocrine pancreatic tumors.
2) Patients in which pancreas is not the primary site of the tumor.
3) Patients treated without histological confirmation of pancreatic adenocarcinoma.

Patients will be identified from electronic hospital records. Medical records will be abstracted for demographic information, Performance status(ECOG), the extent of disease, site of the tumor, CA (carcinogenic antigen) 19-9, previous surgery, previous lines of chemotherapy. Toxicity assessment with FOLFIRINOX (measured using toxicity criteria from National Cancer Institute Common Toxicity Criteria version 4.0), hospital admissions. Response rates (Radiological Response assessed by the radiologist using Response Evaluation Criteria In Solid Tumor (RECIST) 1.1.), progression-free survival, and overall survival.

Standard of care in KFMC was to start full dose of FOLFIRINOX, which consist of oxaliplatin 85mg/m2 followed by irinotecan 180 mg/m^2 and leucovorin 400 mg/m^2, followed by 5-fluorouracil bolus as 400mg/m2 then continuous infusion of 2400 mg/m^2 over 48 hours. Dose reduction and use of prophylactic granulocyte-colony stimulating factor(G-CSF) depend on treating physician. Cycles of chemotherapy were repeated every two weeks until disease progression, developed severe toxicity, or complete treatment course.

Progression-free survival (PFS) described as the time from start treatment with FOLFIRINOX to time of progression or death. Overall survival (OS) described as the time from the date of start treatment to the date of death, a patient who lost of follow up we considered the last date of follow up is the date of death. Association of survival outcome and progression-free survival with baseline prognostic factors was determined using Cox regression univariant analysis and hazard ratios(HR) with 95%confident intervals (CI) were presented. Factor include in the univariant analysis include age, smoking, comorbidity, performance status stage of disease, GCSF use, chemotherapy dose reduction.

Statistical Analyses

Data were described as averages and percentages. Most appropriate tests will make the intergroup comparison as per resectable disease and survival outcome across the distinguished parameters. PFS and OS will be estimated by Kaplan Meier Survival analysis and will be reported by the median and ranges. Cox proportion hazard model will be fitted for both fixed and time-dependent covariates of the study. All the inferences will be drawn at 95% confidence interval. MS Excel 2016 and SPSS 22.0 software will be used for data analysis.

All Categorical variables, age, gender, and diagnosis were presented as numbers and percentages. Paired sample t-test was to determine the mean significant before and after interventions-the intraclass correlation coefficient among all the scores. The p-value of less than 0.05 was considered statistically significant.

Ethical considerations

Ethical approval is granted from the hospital ethics committee (IRB Log No. 17-438).

Results

Patient characteristics

Patient with pancreatic adenocarcinoma between January 2012 and December 2017 was treated with FOLFIRINOX at KFMC. Baseline demographic features and clinical characteristics are shown in Table 1. the median age is 53, and 32 of patients were male, 24 patients have metastatic disease while 25 patient have locally advanced disease (4 patients were borderline resectable, and 21 had unresectable disease (Table 2).

Study treatment and adverse event

The patients received a median of 8 cycles of FOLFIRINOX (Range, 1-54). The dose of 1 or more component of FOLFIRINOX was reduced in 46% of patient including dose reduction of oxaliplatin dose in 37% of patient and the dose reduction of 5 fluorouracil bolus in 26% of patient while omission of bolus 5 fluorouracil in 8% of the patients, 5 fluorouracil infusion dose was reduced < 25% of dose in 16% of patient while >25% dose reduction was observed in 12% of patient, irinotecan dose was reduced < 25% of dose in 12%of patients, while > 25%of dose was reduced in 14% of patients including one patient, was 100%of dose reduction, cycles of chemotherapy were delay in 25% of patients. Treatment-related toxicity was summarized in the Table 3, 42%of patients required one hospital admission during treatment with FOLFIRINOX, while 8% of patients had multiple admissions GCSF (pegfilgrastim or filgrastim) was given as primary prophylaxis in 42%of patients started from cycle one chemotherapy, 57% who did not start primary prophylaxis GSCF, 13 patient (26%)subsequently received GCSF because of neutropenia. fifteen patient (30%) had mortality within 30 days from chemotherapy.

Efficacy

In the whole cohort (LAPC and MPC), ten patient (20%) had a partial response to chemotherapy. Further, 18 patients (36%) have stable disease. Twenty-one patient (42%) had no response as they progressed on FOLFORIRNOX. Eight patient (16%) had a reduction in CA19-9. By the end of our cohort, the overall median survival time 9.27 month, the overall median progression-free survival was 7.44 month. Patient with LAPC had median PFS and OS of 9.7 and 12.7 months, respectively, and patient with MPC median PFS 5.3 month and OS 6.7

months. Forty-seven patients (96%) received FOLFIRINOX in the first line with median PFS 7.4 month and OS 9.27 month.

Prognostic variables

Univariant analysis Table 3, demonstrate age, smoking, comorbidity, metastatic status, reduction in CA19-9 >50%, line of treatment, use of GCSF, blood glucose level, reduction on the dose of chemotherapy, delay on chemotherapy cycle time.

After multivariate analysis, non-metastatic status (p=0.07;HR, 0.530; 95% CI, 0.291-0.963)was significant for PFS; also was significant in OS (p=0.019;HR, 2.07; 95% CI, 1.017-3.83).

1) By the end of the study, 8.7% cumulative probability of surviving was observed within a full-time period of the study.

2) The overall median survival time 9.27 months was observed (Figure 1).

Characteristics	Descriptions	n (n%)
Gender	Male	32 (65.3%)
	Female	17 (34.7%)
Age	(Mean ± SD)	53.76 ± 10.40
Marital Status	Single	3 (6.1%)
	Married	45 (91.8%)
	Widow/Divorced	1 (2.0%)
Smoking	Yes	9 (18.4%)
	No	29 (59.2%)
	No Data	11 (22.4%)
Comorbidity	Diabetes Mellitus	18 (37.5%)
	Hypertension	2 (4.2%)
	HTN & DM	6 (12.5%)
	No Comorbidity	21 (43.8%)
	No Data	1 (2.1%)
Resection of Primary	Yes	6 (12.2%)
	No	43 (87.8%)
Clinical Stage	Borderline Resectable	6 (12.2%)
	Locally Advance Unresectable	19 (38.8%)
	Metastatic	24 (49.0%)
The extent of disease (Metastatic)	Liver	20 (41.7%)
	Peritoneal	3 (6.3%)
Site of the primary tumor	Head or ampulla	34 (69.4%)
	Body	7 (14.3%)
	Neck	3 (6.1%)
	Tail	5 (10.2%)
PFS (ECOG)	I	44 (89.8%)
	II	5 (10.2%)
Line of treatment	1st Line	47 (95.9%)
	2nd Line	2 (4.1%)
Blood Glucose	< 7.2 mmol	12 (24.5%)
	7.3-10 mmol	15 (30.6%)
	> 10 mmol	14 (28.6%)
	No Data	8 (16.3%)

Table 1: Basic characteristics of the patients (n=49).

Grade of Neutropenia	Grade I	1 (2.0%)
	Grade II	3 (6.1%)
	Grade III	11 (22.4%)
	Grade IV	10 (20.4%)
	No Grade	24 (49.0%)
Grade of Renal Toxicity	Grade I	3 (6.1%)
	Grade II	6 (12.2%)
	Grade III	1 (2.0%)
	Grade IV	1 (2.0%)
	No Grade	37 (75.5%)
	NA	1 (2.0%)
Grade of Liver Toxicity	Grade I	7 (14.3%)
	Grade II	11 (22.4%)
	Grade III	3 (6.1%)
	No Toxicity	27 (55.1%)
	No Data	1 (2.1%)

Table 2: Toxicity after treatment with Folfirinox.

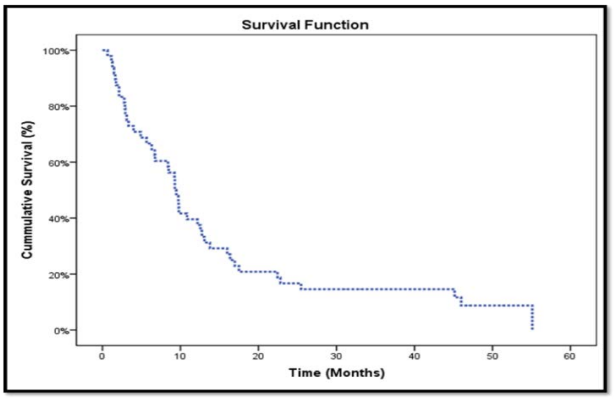

Figure 1: Cumulative probability of surviving was observed within a full-time period of the study.

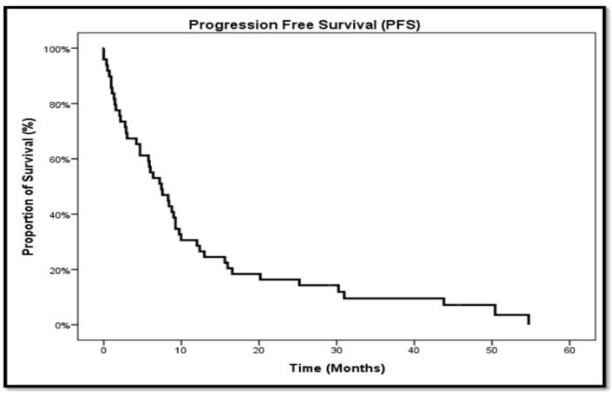

Figure 2: Overall median progression-free survival time.

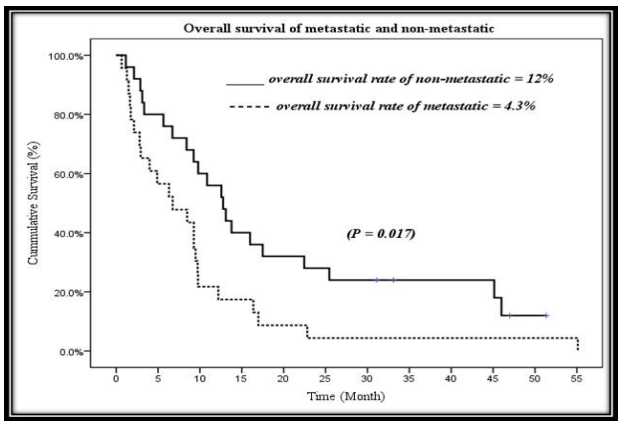

Figure 3: Overall cumulative survival percentage in 6 months.

Characteristics	Descriptions	OS (months)		p–value	PFS (months)		p–value
		Median (95% CI)	Hazard Ratio (95% CI)		Median (95% CI)	Hazard Ratio (95% CI)	
Age	≤ 60	10.32 (10.347 – 20.275)	7.169 (0.128 – 402.761)	0.338	8.28 (8.000 – 17.200)	1.358 (0.710 – 2.599)	0.355
	>60	5.706 (2.098 – 18.757)			3.72 (0.742 – 17.651)		
Smoker	Yes	13.776 (4.64 – 35.36)	0.618 (0.064 – 6.009)	0.678	12.36 (2.039 – 34.040)	1.748 (0.755 – 4.046)	0.192
	No	8.448 (7.316 – 17.992)			5.880 (5.289 – 14.679)		
Comorbidity	Comorbid	9.618 (7.635 – 18.765)	3.78 (0.242 – 59.156)	0.343	9.000 (6.503 – 17.552)	0.783 (0.437 – 1.404)	0.412
	Non-comorbid	8.862 (7.960 – 21.435)			5.880 (5.130 – 17.230)		
Metastatic Status	Metastatic	6.744 (4.418 – 14.368)	2.079(1.127 – 3.838)	*0.019	5.340 (2.854 – 12.265)	0.530 (0.291 – 0.963)	*0.037
	Non-Metastatic	12.756 (11.594 – 24.448)			9.720 (9.370 – 21.704)		
Reduction CA	≤ 50%	16.176 (9.370 – 38.194)	1.994 (0.575 – 6.923)	0.277	12.600 (6.754 – 36.955)	0.582 (0.176 – 1.928)	0.376
	>50%	12.192 (11.320 – 38.662)			8.400 (-3.091 – 36.931)		
Line of treatment	1st line	9.276 (9.115 – 17.311)	0.564 (0.135 – 2.357)	0.433	7.440 (7.368 – 15.395)	1.285 (0.309 – 5.352)	0.730
	2nd line	29.376 (-181.801 – 240.553)			17.460 (-144.925 – 179.845)		
Primary G-CSF prophylaxis	Yes	9.792 (7.282 – 17.913)	0.416 (0.172 – 1.010)	0.053	8.280 (5.349 – 15.690)	2.365 (1.023 – 5.469)	*0.044
	No	16.368 (13.069 – 39.474)			15.960 (10.625 – 36.327)		
Secondary G-CSF prophylaxis	Yes	16.176 (11.956 – 37.025)	2.057 (0.880 – 4.808)	0.096	12.600 (9.819 – 34.000)	0.481 (0.214 – 1.078)	0.076
	No	10.320 (7.440 – 18.526)			8.520 (5.395 – 16.228)		
Blood Glucose	≤ 10 nmol	9.732 (9.470 – 20.911)	1.050 (0.523 – 2.106)	0.892	7.560 (7.034 – 17.765)	1.164 (0.586 – 2.314)	0.665
	>10 nmol	9.276 (5.075 – 24.263)			8.100 (3.887 – 23.112)		
Chemotherapy dose reduction	Yes	12.474 (9.953 – 22.565)	1.561 (0.851 – 2.863)	0.150	9.240 (7.567 – 18.885)	0.697 (0.388 – 1.255)	0.229
	No	7.578 (6.085 – 17.674)			5.940 (4.441 – 15.995)		
Reduce Due to Toxicity	Yes	14.72 (12.476 – 29.634)	2.272 (1.139 – 4.534)	*0.020	12.000 (9.128 – 24.503)	0.496 (0.259 – 0.949)	*0.034
	No	6.510 (6.335 – 15.535)			5.220 (4.751 – 13.933)		
Required delay the cycle	Yes	12.378 (11.414 – 28.874)	1.935 (1.055 – 3.549)	*0.033	9.000 (8.289 – 20.932)	0.588 (0.327 – 1.056)	0.076
	No	6.198 (4.881 – 14.378)			4.440 (3.775 – 13.274)		

Table 3: Univariate analysis of PFS and OS.

3) By the end of the study, 3.7% cumulative probability of progression-free surviving were observed within a full-time period of the study.

4) The overall median progression-free survival time 7.44 months was observed (Figure 2).

Discussion

This cohort aimed to evaluate our experience in KFMC regarding toxicity and efficacy of FOLFIRINOX in a patient with pancreatic cancer. In comparison with the result that seen in the PRODIGE 4/ ACCORD 11 trail, in patients with MPC, PFS was 5.3 month and OS was 6.7 month (compared with 6.4 months and 11.1 months in PRODIGE 4/ACCORD 11 trail. in patient with LAPC, we expected the outcome were better than those with patient with MPC with PFS 9.7 month and OS 12.7 month. Baseline CA 19.9 was greater than 100 in 34 patient (70%), reduction in CA19.9 more than 50% post-treatment with FOLFIRIBOX was observe in 8 patient (16%), CEA level was greater than 5 in 23 patient (64%) and LDH was more than 175 in 32 patient (65%), response to FOLFIRINOX was assessed by (RECIST) 1.1., the response was seen in 28 patient (56%) including partial response in 10 patient(20%) and stable disease in 18 patient (36%), non-response to FOLFIRINOX was observed in 21 patient (42%) (Figure 3).

Other concern is the toxicity of FOLFIRINOX chemotherapy, in our study neutropenia grade 3 /4 was 44%, renal toxicity grade ¾ was 4%, and liver toxicity was 6%. Required hospital admission one time in 21 patient (42%) and multiple patient admission in 4 patient (8%),

chemotherapy reduction was observed in 23 patient (46%), 15 patient (30%) was reduced due to toxicity, 10 patient(20%) was reduced from the 1st cycle. Dose of chemotherapy was reduced in a different way, 5fu bolus was omission in 4 patient (8%) while 25% dose reduction was in 6 patient (12%) dose reduction >25% was seen in 7 patient (14%), oxaliplatin was omitted in 3 patient (6%) while reduction in 25% of the dose was seen in 8 patient (16%), dose reduction >25% of the dose was observed in 7 patient (14%), irinotecan was omitted in 1 patient (2%) while dose reduction 25% was seen in 10 patient (20%)and dose reduction >25% in 6 patient (12%), 5-fu infusion was reduced by 25% in 8 patient (16%) and >25% dose reduction was seen 6 patient (12%). Interestingly found who have dose reduction due to toxicity had PFS 14.7 month versus 6.5 month for who had no dose reduction (P=0.02, HR2.27, 95% CI 1.139-4.3) and OS was 12 month versus 5.2 month for non-dose reduction with P= 0.03, HR.495, 95% CI 0.259-0.94). In our patient, the required delay in chemotherapy was 12%, which is less than seen with other series (14). Toxicity necessary chemotherapy delay cycle was seen 25% (50%). Primary G-CSF prophylaxis was used in 21 patients (42%) while 28 patients were not used as primary, but subsequent use GCSF prophylaxis post neutropenia (secondary) was seen in 13 patient (26%).

Study Limitations

Some identified limitations of the current study are the small sample size from a single-center and select older age group. To explore further studies on a larger diverse, multi-centered population.

Conclusion

This study is retrospective; our result should be interpreted with caution; our institution experience showed that the outcome was less than that seen in PRODIGE 4/ACCORD 11 trail. Toxicity was significant although FOLFIRINOX is used as a 1st line, given the toxicity make other option of chemotherapy gemcitabine /nab-paclitaxel is a valid option. This required future study with head to head comparison. Currently, the choice of chemotherapy should be tailored to patient individualized and availability of medication.

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