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Folfirinox in Advanced Pancreatic Cancer, Nemrock Experience

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Abstract Purpose: The objectives of study are to evaluate efficacy and toxicity of combination chemotherapy FOLFIRINOX in Egyptian patients with inoperable or metastatic pancreatic cancer. Patients and Methods: Between September 2011 and September 2012, twenty patients with inoperable locally advanced or metastatic pancreatic adenocarcinoma were included to receive FOLFIRINOX protocol as first-line therapy. The median age was 54 years,. The majority of patients (70%) had metastatic disease. The median over all treatment period was 14 weeks (range: 8-26 weeks).A total of 168 cycles were administered with a median of 8 cycles (range 4-12) per patient. Results: Over all response rate was 65 % (PR 35%+SD30%). Median Progression Free Survival was 6 months (95% CI: 5.782-6.218). Progression-free survival rates at 6 and 12 months were 73 % and 10% respectively. Median overall survival was 10.5 months (95% CI: 8.309-12.691). Overall survival rates at 6 and 12 months were 84 % and 40% respectively. Grade 3-4 chemotherapy-related toxicities were observed in 30% of patients. Conclusion: The combination of FOLFORINOX had significant improvement in response rate, progression free survival and overall survival in spite of significant manageable toxicity.

Keywords Folforinox –Inoperable Locally Advanced Or Metastatic Pancreatic Cancer

1. Introduction

The overall survival rate of patients with pancreatic cancer is extremely disappointing (1), since most of the patients present with unresectable locally advanced or metastatic disease. The prognosis is dismal with only 1% to 4% surviving at 5 years (2). Gemcitabine was the only approved therapy for inoperable pancreatic cancer (3). In several phase III studies, single agent gemcitabine showed response rates ranged from 5.4% to 26%, with a median survival of about 6 months and 1-year survival of 20% (4-9). In May 2011, new combination chemotherapy FOLFIRINOX was proved to be superior to single agent gemcitabine. The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group. With a median progression-free survival of 6.4 months in the FOLFIRINOX group versus 3.3 months in the gemcitabine group. The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group. More adverse events were noted in the FOLFIRINOX group. Accordingly, FOLFIRINOX becomes an option for the treatment of patients with metastatic pancreatic cancer with good performance status (10). Based on foregoing data, we had to study the efficacy and toxicity of this aggressive combination chemotherapy (FOLFIRINOX) among our patients with locally advanced or metastatic pancreatic adenocarcinoma. To answer a question, Can we change the standard of care in systemic treatment of advanced pancreatic cancer from single agent gemcitabine to combination chemotherapy FOLFIRINOX? Can we give this regimen to our patients without major adverse events?

2. Patient & methods

This prospective study was conducted in Kasr Al-Aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK). This study received approval from scientific committee of NEMROCK. All patients signed on an informed consent.

2.1. Patients

Eligible patients had histologically or cytologically confirmed pancreatic adenocarcinoma not amenable to curative surgery. Age ranged between 18-70 years. All patients had a measurable disease. Both inoperable locally advanced or metastatic disease are eligible. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2. Adequate bone marrow (granulocyte count, ≥1500 per cubic millimeter; platelet count, ≥100,000 per cubic millimeter and Hemoglobin more than 8 g/L). Adequate liver function (bilirubin ≤1.5 times the upper limit of the normal range), adequate renal function (serum creatinine ≤1.5 mg/dl , blood urea ≤ 45 mg/dl and/or creatinine clearance ≥ 60 mol/L). Patients were excluded

from the study if they had history of previous chemotherapy or radiotherapy, brain metastases, a history of another major cancer. Active infection, chronic diarrhea. A clinically significant history of cardiac disease, and pregnancy.

2.2. Patient Evaluation

Prior to treatment, each patient was evaluated by medical history, physical examination, full blood cell count, blood chemistry, Performance status, tumor markers (CEA and CA 19-9). Computed tomography (CT) or magnetic resonant (MRI) scans of chest and abdomen were also performed. For patients who presented with biliary obstruction, adequate biliary drainage was required prior to initiation of this chemotherapy.During chemotherapy, full blood counts and biochemical test were performed before each injection. A CT scan or MRI was done every 4 cycles of chemotherapy to assess objective response or sooner if progression was suspected by symptoms or rising CA19-9. If two consecutive scans during treatment showed similar findings with no improvement, this was considered to be the maximum response. Maximum tolerability was defined as the point when excessive toxicities warranted stopping FOLFIRINOX, even if a patient had not achieved their maximum response. Patients underwent follow-up examination every 2 months.

2.3. Treatment Schedule

FOLFIRINOX consisted of oxaliplatin at a dose of 85 mg /m^2, given as a 2-hour intravenous infusion in 250 ml glucose 5%, immediately followed by leucovorin at a dose of 400 mg /m^2, given as a 2-hour intravenous infusion in 250 ml glucose 5%, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg /m^2, given as a 90-minute intravenous infusion in 250 ml 0.9% Sodium Chloride through a Y-connector. This treatment was immediately followed by fluorouracil at a dose of 400 mg /m^2, administered by intravenous bolus over 5 minutes, followed by a continuous intravenous infusion of 2400 mg /m^2 over a 46-hour. 5FU continuous infusion was given either by continuous peripheral IV infusion over 46 hours in 2 x 1000mls Sodium Chloride 0.9% or by central venous catheter and ambulatory infusion device over 46 hours. This cycle repeated every 2 weeks.

This treatment are preceded by premedication as antiemetic (dexamethasone 8 mg and 5-HT3 receptor antagonists 8 mg ondasteron) , Ranitidine 150 mg and dipheniramine maleate ampoule all are administered intravenously on 250 cc normal saline solution over 30 min. just before chemotherapy.

2.4. Dosage Adjustment Guidelines for Toxicities in the FOLFIRINOX Arm

In the event of predefined toxic events, protocol-specified treatment modifications were permitted in case of grade 3 or 4 neutropenia or diarrhea, FOLFIRINOX administration was delayed until recovery and doses were reduced by 20-25% of original dose. Patients discontinued the study in the event of unacceptable toxic effects or evidence of progressive disease, or at their request. For any febrile neutropenia or a second episode of grade 3/4 neutropenia, G-CSF Prophylaxis should also be initiated with subsequent cycles, starting on Day 5 of each cycle. Prophylactic ciprofloxacin should also be started in patients with neutrophils $<0.5 \times 10^9$/l, even in the absence of diarrhea.

For gastrointestinal toxicities, patients instructed in the use of loperamide as a treatment for diarrhea, and must have a supply of this drug upon starting FOLFIRINOX.

2.5. Assessments

The primary purpose of this study was to evaluate the efficacy and toxicity of the combination regimen (FOLFIRINOX). Primary end point was overall survival; secondary end points were response rate, progression free survival and toxicity profile. The duration of overall survival (OS) was calculated from the date of registration until date of death or last follow-up. The duration of progression free survival (PFS) was calculated from the date of treatment until the date of progression, death or last follow-up. Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria every 2 cycles (11). Toxicity was graded according to National Cancer Institute Common Toxicity Criteria, Version 3.0 (12).

2.6. Statistical Analysis

Data was analyzed using SPSS statistical package version 17.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test is used to examine the relation between qualitative variables. The survival curves were estimated using the Kaplan–Meier technique.

3. Results

Between September 2011 and September 2012, twenty patients with inoperable locally advanced or metastatic pancreatic adenocarcinoma received FOLFIRINOX protocol. The final analysis was conducted on May 2013. Median age was 54 years (range: 40–70 years), including 14 males and 6 females. Most of our patients (55%) presented with performance status (1) according to ECOG scale. Twelve (60%) patients were chronic heavy smokers, 45% cases were diabetics and 17% had a history of cholecystectomy. Baseline demographic and clinical characteristics are listed in Table (1).

Table 1. Baseline patients characteristics

Characteristic	No	%
Age, years		
-Median	54.8±9.4	
-Range	(40-71)	
-≥ 60	5	25
Sex		
- Male	14	70
-Female	6	30
Pancreatic tumor location		
-Head	12	60
-Body	5	25
-Tail	3	15
ECOG performance status		
- 1	11	55
- 2	9	45
Level of tumor marker CA 19-9		
-0-37 U/mL	6	30
-38-500 U/mL	7	35
-500-1000 U/mL	3	15
->1000 U/mL	4	20
Stage of disease		
-Locally advanced	6	30
-Metastatic disease	14	70
Metastatic site		
- Liver	12/14	85.7
- Lymph node	6/14	42.8
- Lung	5/14	35.71
- Peritoneal	4/14	28.57
Presence of stent prior to treatment		
- Yes	7	35
- No	13	65

Abbreviations: ECOG, Eastern Cooperative Oncology Group. CA 19-9, carbohydrate antigen

Head of the pancreas was the commonest site of tumor involved in 12 (60%) out of 20 patients followed by body in 5(25%) patients. Among the 12 patients who had tumors at the head of the pancreas, 7(35 %) patients had metallic stents placed to relieve biliary obstruction other 5 patients had double-bypass operations which included a choledochojejunostomy. All patients who had stents or bypass procedures achieved normalization of their serum bilirubin level prior to the start of chemotherapy, 7 (35%) patients of the study group presented with elevated CA 19-9 above 500U/ml.

The majority of patients (70%) had metastatic disease; liver was the dominant site for metastasis in 85.7 % of metastatic patients. while inoperable locally advanced disease was diagnosed in 30% of patients.

A total of 168 cycles of chemotherapy were given to the 20 patients, with a median of 8 cycles of FOLFIRINOX (range; 4-12 cycles). Seven patients (35%) received 12. Table 2 summarizes the treatment delivery.

Table 2. Treatment delivery, n = 20

Number of cycles	NO. of patients	%
≤ 4	7	35
5-8	4	20
9-12	9	45
Median 8 cycles (range;4-12)		
• Total number of cycles	168	100
• Number of cycles at full dose	120	71.4
• Number of cycles at reduced dose	46	28.6
• Number of cycles delayed by≥ 1 week	10	5.9

4. Efficacy

Seven patients (35%) had partial regression (PR) proved by CT scan. Six (30%) patients had stable disease (SD) and 7 (35%) patients developed progression disease (PD). Objective response rate was 65%. Median duration of response was 5 months (range; 2-11). The response to therapy is summarized in Table (3). Fifteen (75%) patients had a decrease in serum level of CA19–9 by 50% or more from baseline CA19–9.

Table 3. Objective Response rate, n = 20

Response	No. of PATIENTS	(%)
Partial Response (PR)	7	(35)
Stable Disease (SD)	6	(30)
Overall response (PR +SD)	13	(65)
Disease Progression	7	(35)

Second-line therapy was administered in seven (35%) patients. The most common second line regimens were single agent gemcitabine in four metastatic patients and combined chemo-radiotherapy (CCRT) with 5-FU in three (15%) patients with local advanced disease. The radiation therapy was delivered in a standard fashion to a total dose of 50.4 Gy in 28 fractions.

5. Toxicity

With regard to tolerability, all patients experienced at least one grade 1 or 2 adverse event, grade 2 alopecia occurred in 15% of patients. A total 6 out of the 20 patients (30%) experienced at least one grade 3 or 4 adverse event required hospitalization during FOLFIRINOX for neutropenic fevers or dehydration/ diarrhea the median length of stay was7 days (range 5–10) and G-CSF was started prophylactically with all subsequent cycles of FOLFIRINOX. No cholangitis was observed, the adverse event profile is shown in Table (4).

Table 4. Adverse events during treatment, n = 20

Adverse events	Grade 1/2		Grade 3 /4	
	NO	%	NO	%
Non hematologic :				
Fatigue	16	80	4	20
Vomiting	6	30	2	10
Mucositis	4	20	0	0
Diarrhea	10	50	3	15
Sensory neuropath	9	45	4	20
Alopecia	3	15	0	0
Hematologic				
Neutropenia	14	70	3	15
Febrile neutropenia	0	0	3	15
Anemia	12	60	1	5
Thrombocytopenia	8	40	1	5

One patient had to be taken off FOLFIRINOX for toxicity related to treatment. Ten (50 %) patients had a treatment delay of at least one week due to neutropenia or neutropenic fever or diarrhea.

Median follow-up was 8months (range: 4-12 months), 12(60%) patients died and 8(40%) others are alive with progression of disease. One of the patients who died progressed 11 months after the end of treatment. The median progression free survival was 6 months (95% CI: 5.782 - 6.218). Progression-free survival rates at 6 and 12 months were 73 % and 10% respectively figure (1).

6. Survival

Regarding overall survival, median OS was 10.5 months (95% CI: 8.309-12.691). Overall survival rates at 6 and 12 months were 85% and 35% respectively, as shown in figure (2).

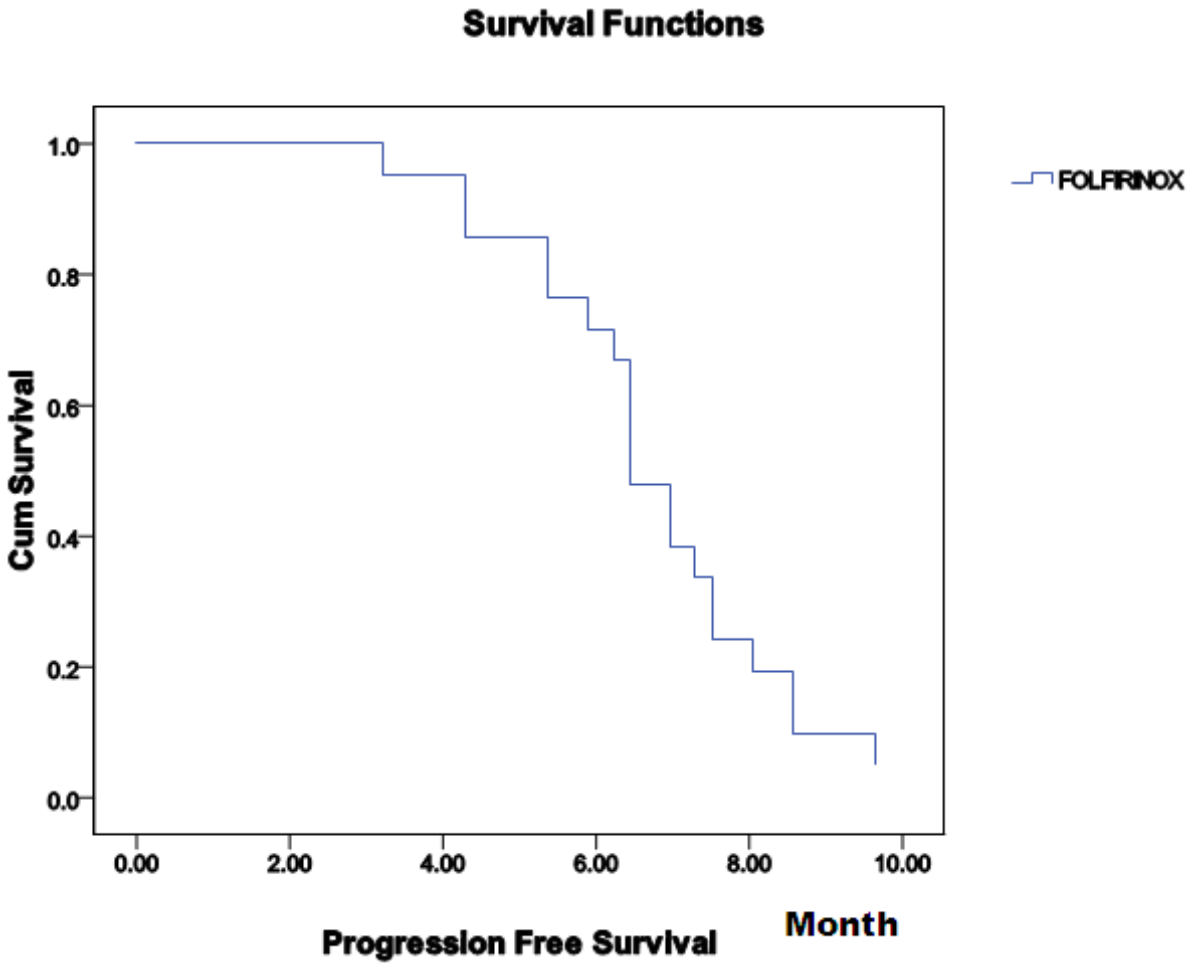

Figure 1. Kaplan-Meier curve of Progression free survival.

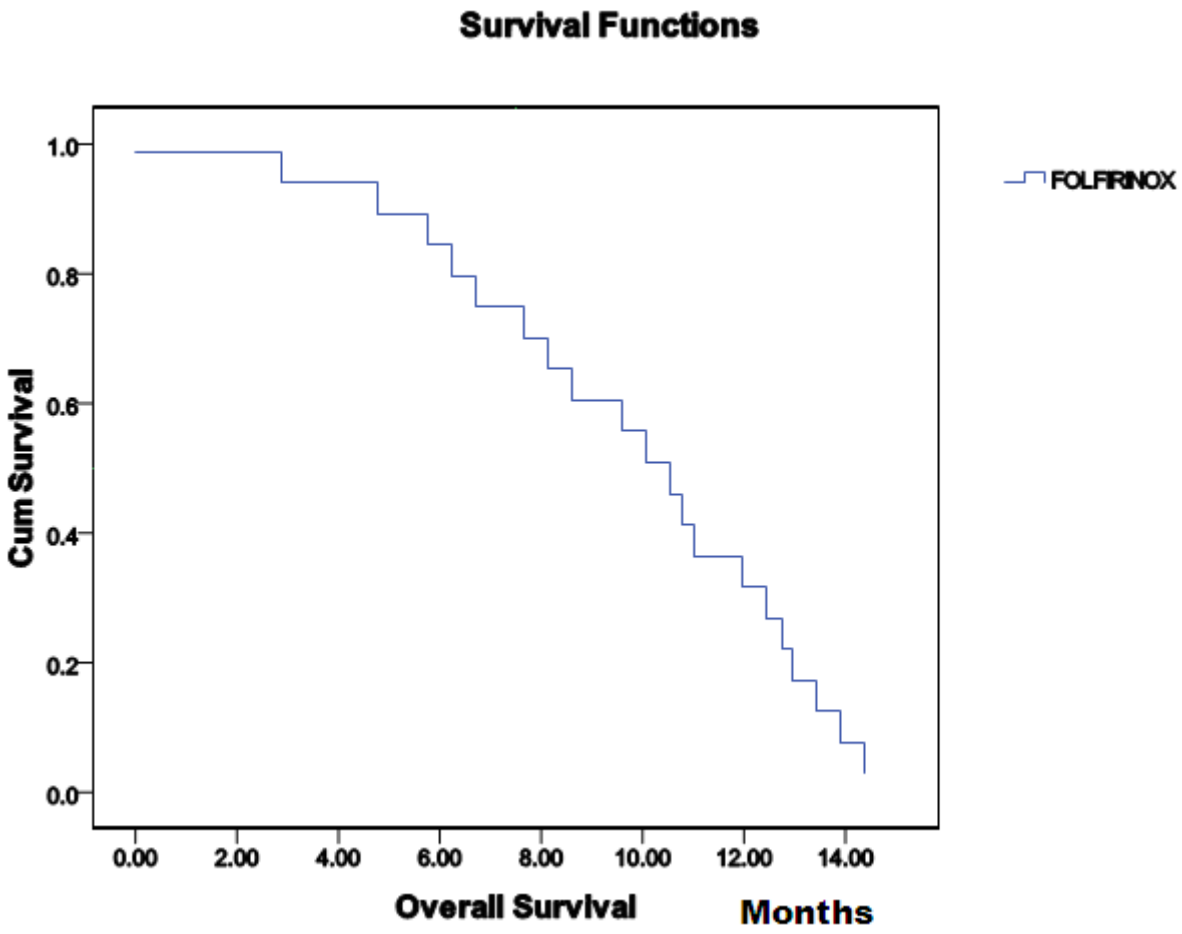

Figure 2. Kaplan-Meier curve of Overall survival.

7. Discussion

Since Burris trial in 1997, gemcitabine became the standard treatment for advanced pancreatic adenocarcinoma. In fact, the median survival recorded was just 5.6 months. The survival advantage was relative to 30 minutes weekly fluorouracil **(3)**. Clinical trials in advanced pancreatic cancer during the last couple of decades have almost uniformly yielded disappointing results. To date, the paradigm for almost all phase III studies has been to compare the long-time reference standard gemcitabine, with a gemcitabine based combination regimen. Agents evaluated in combination with gemcitabine have been myriad; these have included both cytotoxic drugs (platinum analogs, fluoropyrimidines, and camptothecins) and targeted therapies (inhibitors of farnesyl transferase, matrix metalloproteinase, vascular endothelial growth factor, and epidermal growth factor receptor, to name a few). With the exception of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib—which produced a modest incremental improvement when added to gemcitabine (13), none of these individual trials demonstrated a statistically significant survival benefit in favor of doublet therapy, although some have shown improvement in secondary outcome measures such as response rate and time to tumor progression (4-9).

In a randomized phase III PRODIGE trial, a very attractive results achieved by the combination chemotherapy FOLFIRINOX compared with gemcitabine alone (10).

Hence the question is shall our Egyptian patients tolerate this regimen and shall this regimen with this toxicity gives an improvement in survival. The answer is yes; in our study we had achieved significantly prolonged PFS (6 months) and median overall survival (10.5 months) with importantly response rate of 35% and the adverse events were moderate and reversible among our patients treated with FOLFIRINOX.

In PRODIGE trial, grade 3/4 side effects were 45.7% neutropenia, 4% febrile neutropenia, 12.7% diarrhea and 9% sensory neuropathy. About 42% of the patients required granulocyte-colony stimulating factor (G-CSF). In our study we observed grade3/4 toxicities (ie; neutropenia, febrile neutropenia and diarrhea) in 30% of patients and prophylactic G-CSF was administered subsequent cycles and no febril neutropenia recorded after that. Although, we had no toxic death reported, with 30% of patients requiring hospitalization during FOLFIRINOX treatment, this regimen is quite toxic in a patient population that is considered incurable but these toxicities either

hematological or non hematological were for the most part reversible and manageable and early admission of G-CSF and close monitoring of patients is very important issue. Given our experience, upfront dose modification of the FOLFIRINOX regimen might be necessary, particularly in less well-selected populations of patients.

In spite of 35% of our patients with biliary stents, no cholangitis was observed in any patient in our study. Careful monitoring of the bilirubin level is required when irinotecan is administered in patients with biliary drainage. In view of high objective response rates associated with this regimen; it's considered the regimen of choice as neoadjuvant therapy for borderline resectable cases. A pilot study of neoadjuvant FOLFIRINOX in unresectable locally advanced pancreatic carcinoma was presented in 2011 with curative resection (R0) rate of 33% (14) and another study was done in Massachusetts General Hospital Cancer Center. Where FOLFIRINOX followed by chemoradiation were given as a neoadjuvant, with five out of 22 patients (22.7%) were able to undergo (R0) resections (15).The future of research in pancreatic cancer should be directed to FOLFIRINOX regimen, as adjuvant treatment. For older patients with advanced disease, Patients with performance status of 2-3, it is possible to give it initially with 25% to 50% dose reduction.

In conclusion, the new combination chemotherapy FOLFIRINOX appears to be feasible to be given with moderate reversible adverse events and had a better outcome than the standard single agent gemcitabine especially for patients with good performance and symptomatic patients.

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