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A Phase II Trial of Flouro-Gem as a First Line Treatment of Metastatic Adenocarcinoma of the Pancreas (GEFLUPAN trial)

Ahmed Sohaib*[1], Reham Abdelaziz[1], Faten Younis[2], Amira Hegazy[1]
Departments of [1]Clinical Oncology and [2]Community and Occupational Medicine,
Faculty of Medicine, Menoufia University, Egypt
***Corresponding author:** Ahmed Sohaib, **Mobile:** (+20) 01090432337, **E-mail:** dr.ahmed.sohaib@gmail.com

ABSTRACT

Background: Gemcitabine and 5 FU+folinic acid have both proved efficacy in treating patients with advanced pancreatic cancer.

Objective: In our study, we combined the two most active agents against pancreatic cancer; gemcitabine and 5FU that were given every 2 weeks to gain the maximum benefit of both drugs and avoid the toxicity that occurs very frequently with FOLFIRINOX.

Patients and Methods: This prospective phase II study included 42 patients of metastatic cancer pancreas who met the inclusion criteria

Results: The median age at diagnosis was 55 years. Males were more common (59.5%) than females. The most common site of metastasis was the liver (57.1%). Toxicity profile showed that neutropenia and thrombocytopenia were the most common forms of toxicity being high grade in 11.9% of patients. Other forms of toxicity were minimal not exceeding 5%. The overall response rate (ORR) was 33.3% with no reported complete responses. There was a significant correlation between the change of tumor markers levels (CEA, and CA 19.9) and both response and quality of life (QOL). The changes of CEA and CA19.9 levels were found to be independent predictors of progression free survival (PFS). One year OS rate was 49%. The median OS was 11.3 months, while the median PFS was 8.8 months. Response was also found to be a surrogate marker for survival.

Conclusions: Gemcitabine- 5 FU combination was a good alternative option for treating metastatic pancreatic cancer, it had good efficacy and safety profile.

Keywords: Pancreatic, Toxicity, Gemcitabine, Carcinoma, 5 FU.

INTRODUCTION

Among American males, pancreatic cancer ranks as the fourth most prevalent cause of cancer-related mortality (after lung, prostate and colorectal cancer) and among females (after lung, breast, and colorectal cancer) [(1)].

Multiple aetiological factors have been linked to pancreatic cancer including smoking, exposure to heavy metals and chemicals as well as heavy alcohol consumption [(2, 3)]. About 10% of cases have familial component of the disease [(4)].

Gemcitabine showed clinical efficacy when used for metastatic pancreatic adenocarcinoma. It became the standard of care for a considerable duration of time based on results from a randomized trial by **Burris** [(5)] dating back to 1997. In addition, gemcitabine offers better QoL when compared to infusional 5-flourouracil (5FU) regimen, which is also known for its efficacy against pancreatic cancer [(6)]. Numerous studies have investigated gemcitabine combinations for the treatment of pancreatic cancer. Among these trials, the combination of albumin, paclitaxel, and gemcitabine, which has showed improvement in response rates and survival [(7)].

Combination of gemcitabine plus capecitabine has been investigated in several randomized trials with proven benefit in terms of response rates and PFS [(8)]. Gemcitabine was the king of treatment for pancreatic cancer until the PRODIGE study was published showing superiority of another regimen over gemcitabine in terms of response and survival. This regimen is a four-agent protocol known as FOLFIRINOX combining oxaliplatin, irinotecan, leucovorin and 5FU. As expected, the toxicity profile of this regimen hindered its use in clinical practice to a great extent [(9)].

In our study, we combined the two most active agents against pancreatic cancer; gemcitabine and 5FU, which were given every 2 weeks to gain the maximum benefit of both drugs and avoid the toxicity that occurs very frequently with FOLFIRINOX.

PATIENTS AND METHODS

Patients: This study was a prospective phase II clinical trial that included 42 patients with metastatic pancreatic cancer presented to Clinical Oncology Department, Menoufia University through the period from February 2021 to July 2022.

Inclusion criteria: Chemotherapy naïve adult patients aged between 18 and 70 years with metastatic carcinoma of the pancreas with histopathological evidence of adenocarcinoma, with radiological proof of metastatic disease as defined by AJCC [(10)], ECOG performance status (PS) $\leq$ 2 [(11)], with adequate hematologic parameters and normal liver and kidney functions.

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Exclusion criteria: Patients with end stage renal disease who are under regular dialysis, other histologies of pancreatic cancer, non-metastatic irresectable pancreatic cancer.

All patients were subjected to the following: Thorough history taking and clinical examination, CBC, liver and kidney profiles, CEA, CA19-9, CT scan of the chest, abdomen and pelvis with contrast, or PET/CT as well as QLQ-C30 questionnaire Arabic version [12].

We enrolled 48 patients but 6 of them were excluded either due to refusal of completing treatment or early death before assessment of response.

Treatment:

The included patients received Gemcitabine at a dose of 1000 mg/m^2 IV short infusion over 30 minutes, Leucovorin 400 mg/m^2 IV short infusion over 30 minutes, Flourouracil 400 mg/m^2 direct IV shot and Flourouracil 2000 mg/m^2 continuous infusion over 46 hours. The whole regimen was cycled every 2 weeks. This regimen is abbreviated as Flouro-Gem.

The whole protocol was given for a duration of six months for responding patients. Meanwhile, patients with progressive disease were shifted to a second line treatment as per physician's choice.

Filgrastim was not routinely used unless indicated. Toxicities of grade II or III were managed by dose reductions if occurred more than once. However, grade IV toxicity was a clear indication for permanent stopping of this protocol.

Patients who presented with bilirubin level higher than 3 mg/dl were allowed to receive one or two cycles of the protocol without gemcitabine until improvement of bilirubin level. Counting of treatment cycles in these patients started with the use of gemcitabine not with the initiation of treatment.

Evaluation:

All patients had weekly CBC one day before chemotherapy administration and chemistry profile for liver functions (LFT) and kidney functions (KFT) every 2 weeks.

Interim evaluation was done after 2-3 months of treatment with CT scan or PET/CT. We repeated the same investigation that was done in baseline assessment. CEA and CA19-9 were also repeated. Patients who had interim progression were subjected to re-assessment of quality of life (QoL). However, responding patients had QoL reassessed at the end of treatment.

End-of-treatment evaluation was also done by CT scan or PET/CT in addition to tumor markers and QoL assessment.

Response evaluation was done using RECIST criteria version 1.1 [13].

Toxicity was evaluated every cycle including: diarrhea, vomiting, mucositis, neutropenia, anemia, thrombocytopenia, and neuropathy. Toxicity grade was described according to CTCAE version 5 [13].

QoL was assessed for all patients using QoL-C30 at base line and at end of treatment or disease progression whichever earlier. Overall survival (OS) was assessed from the time of diagnosis to death or the final follow-up. PFS was computed from the time of diagnosis to the date of progression or the final follow-up.

Ethical approval: The study protocol was approved by The Research Ethics Committee of Menoufia University {number 1-2021ONCO-5}. Before being enrolled in the trial, all patients gave their informed consents. The trial was conducted according to Declaration of Helsinki. It was registered in ClinicalTrials.gov under the name "A Phase II Trial of Flouro-Gem as a first line treatment of metastatic adenocarcinoma of the pancreas (GEFLUPAN)", NCT04769414.

Statistical analysis

Data were tabulated and analysed using the SPSS programme version 20. The primary endpoint was response rate, with secondary endpoints including toxicity, QoL, and survival (PFS and OS). The chi-square test was performed to investigate the relationship between qualitative factors. For quantitative data (changes in CA19-9, CEA, and QoL), the Kruskall Wallis test (non-parametric t-test) was used to compare three response groups (partial, stable, and progressive). All tests were two-sided, and a P value ≤ 0.05 was deemed statistically significant. The data were shown with 95% confidence ranges. The Kaplan Meier technique was used to determine PFS and OS. QoL analysis was done according to EORTC guidelines [14].

RESULTS

Over the period of one and a half years, we recruited 48 patients for the study. Only 42 patients completed the study and their data were submitted for analysis. Six patients were excluded either due to refusal of completing treatment or early death before assessment of response. The median age of diagnosis was 55 years being more common in males (59.5%) than females (40.5%). The most common site of metastasis was the liver (57.1%). The most common clinical presentations were abdominal pain (30.9%), jaundice (23.8%), vomiting (16.7%) and bony pains (16.7%) (Table 1).

Table (1): Demographic and clinical characteristics of studied patients

Parameter	Studied patients (No.=42)
Age (year)	
Mean ± SD	54.4±7.0
Median (Range)	55 (39 – 65)
Gender	
Male	25 59.5%
Female	17 40.5%
Site of metastasis	
-Bone	16 38.1%
-Liver	24 57.1%
-Brain	1 2.4%
-LN	8 19.0%
-Lung	16 38.1%
Clinical presentation	
-Abdominal pain	13 30.9%
-Bone pain	7 16.7%
-DVT	4 9.5%
-Vomiting	7 16.7%
-Back pain	8 19.0%
-Cord compression	1 2.4%
-Cough	2 4.8%
-Dyspnea	1 2.4%
-Jaundice	10 23.8%
Baseline CEA	
Mean ± SD	143.8±131.7
Median (Range)	105.5 (5 – 516)
Final CEA	
Mean ± SD	216.9±182.5
Median (Range)	225 (4 – 760)
Baseline CA19-9	
Mean ± SD	1129.4±1026.9
Median (Range)	743 (120 – 4500)
Final CA19-9	
Mean ± SD	1570.9±1442.3
Median (Range)	850 (40 – 4900)
Presence of DVT	
Yes	6 14.3%
No	36 85.7%
Number of cycles	
2	1 2.4%
3	4 9.5%
4	9 21.4%
6	28 66.7%
Regularity	
Irregular	3 7.1%
Regular	39 92.9%
Dose density	
50%	1 2.4%
75%	3 7.1%
80%	1 2.4%
100%	37 88.1%

Baseline median CEA was 105.5 ng/ml that increased to 225 ng/ml at the end of treatment. Likewise, baseline median CA19-9 was 743 ng/ml that increased at end of treatment to 850 ng/ml. Deep vein thrombosis was detected in 14.3% of patients at presentation. The treatment protocol was given regularly in 92.9% of patients. The full dose regimen was given to 88.1% of patients meanwhile, 9.5% of patients had dose reductions in the range of 20-25%. One patient only had 50% dose reduction. Regarding the number of cycles, 66.7% of patients completed 6 months of treatment. Toxicity profile showed that neutropenia was the most common form of toxicity being of high grade in 11.9% of patients. Thrombocytopenia had a similar profile as it occurred in a high grade in 11.9% of patients. Other forms of toxicity were minimal not exceeding 5%. Low grade toxicities showed higher numbers with neutropenia being the highest occurring in 78.6% of patients and neuropathy being the least at 9.5% (Table 2).

Table (2): Toxicity profile of studied patients

Parameter	Grades of toxicity among studied patients (No.=42)	
	Low grade (1, 2)	High grade (3, 4)
Diarrhea	20 (47.6%)	2 (4.8%)
Vomiting	13 (31.0%)	2 (4.8%)
Mucositis	14 (33.3%)	1 (2.4%)
Neutropenia	33 (78.6%)	5 (11.9%)
Anemia	10 (23.8%)	1 (2.4%)
Thrombocytopenia	22 (52.4%)	5 (11.9%)
Neuropathy	4 (9.5%)	0 (0.0%)

The overall response rate was 33.3% with no patients achieving complete response. The changes in the levels of tumor markers was a significant factor for response. CA19-9 had more correlation with response than CEA. Median decrease by 70 ng/ml in the level of CA19-9 was associated with partial response, while increases around 51.9 ng/ml was associated with disease progression. Likewise, their level had a significant relation with PFS and OS. The one-year overall survival was 49% while the one year progression free survival was 34.7%. The median overall survival was 11.3 months (95%CI= 10.17-12.45) and the median PFS was 8.8 months (95%CI= 7.3-10.4). Cox regression analysis showed that changes of CEA and CA19.9 were predictors of PFS (P. value=0.01, 0.02 respectively) (Tables 3 & 4 and figure 1)).

Table (3): Response of studied patients after end of treatment

Parameter	Studied patients (No.=42)
Overall response rate (ORR)	**14 33.3%**
-Complete response	0 0.0%
-Partial response	6 14.3%
-Stable disease	8 19.0%
Progressive disease	**28 66.7%**

Table (4): Relation between changes in the levels of tumor markers and response

Parameter	Response after end of treatment among studied patients			Test of significance	P value
	Partial response (No.=6)	Stable disease (No.=8)	Progressive disease (No.=28)		
Change of CEA (%) Median (Range)	34 (18 – 159)	58 (15 – 318)	136 (5 – 516)	Kruskal Wallis test=4.85	0.09
Change of CEA (%) -Decreased	6 100%	7 87.5%	2 7.1%	$\chi 2$ test= 30.10	<0.001*
-Increased	0 0.0%	1 12.5%	26 92.9%		
Change of CA19-9 (%) Median (Range)	70 (51.2 – 80.5)	6.6 (-21.9–35.7)	-51.9 (-448-6.5)	Kruskal Wallis test=24.51	<0.001*
Change of CA19-9 (%) -Decreased	6 100%	4 50.0%	1 3.6%	$\chi 2$ test= 26.67	<0.001*
-Increased	0 0.0%	4 50.0%	27 96.4%		

Median and Range: non parametric test.

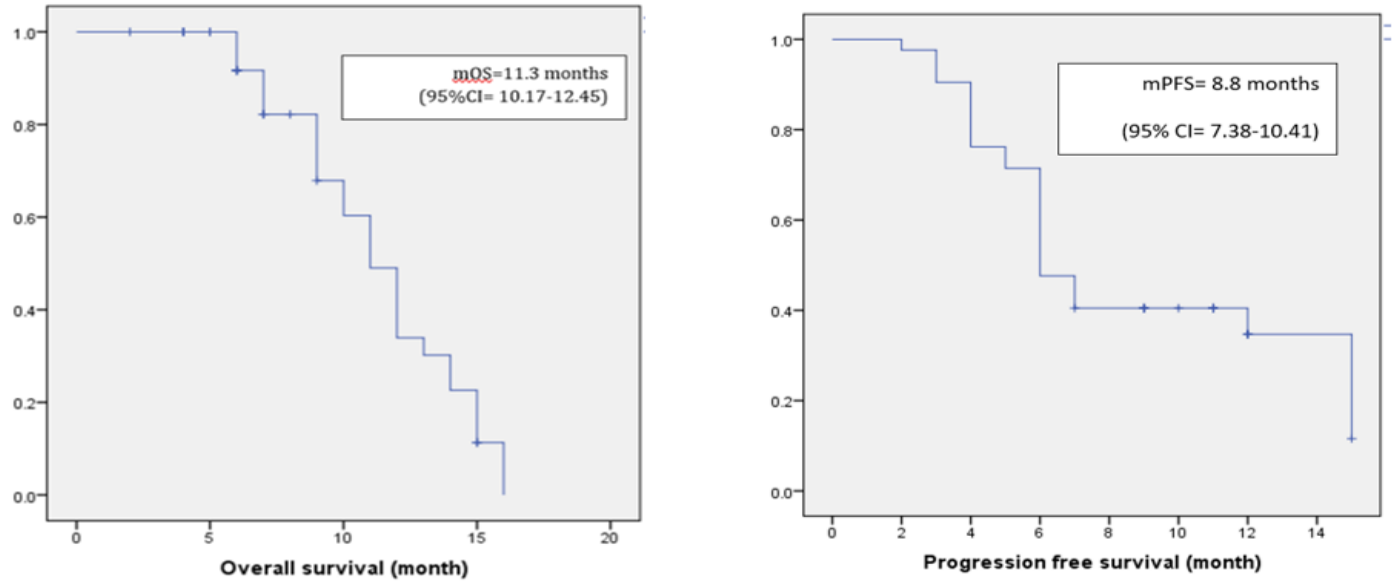

Figure (1): Kaplan Meier curve for overall survival and progression free survival

Global health status improved for responding patients at end of treatment with a median score of 58.3 and 66.7 for partial response and stable disease respectively (Table 5).

Table (5): Association between response and QoL

Parameter	Interim Response among studied patients			Test of significance	P value
	Partial response (No.=15)	Stable disease (No.=13)	Progressive disease (No.=14)		
Before treatment Global health status/QoL Median(Range)	33.3 (0 – 50)	16.7 (0 – 50)	16.7 (0 – 50)	Kruskall Wallis test=4.68 P=0.09	P1=0.13 P2=0.04* P3=0.76
	Response after the end of treatment among studied patients				
	Partial response (No.=6)	**Stable Disease (No.=8)**	**Progressive disease (No.=28)**		
After treatment Global health status/QoL Median(Range)	58.3 (58.3 - 83.3)	66.7 (50 - 83.3)	25 (0 – 58.3)	Kruskall Wallis test=26.99 P<0.001*	P1=0.73 P2<0.001* P3<0.001*

DISCUSSION

In our investigation, we observed a male predominance, with males constituting 59.5% of the patient population. This is in line with the findings of **Oettle *et al.*** [15] who reported a 65.8% male patient population, and **Louvet *et al.*** [16] who found that 64.5% of their patient population were males. A similar trend was also reported by **Oliani *et al.*** [17] where the median age of patients in their study was 55 years, which is slightly lower than the median ages reported by **Oettle *et al.*** [15] and **Oliani *et al.*** [17] (60 years), and **Louvet *et al.*** [16] (61.8 years). This variation could be due to the recruitment of a larger number of younger patients in our study, possibly due to the poorer performance status of older patients. As for the site of metastasis, our study identified the liver as the most common site in 57.1% of cases. This finding is consistent with those of **Louvet *et al.*** [16] and **Oliani *et al.*** [17] who reported a rate of 77.5%,

Our study found that the most frequently reported toxicities were neutropenia and thrombocytopenia. This aligns with the results of **Louvet *et al.*** [16]. However, the incidence of grade 3 and 4 toxicities in our study was lower. Specifically, we observed grade 3 neutropenia in 31.6% of patients and grade 4 neutropenia in 18.4% of patients. Thrombocytopenia of grade 3 was seen in 15.8% of patients, while grade 4 thrombocytopenia was observed in 2.6% of patients. These results were obtained with a 5-FU dosage of 2 gm/m^2.

In this study, Flouro-Gem regimen offered a good alternative option in treating patients with pancreatic adenocarcinoma. This regimen achieved a one-year survival in nearly half of the patients (49%). The median overall survival was 11.3 months, which is better than numbers observed in similar studies by **Oettle *et al.*** [15] (9 months), and **Louvet *et al.*** [16] (8.4 months). Theses 2 trials used gemcitabine fluorouracil, while the last one used the same protocol as our study with the same dose and schedule. This observation is consistent with and comparable to reports from other studies of gemcitabine in combination with 5-FU with or without folinic acid (FA). The median overall survivals for these studies were in the range 5.5-13 months [18-21]. Similarly, the median PFS in this study was better (8.8 months versus 7.1 months). By far, these numbers are better than many regimens that included gemcitabine.

Gemcitabine, both as a standalone treatment and in combination with other agents, has been globally studied for its effectiveness in treating pancreatic cancer. Phase III studies have demonstrated its efficacy, with a one-year overall survival rate of 18-20% and a median overall survival of approximately 6 months [22]. The combination of nab-paclitaxel and gemcitabine has shown improved overall survival, extending from 6.7 months to 8.5 months. These figures reached their peak in a Swedish study, which reported a median overall survival of 10.9 months [23, 24].

The response rates were variable among trials ranging from 9 to 31%. In this study, the overall response rate was 33.3% which is very comparable to FOLFIRINOX which was 34.1%. However, the toxicity profile and safety were much better with Flouro-Gem. Neutropenia was the most frequent high grade toxicity being 11.9% versus 45% seen with FOLFIRINOX in some studies [9].

Our results showed that no complete response (0%) was observed in this metastatic setting. This finding is also seen in other studies conducted on metastatic pancreatic cancer [15].

Similar to this study, gemcitabine in combination with cisplatin has demonstrated evidence of increased efficacy compared to gemcitabine alone, with response rates ranging from 11.5% to 36.4% [25]. However, in all of these studies, the patients required hydration, and the treatment was linked to significant nephrotoxicity, alopecia, and haematological toxicity, which are not present in this study. Also this study was more tolerable than gemcitabine-docetaxel, which was associated with significant haematological toxicity [26].

Quality of life (QoL) has improved in patients responding to Flouro-Gem. The global health status scored 33.3 at interim evaluation and increased to 58 at end of treatment for patients with partial response. Interestingly, patients who had disease progression experienced numerical improvement in their QoL scores despite being non-statistically significant. This - at least- showed that this regimen is tolerable and does not impair the QoL. This result is consistent with **Oettle *et al.*** [15]**,** who showed that ≥ seventy-nine percent of patients showed a stabilization if not an improvement in their karnofosky performance status (KPS), and mild toxicity profile.

On the contrary, FOLFIRINOX has resulted in impaired QoL when compared with gemcitabine single agent. 31% of patients had decreased global health status scale. However, in the same study 66% of patients in the gemcitabine arm had experienced decline in the QoL; a finding, which is not observed in our study [9].

CONCLUSION

Flouro-Gem was a well-tolerated acceptable option for the first line treatment of metastatic pancreatic cancer with comparable results to other more toxic regimens and better outcomes than single agent protocols.

Declaration of interest: All authors declare no conflict of interest.

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LIST OF ABBREVIATIONS

5FU: 5 flourouracil
AJCC: American joint committee on cancer
CA19-9: Cancer antigen 19-9
CBC: Complete blood count
CEA: Carcinoembryonic antigen
CT: Computed tomography
CTCAE: Common terminology criteria for adverse events

DVT: Deep vein thrombosis
ECOG: Eastern co-operative oncology group
EORTC: European organization for research and treatment of cancer
IV: Intravenous
KFT: Kidney function test
LFT: Liver function test
ORR: Overall response rate
OS: Overall survival
PET/CT: Positron emission tomography/computed tomography
PFS: Progression free survival
QoL: Quality of life
RECIST: Response evaluation criteria in solid tumors
SD: Standard deviation

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