RESEARCH ARTICLE

Progression-free Survival of Advanced Pancreatic Cancer in Iraqi Patients Treated with First-line Chemotherapy

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ABSTRACT

Background: Pancreatic cancer is a highly aggressive cancer. According to the latest data published by the World Health Organization, the number of new cases in 2020 in Iraq was 674 and represented 2% of all new cancer cases. Most of the pancreatic adenocarcinomas have spread outside the pancreas at the time of diagnosis. Progression free survival is the time between the date of diagnosis to disease progression or death. The current study aims to compare progression free survival between three chemotherapy regimens; Gemcitabine, Gemcitabine/Nab-paclitaxel and FOLFIRINOX of advanced and metastatic pancreatic cancer in Iraqi patients.

Methods: Patients were divided into three groups; patients who will receive Gemcitabine, those who will receive Gemcitabine/Nab-paclitaxel, and patients who will receive FOLFIRINOX. The patients were observed for disease progression by computed tomography which was performed every three months for the tumor response and progression.

Results: In the Gemcitabine, Gemcitabine/Nab-paclitaxel, and FOLFIRINOX groups, the median Progression Free Survivals were (4, 5, and 5.7 months, respectively; $p < 0.05$), where FOLFIRINOX was superior to Gemcitabine monotherapy and Gemcitabine/Nab-paclitaxel. In addition, neutropenia, febrile neutropenia, diarrhoea, nausea, vomiting, fatigue, hypokalaemia and neuropathy were highly in the FOLFIRINOX-treated patients than in both Gemcitabine and Gemcitabine/Nab-paclitaxel groups of patients. However, anaemia and thrombocytopenia were higher with Gemcitabine and Gemcitabine/Nab-paclitaxel than were with FOLFIRINOX.

Conclusion: The median Progression free survival is better for the Gemcitabine/Nab-paclitaxel and FOLFIRNOX than for Gemcitabine alone. Also, adverse effects are more common with FOLFIRINOX than with other first-line chemotherapeutic agents.

Keywords: FOLFIRINOX, Gemcitabine, Gemcitabine/Nab-paclitaxel, Progression-free survival, Pancreatic carcinoma.

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INTRODUCTION

Pancreatic cancer (PC) is a highly aggressive with poor prognosis cancer.[1,2] About 80% of patients are diagnosed with advanced cancer, and mortality is high since the tumor infiltrates the abdominal blood vessels and spreads early to regional lymph nodes and the liver.[3] The one- and five-year overall survival (OS) rates are 26% and 5%, respectively.[4] In addition, in most cases, most of the PC has spread outside the pancreas at the time of diagnosis, and nodal metastases are common. About 60–70% of pancreatic adenocarcinomas occur in the head of the pancreas, with the rest found in the body and tail.[5] Also, pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms (MCN) are the three well-studied precursors of this cancer.

Alcohol consumption increases the risk of PC, but there is no association between low-to-moderate alcohol intake and PC.[6] In addition, tobacco smoking is associated with an estimated 26.2% and 31.0%of all pancreatic cancers in men and women, respectively.[2] Also, an individual's risk of PC grows exponentially if they have a parent, sibling, or child with the disease.[5,7]

The role of H pylori infection in the development of PC was controversial as some previous studies found an association between them while others did not.[1,2] Moreover, patients with blood group O have an elevated risk of developing

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pancreatic adenocarcinoma compared to patients with blood group A.[7]

Furthermore, previous studies revealed that patients who recentlydeveloped diabetes and lost weight are at a higher risk for PC.[8,9]

Typically, pancreatic cancer is not diagnosed for several months after the initial presentation of vague abdominal symptoms or back pain. A CT scan, magnetic resonance imaging (MRI), and ultrasound are most commonly used for diagnosis. When these standard procedures of imaging reveal that the tumor is a non-resectable with pathological or cytological neoplastic features, verification must be carried out before oncological treatment can be started properly.[5,10]

The time to objective tumor progression is known as time to progression (TTP). The latter does not encompass deaths. Deaths are censored in the study concerning the endpoint of TTP and are not included in the time value. Moreover, regulatory authorities prefer progression-free survival (PFS) to TTP for drug approval since PFS might be best associated with overall survival (OS).[11]

Progression-free survival (PFS) is the time between randomization and date of extension (detection), to disease progression or death.[12]

The concept PFS was initially developed to measure the "signal of activity" in early drug development. In randomized clinical trials (RCTs), the appeal of the use of PFS illustrates OS-related drawbacks, including higher prices, longer follow-up, broader sample sizes, and conflicting results resulting from crossover designs and subsequent post-progression therapies.

There are only two possible explanations for PFS as endpoint; the first interpretation is the assumption that PFS is a legitimate overall survival surrogate marker. The second is the expectation that even without prolonged survival, patients living without disease progression would have a better quality of life.[13]

The potential of PFS as a surrogate endpoint for survival sparked the initial interest in it as a clinical benefit measure. PFS is a valid substitute for OS in first-line therapy, but the relationship is less clear for second-line and subsequent treatments. In addition, besides total survival, the patient needs to be examined in addition to the effects such as enhanced quality of life QoL, complication delay, and symptom relief.[12]

The endpoint most used to replace OS in advanced solid tumors is PFS. The latter, approved by regulatory authorities in the US and Europe, is superior to TTP, an endpoint for which the study censors' patients who die without previous reports of disease progression.[14]

Moreover, an intermediate endpoint, such as PFS, may allow new anti-neoplastic agents to be more effectively tested by minimizing time and costs associated with the design of randomized trials.[15]

On the other hand, advanced and metastatic pancreatic cancer treatment aims at palliation and improved survival. In the early stages of advanced pancreatic cancer, systemic chemotherapy is recommended and is expected to prolong survival; chemotherapy may be administered as a single agent or in combination.[16] Also, surgery, radiation therapy, concurrent or sequential chemoradiation, and targeted therapy are standard treatments[4] However, many factors are involved in choosing first-line treatment in metastatic pancreatic cancer (mPAC).[4] FOLFIRINOX (FFX) and Gemcitabine (Gem) with Nab-paclitaxel (GNP) have been widely used as first-line chemotherapy treatment for metastatic pancreatic cancer since their approval in 2010. The outcomes in mPC patients were about the same regarding efficacy and toxicity in FFX and GNP. Despite having a better chance of receiving second-line chemotherapy, the GNP group OS was not improved.[17]

Given the importance, prevalence and poor prognosis of PC as well as the adverse effects associated with its chemotherapy, current study was conducted to assess and compare progression-free survival among three regimens (Gemcitabine, Gemcitabine/Nab-paclitaxel, and FOLFIRINOX) of first-line chemotherapy treatment of locally advanced and metastatic pancreatic cancer with evaluation of their adverse effects, in Iraqi patients.

METHODS

Study Design

This study was a prospective cohort study conducted at two medical centers of oncology at Baghdad Medical City (Oncology Teaching Hospital and Al-Amal National Hospital for Oncology) during the period from September 2020 to June 2021. The endpoint was progression-free survival (PFS) of Gemcitabine, Gemcitabine/Nab-paclitaxel, and FOLFIRINOX treatments.

Ethical Consideration

Ethical clearance was obtained from the Research Ethics Committees at Baghdad College of Medicine and Medical City, Baghdad. Iraq.

Patients' Selection Criteria and Grouping

Patients who were included in the study were those had pancreatic carcinoma confirmed by histopathology or cytology and had staging imaging modalities by CT scans to show the extent of advances and metastasis stage III pancreatic adenocarcinoma with reported extra-pancreatic metastases; those with locally advanced unresectable disease; patients aged 18–80 years; patients with a performance status (PS) of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) ; did not receive any chemotherapy previously; those with adequate haematological function (haemoglobin ≥9g/dL; neutrophils count ≥500/mm^3; platelets count ≥100,000/mm^3), renal function (serum creatinine ≤2.0 mg/dL), hepatic function (bilirubin ≤ 2.0 mg/dL).

Patients who were excluded from the study were those with no local advances or metastasis, poorly controlled comorbid conditions, liver or renal failure, other cancer (s), severe heart disease as well as breastfeeding and pregnant women. Patients with haematological abnormalities such as thrombocytopenia, anaemia, and neutropenia were also excluded.

Patient included in current study were grouped into three different groups; patients who will receive Gemcitabine alone, those who will receive Gemcitabine/Nab-paclitaxel, and patients who will receive FOLFIRINOX.

Assessments of Patients

At the beginning of each treatment cycle, patient's status was determined based on his/her medical history, a detailed review by a doctor, ECOG performance status, blood counts and chemical tests of blood. Also, serum carbohydrate antigen 19-9 test and computed tomography were performed for patients.

Treatment Regimens

Gemcitabine (GEM) was taken weekly for 3 weeks out of a 4-weeks cycle at a dose of 1000 mg/m^2 as a 30 minutes intravenous infusion. The doctor's decision usually modifies the dosage and frequency of GEM according to grade 3/4 toxicity. In the majority of patients, GEM for all grade 3 toxicities was reduced by 20%. In addition, 8mg ondansetron and 8mg dexamethasone were administered before chemical therapy to avoid chemotherapy induced nausea and vomiting (CINV) if necessary. Associated neutropenia was treated with granulocyte colony-stimulating factor (GCS-F).

Gemcitabine with Nab-paclitaxel (GNP): The Nab-paclitaxel was administered at a dose of 125 mg/m^2 for 30 minutes, followed by gemcitabine at dose of 1-g/m^2 for 30 minutes on days 1, 8, and 15. Cycles of treatment were repeated every four weeks until tumor progression or toxicity has become intolerable.

In addition, 8 mg ondansetron and 8mg dexamethasone were administered before chemical therapy to avoid chemotherapy induced nausea and vomiting (CINV) if necessary. Associated neutropenia was treated with granulocyte colony-stimulating factor (GCS-F).

FOLFIRINOX (FFX): The intravenous infusion consisted of 85 mg/m^2 oxaliplatin and was dissolved in 5% dextrose, preceded by 180 mg/m^2 irinotecan and 500 mL dextrose, infused over 90 minutes, or normal saline over 1-hour after oxaliplatin infusion. Following the irinotecan infusion, a simplified leucovorin/5-fluorouracil (LV/5-FU) regimen was administered as follows: LV 400 mg/m^2 for 2 hours, followed by FU 400 mg/m^2 for bolus and FU 2, 400 mg/m^2 for a 46-hours continuous infusion.

Also, 8mg ondansetron, 9.9 mg dexamethasone, and 125 mg aprepitant were given to all patients before chemotherapy, followed by 80 mg aprepitant within two days for prevention of chemotherapy-induced nausea and vomiting. Cycles of therapy were repeated every two weeks before the progression of tumors or intolerable toxicity.

Duration of Treatment and Follow-up

Treatment was stopped according to physician's discretion due to unacceptable toxicity, disease progression, or the introduction of alternative therapies. On follow-up, the patients were observed for disease progression-free survival. A computed tomography or magnetic resonance imaging was performed every three months for the tumor response and progression. Clinicians and independent radiological assessments using RECIST version 1.0 did analyze the scans. Baseline assessment of CA19-9 was performed every three months.

Statistical Analysis

Statistical analysis was performed using SPSS statistical package (Version 20.0; SPSS Inc. Chicago, IL, USA). For baseline characteristics and safety evaluation by data type, descriptive statistics were used. The period from first dose of the study drugs to disease progression or death from cancer, was estimated as progression-free survival. For a progression-free survival study, the Kaplan–Meier approach had been used. The statistically significant $p < 0.05$ was identified.

RESULTS

Patients' Characteristics

Current study was conducted from September 2020 to June 2021. Sixty patients, confirmed with stages III and IV pancreatic carcinoma (PC), were enrolled. All patients did not receive chemotherapy previously. Three first-line chemotherapies were given to three groups of patients; 31 received GEM, 11 received GNP and 18 received FFX. Characteristics of patients enrolled in current study were presented in Table 1. Moreover, the advances of the tumor to

Table 1: Patients' characteristics

Age (years)	
Mean	57.25
Median	58
Range	62
Sex	*No. (%)*
Male	44 (73.3)
Female	16 (26.7)
ECOG PS	*No. (%)*
0	31 (51.7)
1	26 (43.3)
2	3 (5)
Body surface area (BSA)	*m^2*
Mean	1.595
Median	1.600
Range	0.6
Family history of cancer	*No. (%)*
Family history of ca pancreas	0 (0)
Family history of another ca	5 (8.3)
No family history of ca	55 (91.7)
History of smoking	*No. (%)*
Patients who are smoking	18 (30)
Patients with no smoking history	42 (70)
Alcoholism	*No. (%)*
Patients with a history of alcoholism	6 (10)
Patients with no history of alcoholism	54 (90)
CA19-9 at baseline	*u/mL*
Mean	487.72
Median	230
Range	3222

lymph nodes, metastasis to body organs, and histopathological grades of tumor were summarized in Table 2.

Progression-free Survival

The results concerning progression-free survival (PFS) obtained from current study will be presented under the respective treatment regimens.

Gemcitabine (GEM)

For 31 patients who received GEM, the mean PFS in months was 3.5. The median PFS was 4 months. Moreove, Seven patients were with locally advanced PC; the mean PFS was 3.286 months and the median PFS was 3 months. In addition, for the 22 patients with metastasis PC, the mean PFS was 3.6 months. The p-value by log-rank (Mantel-Cox) test for significant difference between advanced and metastatic PC was >0.05. Data for 29 patients (two were lost from follow-up) were presented in Table 3 and Figure 1.

Gemcitabine/Nab-paclitaxel (GNP)

For 11 patients who received the GNP regimen, the mean PFS was 5.3 months and the median PFS was 5 months for the three patients with locally advanced PC, the mean PFS was 5.6 months and the median PFS was 7 months. For eight patients with metastasis PC, the mean PFS was 5 months and the median PFS was 4.9 months. The P-value for significant difference between locally advanced and metastatic PC by log-rank (Mantel-Cox) was >0.05 (Table 4 and Figure 2).

FOLFIRINOX (FFX)

For 18 patients who received the FFX regimen, the mean PFS was 5.176 months and the median PFS was 5.7 months. For five patients with locally advanced PC, the mean PFS was 4.6 months and the median PFS was 4 months. For 12 patients with metastasis, the mean PFS was 5.417 months and the median PFS was 5.7 months.

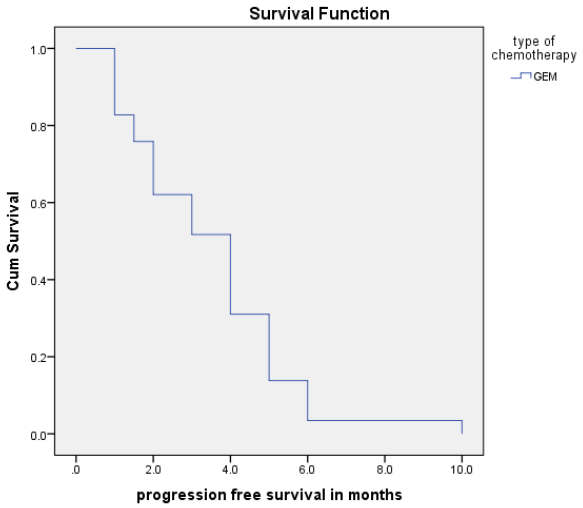

Figure 1: Progression-free survival in months for Gemcitabine in locally advanced and metastatic PC by Kaplan Meier method.

Table 2: Sites of metastasis and histopathological tumor grades

Advanced and metastatic sites	*No. (%)*
Lymph node	15 (25)
Liver	31 (51.6)
Lung	1 (1.7)
Bone	1 (1.7)
Peritoneum	2 (3.3)
Two or more metastatic sites	10 (16.7)
Tumor grade	*No. (%)*
Grade 1	5 (8.3)
Grade 2	12 (20)
Grade 3	43 (71.7)

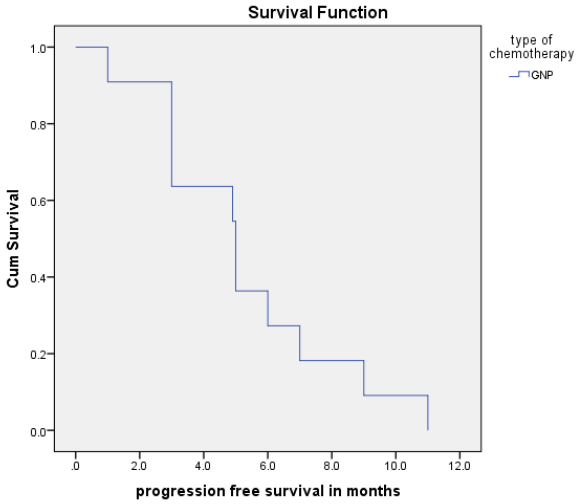

Figure 2: Progression-free survival in months for Gemcitabine/Nab-paclitaxel in locally advanced and metastatic PC by Kaplan Meier method.

Table 3: Survival Results for Treatment with Gemcitabine

Type of chemotherapy	*No. of valid cases/ (PFS)*	*Cumulative proportion surviving at the time*	
		Estimate	*St. error*
Gemcitabine	6 (1)	0.793	0.075
	1 (1.5)	0.759	0.079
	4 (2)	0.621	0.090
	3 (3)	0.517	0.093
	6 (4)	0.310	0.086
	5 (5)	0. 138	0.064
	3 (6)	0.034	0.034
	1 (10)	0.000	0.000

Table 4: Survival results for treatment with Gemcitabine/Nab-paclitaxel

Type of chemotherapy	*No. of valid cases/ (PFS)*	*Cumulative proportion surviving at the time*	
		Estimate	*St. error*
Gemcitabine/Nab-Paclitaxel	1 (1)	0.909	0.087
	3 (3)	0.636	0.145
	1 (4.9)	0.273	0.134
	2 (5)	0.364	0.145
	1 (6)	0.273	0.116
	1 (7)	0.182	0.116
	1 (9)	0.091	0.087
	1 (11)	0.000	0.000

The p-value for significant difference between locally advanced and metastatic by log-rank (Mantel-Cox) was >0.05. Data for 17 patients (one was lost from follow-up) were presented in Table 5 and Figure 3.

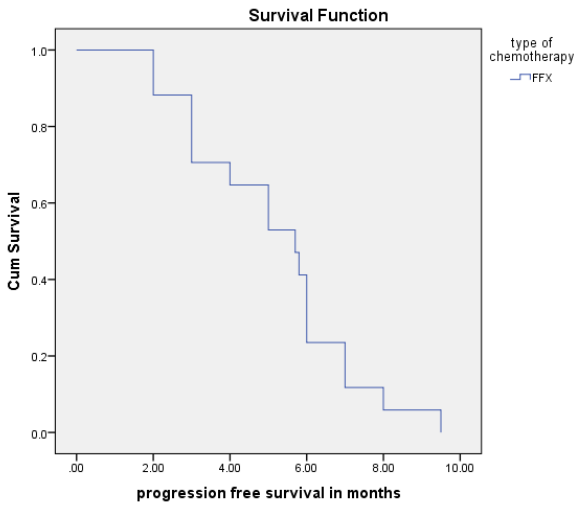

Figure 3: Progression-free survival in months for FOLFIRINOX in locally advanced and metastatic PC by Kaplan Meier.

Table 5: Survival results for treatment by FOLFIRINOX

Type of chemotherapy	*No. of valid cases/ (PFS)*	*Cumulative proportion surviving at the time*	
		Estimate	*St. error*
FOLFIRINOX	2 (2)	0.882	0.078
	3 (3)	0.706	0.111
	1 (4)	0.647	0.116
	2 (5)	0.529	0.121
	1 (5.7)	0.471	0.121
	1 (5.8)	0.412	0.119
	3 (6)	0.235	0.103
	2 (7)	0.118	0.078
	1 (8)	0.059	0.057
	1 (9.5)	0.000	0.000

3.3 Comparison Between Chemotherapy Regimens.

The P-values for significant difference between the three first-line chemotherapies were<0.05, by using three statistical tests of survival log-rank (Mental-Cox), Breslow (Generalized Wilcoxon), and (Tarone-Wave), they were 0.042,0.022 and 0.023, respectively. The mean, median, standard error and confidence interval were summarized in Tables 6 and 7.

Moreover, the progression-free survival times for the three treatment regimens were merged in Figure 4.

Adverse Events

The most common haematological and non-haematological adverse events and toxicities of chemotherapy of grade 3 or more were reported during follow-up and assessment, were summarized in Tables 3 and 4.

DISCUSSION

Patients' Demographic Characteristics

The mean and range of age of our participants (Table 1) were compatible with data suggesting that the most suspected age of PC appearing during the fifth and sixth decade of life.[1,2]

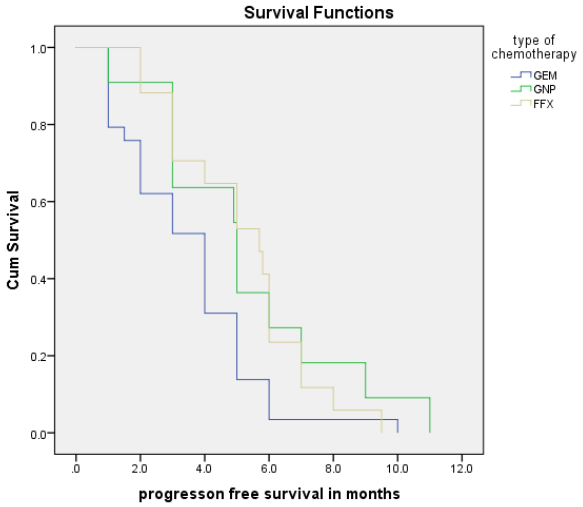

Figure 4: Progression-free survival for three treatment regimens.

Table 6: Estimated mean progression-free survival for the three treatment regimens (Gem, GNP and FFX)

Mean				
			95% confidence interval	
Type of chemotherapy	*Estimate*	*Std. error*	*Lower bound*	*Upper bound*
Gemcitabine	3.5	0.392	2.731	4.269
Gemcitabine/Nab-paclitaxel	5.264	0.875	3.548	6.979
FOLFIRINOX	5.176	0.514	4.169	6.184

Table 7: Estimated median progression-free survival for the three treatment regimens (Gem, GNP, and FFX)

Median				
Type of chemotherapy	*Estimate*	*Std. error*	*95% confidence interval*	
			Lower bound	*Upper bound*
Gemcitabine	4.00	0.554	2.915	5.085
Gemcitabine/Nab-paclitaxel	5.00	1.064	2.915	7.085
Folfirinox	5.70	0.926	3.885	7.515

Table 8: Significant grade 3 or more haematological adverse events related to the three treatments regimens

	Gemcitabine	*Gemcitabine/Nab-paclitaxel*	*FOLFIRINOX*
Adverse events	*% of patients*	*% of patients*	*% of patients*
Neutropenia	35	40	45
Febrile neutropenia	2	3	5
Anaemia	50	50	40
Thrombocytopenia	50	55	40
Hypokalaemia	5	7	10

Table 9: Significant grade 3 or more non-haematological adverse events related to the three treatment regimens

	Gemcitabine	*Gemcitabine/Nab-paclitaxel*	*FOLFIRINOX*
Adverse events	*% of patients*	*% of patients*	*% of patients*
Nausea	2	15	35
Vomiting	0	10	30
Diarrhoea	0	5	45
Fatigue	5	15	25
Neuropathy	5	10	30
Dehydration	5	8	25

In addition, our data revealed that the most cases diagnosed with PC were males. Also, previous studies revealed that genetic factors, smoking and alcohol consumption are suspected to have a role in this higher incidence of PC in males than in females.[7]

In terms of Performance Status (PS), current results showed that the majority of our subjects had PS between 0 and 1 (Table 1), These data were compatible with the ASCO guidelines recommend that the first line treatment of PC in patients with PS of 0-1 is FFX and GNP, and with single agent (GEM) in those with PS not more than 2.[18]

Furthermore, data from current study showed that 6% of patients were with history of alcohol consumption and 30% of them were with history of smoking (Table 1). The consumption of alcohol is of importance in PC development as it is established to be associated with PC by the International Agency for Research on Cancer.[6,19]

CA 19-9 Level

The serum level of CA 19-9was low or normal in some participants while others had high serum CA19-9 level (Table 1). However, CA19-9 is a potential complement for diagnosis and monitoring of PC.[20]

Treatment

Many randomized trials have been conducted to see whether GEM combined with different cytotoxic or selective agents could improve patient outcomes with LA/MPC, in some of these trials, median OS and one-year survival rates had increased. However, it is still uncertain if Gemcitabine-based combinations are better than Gemcitabine monotherapy.[21]

There is a great discussion about the option of the proper first-line treatment after the introduction of GNP and FFX plans for the treatment of advanced PC.[4]

Data on the effectiveness and safety of double and triple chemotherapy for older adults with advanced PC are currently limited. Since older patients oftenpresent with comorbidities, monotherapy or best supportive treatment is usually favoured in routine clinical care.[22]

A result by MPACT trials which used GEM monotherapy as a control arm, found that Nab-paclitaxel plus Gemcitabine (gemcitabine-based regimen) and FOLFIRINOX (gemcitabine-free regimen) improved OS compared to gemcitabine monotherapy, thus expanding the first-line treatment choices.[23]

Progression Free Survival Endpoint

According to our study of three different agents, Gem, GNP, and FFX, there was an improvement in PFS (4, 5 and 5.7 months, respectively; $p < 0.05$), where GNP combination was superior to Gem alone and FFX was superior to Gem monotherapy and Gem combination. As a result, the FFX and GNP regimes were superior to Gem alone. On the other hand, FFX was superior to GNP with more improvement compared to Gem alone. Moreover, the three patients who died (two on GEM and one on GNP) had complications of metastasis on liver function and consequently liver failure.

In our prospective study, PFS in locally advanced PC (LAPC) advanced and metastatic unresectable pancreatic cancer (MPC), Gem monotherapy, GNP combination, and FFX regimen, produced no significant difference in PFS for LAPC and MPC patients ($p > 0.05$).

Previous data concluded that the combination of GNP had improved median PFS for patients with metastatic PC compared to Gem alone.[22,24]

Moreover, for metastatic pancreatic cancer, FFX and GNP regimens had an excellent prognosis than GEM monotherapy.[25]

Furthermore, another study showed significantly higher PFS related to Gem-based combination compared to gemcitabine monotherapy.[21] These findings were consistent with results of our study.

Adverse Events of Chemotherapy

Data from current study reported a variety of haematological and non-haematological adverse effects associated with the use of treatment regimens in question (Tables 8 and 9). These data were consistent with those reported by previous studies even though these studies, including current one, had recruited different numbers of patients.[4,26]

CONCLUSION

The median PFS for the GNP group and FFX are better than is for GEM alone but may need more supportive care for suspected toxicity, especially in FFX. Also, FFX requires good monitoring for administration infusion to avoid local and systemic rapid infusion toxicity, and it needs a central infusion venous line.

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