

Efficacy of Chemotherapy for Locally Advanced and Metastatic Pancreatic Cancer: A Real-life Experience and Outcome from a Tertiary Care Centre

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Abstract

Introduction: To report response rates, progression-free survival (PFS) and overall survival (OS) in patients with advanced pancreatic cancer treated with different available chemotherapeutic regimens over 10 years. **Materials and Methods:** This is a retrospective observational study. All patients with locally advanced and metastatic pancreatic cancer (MPC) at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, from January 2008 to December 2017 were studied. Data were collected from the hospital information system. The characteristics and outcomes of all the patients were analysed. PFS and OS were also estimated. Kaplan-Meier curves and log-rank test were applied, and SPSS version 20 was used for data analysis. **Results:** Eighty-seven subjects with a median age of 56 years (range 21-76) were included. Sixty-two (71%) subjects were male. The most common tumour location was the head of the pancreas in 46 (53%) of all the subjects. Sixty-three (72%) subjects had elevated carbohydrate antigen-19.9 values. About 47 (54%) subjects had locally advanced pancreatic cancer (LAPC), and 40 (46%) subjects had MPC. Chemotherapy regimens used were FOLFIRINOX in 23 (26%), gemcitabine (GEM) based in 66 (65%) and capecitabine (CAP) based in 8 (9%) of the subjects. One (1%) subject had a complete response, 12 (14%) had a partial response, 10 (11%) had stable disease and 59 (68%) of the subjects had progressive disease. The objective response rate (ORR) was 15% and the disease control rate (DCR) was 26%. In MPC, the ORR was 10%, DCR was 18% and tumour progression was seen in 72% of the patients, while in LAPC, the ORR was 19.1, DCR 34% and tumour progression was documented in 64% of the patients, respectively. The FOLFIRINOX chemotherapy regimen had better ORR, DCR and lesser number of progressions as compared to GEM- and CAP-based chemotherapy regimens. The median PFS of the whole group was 32 weeks, and the median OS was 54 weeks. The PFS was significantly higher for LAPC (39 weeks) as compared to the MPC group (25 weeks)

($P = 0.028$). There was no statistically significant difference between the OS of these two groups ($P = 0.451$). In addition, PFS was significantly higher with FOLFIRINOX chemotherapy as compared to the other chemotherapy regimens. Regarding OS, there was no statistically significant difference among all chemotherapy regimen groups ($P = 0.267$). **Conclusion:** Based on our results, FOLFIRINOX remained the most effective chemotherapy regimen despite the dose modifications and toxicities in all groups, indicating that modified FOLFIRINOX could be considered as a first-line regimen in Southeast Asian population.

Key words: 5-fluorouracil, cancer, capecitabine, chemotherapy, gemcitabine, pancreatic cancer, response rate, survival

Introduction

Pancreatic ductal adenocarcinoma is one of the most typical gastrointestinal tract malignancies associated with dismal prognosis and an increasing impact on cancer-related mortality and one of the top five causes of cancer death worldwide despite being only the 11th most common cancer overall.^[1-3]

Pancreatic cancer is clinically classified into three stages: Resectable, locally advanced and metastatic disease. The treatment strategy differs by the clinical stage, and it is important to determine the clinical stage in each pancreatic cancer patient to select the most appropriate treatment method.^[4]

It usually arises in elderly patients with a mean age at onset of 71 years for men and 75 years for women with roughly equal incidence for both sexes. The clinical course of pancreatic cancer usually is aggressive, with a high symptom burden and potential for a substantial deterioration in the quality of life. The red flag symptoms prompting diagnosis appear only once the disease has already progressed or metastasised; thus, only 10-20% of pancreatic cancers are resectable at the time of presentation.^[5-7]

The majority of patients present with advanced pancreatic cancers (locally advanced pancreatic cancer [LAPC] or metastatic pancreatic cancer [MPC]) have a very poor prognosis. The median overall survival (OS) is estimated to be 3-8 months. Moreover, the 5-year survival is around 1-3%, and the median life expectancy is approximately one year with current treatments.^[6,8]

A few years back, the only chemotherapy shown to provide a modest survival benefit had been gemcitabine (GEM), which improved median OS from 4.4 to 5.6 months compared to fluorouracil in a Phase III study.^[9] Attempts at improving survival with the combination of GEM and a variety of cytotoxic and molecularly targeted agents have failed to provide substantial additional benefit apart from the addition of erlotinib to GEM which was the only combination to provide a modest additional survival benefit of 6% at 1 year, resulting in an FDA approval for this agent.^[1,10-12]

In May 2011, Conroy *et al.* published the trial results on FOLFIRINOX as the first regimen to improve the median OS of patients with MPC beyond 10 months. This landmark trial was based on results of the initial Phase-II trial by Conroy *et al.* in 2005, which confirmed the efficacy of FOLFIRINOX with promising response rates and a good safety profile.^[13-15]

This study analysed the response rates in patients with advanced pancreatic cancer treated with different available chemotherapeutic regimens over 10 years. Furthermore, progression-free survival (PFS) and OS were calculated.

Methods

This retrospective study was done in a tertiary-level cancer hospital, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. A total of 104 patients were registered with a proven diagnosis of advanced pancreatic cancer (both LAPC and MPC) from January

2008 to December 2017. Inclusion criteria were histopathological diagnosis of advanced pancreatic cancer, age above 18 years and receipt of chemotherapy. Patients lost to follow-up before treatment completion were excluded from the analysis because their survival intervals were not available. The study protocols were reviewed by the Institutional Review Board of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and exemption was taken for informed consent as no direct interaction with patients was involved (EX-17-02-17-15).

The cancer diagnosis was made according to standard guidelines.^[16] Patient characteristics such as age, gender, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), pancreatic tumour location, the extent of disease, level of carbohydrate antigen (CA) - 19.9 and computed tomography scan results (before and after treatment) were analysed. Types of chemotherapy regimen were also recorded. The objective tumour responses included complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD). The objective response rate (ORR) was defined as the ratio between the number of patients achieving objective response (complete or PR) and the total number of patients in the study regardless of the number of patients that underwent disease response evaluation. Likewise, disease control rate (DCR) was defined as the ratio between the number of patients achieving disease control (CR, PR and SD) and the total number of patients in the study, regardless of the number of patients that underwent disease response evaluation. All of these evaluations were done using the standard RECIST criteria.^[17]

PFS was defined as the duration from the start of treatment to disease progression or death, whichever occurred first. OS was defined as the time interval from enrolment of the patient in the hospital to death from any cause or to last clinical follow-up.

Distributions were determined as frequencies and percentages for categorical variables. For continuous

variables, mean, median, standard deviation and range were computed. The primary efficacy variable was OS, and the secondary endpoints of the study were tumour response and PFS.

Log-rank test and Kaplan-Meier estimations were performed for both PFS and OS. Response rates were calculated. Chi-square and Fisher exact tests, when suitable, were used to compare qualitative data. The difference was assumed to be significant when $P \leq 0.05$ and all tests were two sided. The analysis was conducted using SPSS version 20.

Results

A total of 104 patients were identified. However, 17 patients were excluded from the analysis because they had left the treatment before completion.

Eighty-seven patients met the inclusion criteria and were included in the analysis. Among the 87 subjects included in the analysis, 62 (71%) subjects were male, and 25 (29%) were female. The median age was 56 ± 12.03 years (range 21-76 years). The ECOG-PS was 0, 1 and 2 in 24 (28%), 50 (57%) and 13 (15%) subjects, respectively. The most common tumour location was the head of the pancreas in 46 (53%) subjects. Twenty-four (28%) subjects had normal CA - 19.9 values and it was elevated in 63 (72%) subjects. Forty-seven (54%) subjects had LAPC, and 40 (46%) subjects had MPC. Chemotherapy regimens used were FOLFIRINOX in 23 (26%), GEM based in 66 (65%) and capecitabine (CAP) based in 8 (9%) of the subjects [Table 1].

One (1%) subject had a CR, 12 (14%) had a PR, 10 (11%) had SD and 59 (68%) of the subjects had PD. The ORR was 15%, and the DCR was 26%. In contrast, the response could not be evaluated in 5 (6%) of the subjects due to various reasons, including complications during treatment leading to referral to best supportive care or death. In MPC, the ORR was 10%, DCR was 18% and tumour progression was seen in 72% of the subjects, while in LAPC, the ORR was 19.1, DCR 34% and

Table 1: This table shows the baseline characteristics and chemotherapy regimens

Characteristics	Category	Number (%)
Age (years)		56±12.03 (median)
Gender	Male	62 (71)
	Female	25 (29)
ECOG-PS	0	24 (28)
	1	50 (57)
	2	13 (15)
Pancreatic tumour location	Head	46 (53)
	Body	10 (12)
	Tail	2 (2)
	Neck	3 (3)
	Uncinate	2 (2)
	Periampullary	6 (7)
	Others	18 (21)
CA 19.9 (units/ml)	Normal	
	Low <59×ULN	35 (40)
	Elevated ≥59×ULN	28 (32)
Extent of disease	Locally advanced	47 (54)
	Metastatic	40 (46)
Chemotherapy regimens	FOLFIRINOX based	23 (26)
	GEM based	56 (65)
	CAP based	8 (9)

ECOG-PS: Eastern Cooperative Oncology Group-Performance status, ULN: Upper limit of normal, 5-FU: 5-fluorouracil, GEM: Gemcitabine, CAP: Capecitabine

tumour progression was documented in 64% of the subjects, respectively [Table 2].

The tumour responses according to chemotherapy regimens are shown in Table 2, which demonstrates that 5-fluorouracil (5-FU)-based (FOLFIRINOX) chemotherapy regimen had better ORR, DCR as compared to GEM-based and CAP-based chemotherapy regimens. Furthermore, fewer subjects progressed in the FOLFIRINOX regimen as compared to other regimens. However, due to the unequal distribution of sample size, further statistical analysis for significance, could not be possible [Table 2].

The median PFS of the whole group was 32 weeks, and the median OS was 54 weeks. The PFS

was significantly higher for LAPC (39 weeks) as compared to the MPC group (25 weeks) ($P = 0.028$) [Figure 1a]. However, there was no statistically significant difference between OS of these two groups (66 weeks for LAPC vs. 49 weeks MPC, respectively, $P = 0.451$) [Figure 1b].

Three subjects had successful surgical resection (Whipple), and two subjects had R1 resection. Unfortunately, all of these three subjects passed away within a year.

In addition, PFS was significantly higher with 5-FU-based chemotherapy regimen (FOLFIRINOX) as compared to the other two chemotherapy regimens (101 weeks vs. 31 weeks vs. 19 weeks for 5-FU-, GEM- and CAP-based chemotherapy, respectively, with $P = 0.001$) [Figure 2a]. Regarding OS, there was no statistically significant difference among all chemotherapy regimen groups (65 weeks vs. 63 weeks vs. 14 weeks for 5-FU-, GEM- and CAP-based chemotherapy regimens, respectively, $P = 0.267$) [Figure 2b].

Discussion

The treatment for MPC is chemotherapy only, whereas, in LAPC, chemotherapy and radiotherapy have been employed to improve response rates and make them resectable in <5% of cases.^[13] The purpose of this study was to assess the outcome of locally advanced and metastatic pancreatic cancer in the local population. The results of this study are consistent with the investigations conducted in the West and the South Asian region.

In this study, 87 subjects were analysed, of which 62 (71%) were male. This is not in line with the findings from other investigators.^[18,19] This disparity in gender distribution could be secondary to the regional culture or that the incidence of pancreatic cancer is different in this part of the world. The median age of the cohort was 56 years, which is not in broad agreement with the results from other international studies as they show a trend toward more advanced age.^[18,19] The exact reason for the earlier onset of disease in the present study

Table 2: This table summarises the tumour responses based on chemotherapy regimens

Characteristics	Category	5-FU-based chemotherapy (n=23) (%)	Gemcitabine-based chemotherapy (n=56) (%)	Capecitabine-based chemotherapy (n=8) (%)
Tumour response	CR	0 (0)	1 (2)	0 (0)
	PR	7 (31)	5 (9)	0 (0)
	SD	4 (17)	6 (11)	0 (0)
	PD	11 (48)	42 (75)	6 (75)
	Could not be assessed	1 (4)	2 (3)	2 (25)
ORR	Overall	7 (31)	6 (11)	0 (0)
	Locally advanced	5 (72)	4 (67)	0 (0)
	Metastatic	2 (28)	2 (33)	0 (0)
DCR	Overall	11 (48)	12 (22)	0 (0)
	Locally advanced	8 (73)	8 (67)	0 (0)
	Metastatic	3 (27)	4 (33)	0 (0%)
Tumour progression	Overall	11 (48)	42 (75)	6 (75)
	Locally advanced	7 (64)	21 (50)	2 (33)
	Metastatic	4 (36)	21 (50)	4 (66)

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, 5-FU: 5-fluorouracil, GEM: Gemcitabine, CAP: Capecitabine, ORR: Overall response rate, DCR: Disease Control rate

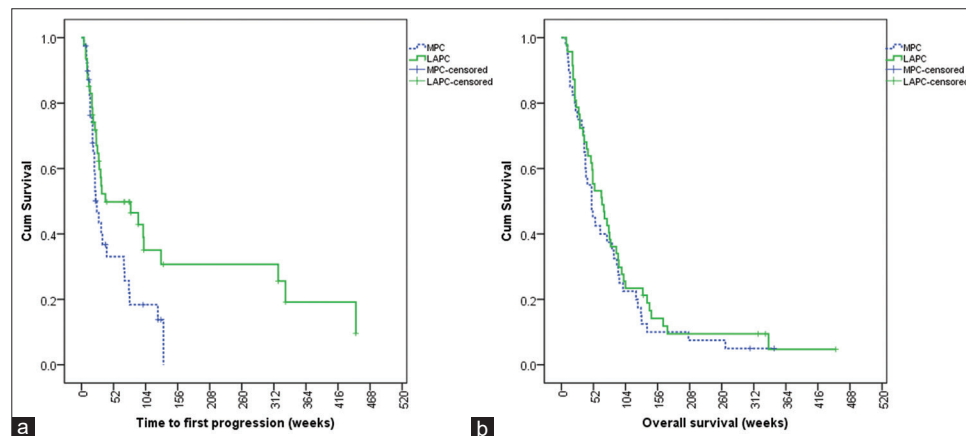


Figure 1: (a) This Kaplan-Meier survival curve summarises the progression-free survival according to the extent of disease. (b) This Kaplan-Meier survival curve depicts the overall survival according to the extent of disease (LAPC: Locally advanced pancreatic cancer, MPC: Metastatic pancreatic cancer)

is beyond the scope of this paper. However, it could be possible that elderly subjects were not well represented as they were too frail to receive chemotherapy.

Most of the patient had ECOG-PS 1, and 47 (54%) had LAPC, and 40 (46%) had MPC. Interestingly,

most of the subjects had GEM 66 (65%), while only 23 (26%) subjects went on to have FOLFIRINOX. The reasons for this could be the patient's choice, physician's recommendation due to patient's logistics and risk of toxicities that might have affected the chemotherapy choice. Furthermore, the need for the PICC line flush required every

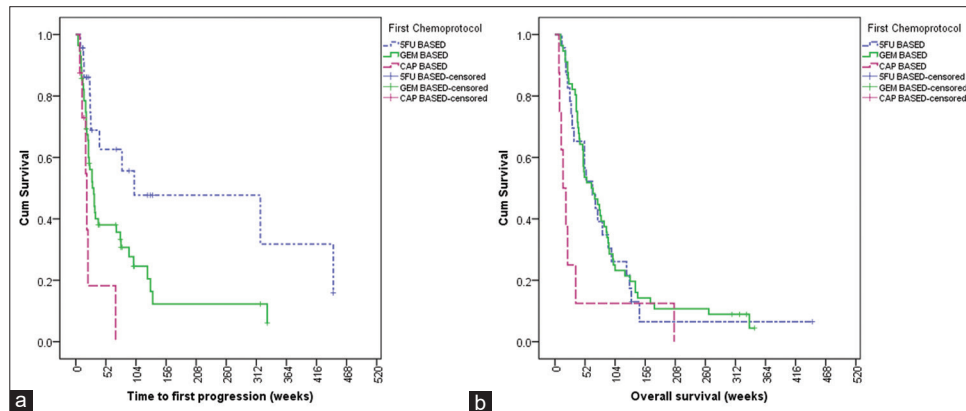


Figure 2: (a) This Kaplan-Meier survival curve shows the progression-free survival according to chemotherapy regimens. (b) This Kaplan-Meier survival curve summarises the overall survival according to chemotherapy regimens (5-FU: 5-fluorouracil, GEM: Gemcitabine, CAP: Capecitabine)

week, and logistic issues might affect the choice of chemotherapy. None of the subjects in the present study had GEM and nanoparticle albumin-bound paclitaxel (Nab-Paclitaxel) as it was not available in the hospital. The choice of chemotherapy has a significant bearing on the outcome, especially in good performance status, which needs to be looked at in future studies.

The median PFS in this study was 32 weeks, and OS was 54 weeks. However, after breaking down into the subjects with LAPC, the median PFS was clinically significant, 39 weeks and OS of 66 weeks. Median-free survival in MPC was 25 weeks, and OS was 49 weeks, consistent with other studies.^[19,20]

The tumour control rate was 48% (11 out of 23 subjects) in the FOLFIRINOX group compared to the 22% (12 out of 56 subjects) in the GEM group during the same time. PFS was significantly higher in the LAPC group than MPC. There might be multiple reasons for this, including better performance status, less dose reduction, choice of treatment (more 5FU-based chemotherapy in LAPC than in MPC) and perhaps the biology of cancer itself. More subjects were treated with 5FU-based chemotherapy in LAPC $n = 16$, 70%; MPC $n = 7$, 30%. These results were similar to those reported in previous Phase III trials of chemotherapy in advanced pancreatic cancer.^[13]

Unfortunately, the OS in this study was not different between the two groups. This is intriguing and could be explained by the smaller size of the cohort and warrant further studies. The ORR is compatible with the published international literature with more responses in FOLFIRINOX than GEM or CAP alone.^[20]

For LAPC, the resection rates vary in different studies. In a systemic review of nearly 13 trials using FOLFIRINOX as neoadjuvant chemotherapy, the resection rates were reported from 0 to 43%, and R0 resection was reported in 74%.^[21] Most of the studies from the South Asia region have looked at the surgical outcome in LAPC, and the data are very sparse on the long-term survival outcome of the patient who received any chemotherapy.^[22] In this study, only three subjects out of 47 (6%) were deemed resectable, and out of three, two had R1 resection. These subjects unfortunately relapsed within 3 months, and all of them died within 12 months. All of these subjects were treated with FOLFIRINOX. This is again interesting as it seems that the outcome of these subjects was not much different from the one who did not have surgery. This is difficult to say with certainty as the number of subjects was small to make any robust conclusion.

This study had few limitations. First, this was a retrospective analysis, therefore liable to have

selection bias and incomplete data collection, but as the electronic patient record was used to document and retrieve data, therefore, this should not be a case. Due to the small sample size, the outcome of subjects with LAPC who had curative surgery after chemotherapy could not be inferred robustly and need further studies with more significant numbers. Another limitation was the small number of subjects, which makes the analysis less robust. This is because the metastatic pancreatic subjects presenting to the hospital were not accepted for treatment as per the hospital policy. Therefore, only subjects who had LAPC or metastatic cancer not evident on the initial investigations (ultrasound liver and chest radiograph) were accepted, who later showed evidence of metastases on the subsequent imaging or during follow-up.

FOLFIRINOX emerged as the most successful chemotherapy regimen, albeit with dose reductions and toxicities. The subjects with both LAPC and MPC fared better on it. Modified FOLFIRINOX could be easily used in the Southeast Asian population with a similar outcome as shown in Western populations.

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Authorship Contributions

Conceived and designed the analysis: SY, SASK and UA, collected the data: SY, FA and SS, contributed data or analysis tools: SY, FA, SS and FB, performed the analysis: SY and FB, wrote the paper: SY, SASK and UA.