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ORIGINAL ARTICLE

Efficacy and Safety of FOLFIRINOX in Locally Advanced Pancreatic Cancer. A Single Center Experience.

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Abstract The management of locally advanced pancreatic cancer (LAPC) is a major challenge. Although new drugs are available for the treatment of metastatic disease, the optimal treatment of non-metastatic cases remains controversial. The role of neoadjuvant therapy is still a question of debate in this setting. The aim of the study was to prospectively collect and analyse data on efficacy and safety of a modified FOLFIRINOX regimen in LAPC patients treated in a single institution. Another major objective was to assess the capability of FOLFIRINOX to render primary non-resectable cancer to resectable. No bolus fluorouracil was given and a 20% dose reduction of oxaliplatin and irinotecan was applied. Primary G-CSF prophylaxis was applied to prevent febrile neutropenia. Thirty-two patients (mean age 60.2 years, range: 40–77 years) have been enrolled into the study. All patients had ECOG performance status of 0 or 1. Best response to therapy was stable disease (SD) or partial regression (PR) in 18 (56.2%) and 6 (18.8%) cases. Two patients (6.3%) underwent surgical resection (100% R0). The most frequent grade 3/4 adverse events were nausea (18.8%), fatigue (12.5%) and diarrhea (12.5%). The incidence of severe neutropenia was 28.1%, with only one documented case of febrile neutropenia. The probability of disease progression was 25% and 50% after 75 and 160 days with 88.4% of possibility of disease progression after 500 days. OS probability was 92.1, 71.5% and 49.5% at 180-, 365 and 540 days. Our data does not support the capability of FOLFIRINOX to render primary non-resectable cancer to resectable. However, due to the high disease control rate observed, FOLFRINOX might be recommended as first line option for the palliative treatment of LAPC. Despite reduced chemotherapy doses significant toxicity has been seen.

Keywords Pancreatic cancer · Locally advanced · FOLFIRINOX

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Introduction

Although new treatment options have become available for the treatment of pancreatic cancer (PC) during the last years, the management of advanced disease remains a major challenge. The number of cases with PC is increasing worldwide. It is estimated that by the year of 2017 the number of death from PC will exceed the death rate caused by breast cancer in the EU. [1] There are data reporting even higher incidence and mortality rates in Central Europe compared to western countries. [2] The rate of PC in 2012 was highest in the Czech Republic, followed by Slovakia, Armenia and Hungary. [3] The number of new cases was 2373, while 1837 died due to PC in Hungary in 2010. [4].

In metastatic cancer the FOLFIRINOX regimen has recently shown survival benefit compared to gemcitabine chemotherapy, which was the state of the art therapeutic choice in the last decade. [5] Previously untreated metastatic pancreatic cancer patients were randomized to receive either

FOLFIRINOX or gemcitabine alone. Patients treated with the FOLFIRINOX regimen had a significantly improved median overall survival (OS) compared to the gemcitabine arm (11.1 months vs. 6.8 months). Additionally, improved progression free survival (PFS) and higher response rate were seen in the experimental arm. Due to significant higher rate of grade 3 and 4 toxicities the FOLFIRINOX regimen is considered as first line option for younger patients with good performance status in metastatic PC.

In contrast, the role of FOLFIRINOX in borderline resectable disease and locally advanced pancreatic cancer (LAPC) is a question of debate. Approximately 35% of patients with PC are not eligible for surgical resection at diagnosis. Most studies evaluating the value of FOLFIRINOX in non-resectable PC have a small sample size and retrospective design. A recently published meta-analysis from the US and Europe comprising 315 patients of 11 studies showed that patients with LAPC treated with FOLFIRINOX had a longer median overall survival compared to gemcitabine (24,2 months vs. 6–13 months). [6].

The purpose of the neoadjuvant approach in PC is to reduce tumor size, enhance R0 resection rates and improve survival. The borderline resectable group of PC patients is considered as the potential target population of neoadjuvant therapy, while treatment of LAPC is rather palliative. There is no widely accepted procedure for neoadjuvant treatment at this point. The optimal type of chemotherapy and the role of chemoradiation is still unknown. FOLFIRINOX has shown promising results in the borderline setting, however, in small series remarkable resection rates have been reported also for LAPC. [7] The question is highly controversial, due to small sample sizes and the heterogeneity of trials available no clear recommendation can be given.

The aim of the present study was to prospectively collect and analyse data on efficacy and safety of FOLFIRINOX in LAPC patients. The secondary main objective was to assess the capability of FOLFIRINOX to render primary non-resectable cancer to resectable.

Patients and Methods

Consecutive patients diagnosed with locally advanced pancreatic cancer were enrolled into the study prospectively between January 2014 and november 2016. All patients had cytological or histological verification of pancreatic ductal adenocarcinoma. Only patients having locally advanced non-resectable disease were enrolled into the analysis, borderline resectable cases were excluded from the study. Tumor resectability was assessed through exploratory laparotomy or according to the radiologic definition criteria of resectability of the NCCN guidelines. [8].

Enrollment was limited to patients with good performance status (Eastern Cooperative Oncology Group performance status score of 0 or 1), adequate bone marrow parameters (Absolute Neutrophil Count, $\geq 1.5 \times 10^9$/L and platelet count, ≥100,000 G/L), liver function (bilirubin ≤1.5 times the upper limit of the normal range), and renal function.

A modified FOLFIRINOX protocol was used: no bolus fluorouracil was given and a 20% dose reduction of oxaliplatin and irinotecan was applied from the beginning of the therapy. The following regimen was applied: oxaliplatin, 70 mg per square meter of body-surface area; irinotecan, 145 mg per square meter; and leucovorin, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-h continuous infusion, every 2 weeks.

Primary prophylaxis of chemotherapy-induced febrile neutropenia using granulocyte colony-stimulating factor (*G-CSF*) was applied. Subcutaneous injection of filgastrim 48 MU/0.5 ml was administered for 5 consecutive days starting 5 days after each cyle of FOLFIRINOX.

Treatment response was assessed every 2 months after beginnig of chemotherapy using multiple detector computed tomography (MDCT). The level of CA 19–9 was determined at the same time as CT was performed. After finishing FOLFIRINOX treatment, further follow up measurements were performed every 3 months.

Statistical Analysis

For categorical data frequency distributions were determined, for continuous variables medians and interquartile ranges were calculated. Chi-squared test was used to evaluate differences within subgroups of patients. For time-dependent survival outcomes Kaplan-Meier analysis was performed. A p value of <0.05 was regarded as statistically significant. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL).

Table 1 Patient characteristics

Number of patients	32
Age	mean: 60.2 years, min-max 40–77 y.
Gender (male/female)	17/15 (53.1/46.9%)
ECOG PS	ECOG 0: 21 (65.3%)
	ECOG 1: 11 (34.7%)
Localisation	
•head	19 (59.3%)
•body	7 (21.8%)
•tail	4 (12.5%)
•processus uncinatus	2 (6.3%)
Stent implantation	8 (25%)
Explorative laparotomy	18 (56.2%)

Table 2 Chemotherapy related data

Number of Cx cycles	6.9
FOLFIRINOX as 1st/2nd line therapy	31/1 (97/3/%)
Dose reduction	11 (34.3%)
Dose discontinuation	6 (18.8%)
2nd line treatment	23/31 (74.2%)

Ethical Statement

The study complies with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Research Ethics Committee.

Results

Patient Characteristics

Data of thirty-two consecutive patients have been collected and analised. Median age of the population was 62 years (IQR: 51–67.8 years). There were more males than females (53.1% vs. 46.9%, respectively). All patients had ECOG performance status of 0 or 1. In the majority of the cases (59.3%) the tumor was localised in the head of the pancreas. Stent placement for biliary occlusion was performed in 8 cases (25%) before starting therapy. In 18 patients (56.2%) non-resectable disease was assessed through exploratory laparotomy. Patient characteristics are summarized in Table 1.

Chemotherapy Related Data

Treatment plan included the administration of maximum 12 FOLFIRINOX cycles. The mean number of Cx cycles applied was 6.9 (range: 2–12). With the exception of one patient receiving previous gemcitabine, FOLFIRINOX was used as first line therapy in all cases. Further dose reduction was needed in approximately one third of the patients (34.3%), while six patients (18.8%) discontinued treatment for toxicity. Second line chemotherapy was feasible in 74.2% of the cases treated with FOLFIRINOX as first line regimen. (Table 2). FOLFIRINOX reinduction was applied in one case, all other patients received gemcitabine-based therapy as second line treatment. Erlotinib was used in two cases as combination with gemcitabine, while nab-paclitaxel was administered in one patient. Currently nab-paclitaxel is not reimbursed in Hungary for the treatment of PC.

Treatment Response

Treatment response was evaluated every 2 months, using CT scan and measurement of CA 19–9 level while patients were on treatment. Best response to therapy (range: 2–6 months after beginning of FOLFIRINOX) was stable disease (SD) in 18 cases (56.2%), partial regression (PR) was seen in 6 cases (18.8%). Rapid disease pogression occured in 8 patents (25%). The rate of progressive disease was 53.3% at 6 month and 76.7% at 9 month after the beginning of Folfirinox. Only 2 patients (6.3%) underwent surgical resection with curative intent. R0 resection could have been achieved in both cases (Table 3).

Determination of CA 19–9

The level of serum CA 19–9 was followed up before the beginning of FOLFIRINOX therapy and while patients were on treatment. Elevated CA 19–9 was found in 24 (75%) of the cases at diagnosis. Normalisation or decrease of tumor marker values were seen in four out of six cases with objective tumor response (PR). No improvement of CA 19–9 level was detected in case of disease progression (Table 4).

Toxicity

Nausea (62.5%) and fatigue (71.9%) were noted as the most frequent adverse events (with severity grades 3 or 4 of 18.8% and 12.5% respectively). Alopecia occured in 34.4% of the patients. Regarding hematologic toxicity neutropenia was observed in 43.8%, with a 28.1% rate of grade 3/4 events. As a result of the application of primary G-CSF prophylaxis there was only one documented case of febrile

Table 3 Treatment response and resection rate

Best response	Treatment response 2 months	Treatment response 4 months	Treatment response 6 months	Treatment response 9 months
CR: 0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PR: 6 (18.8%)	5 (15.6%)	3 (9.7%)	3 (10%)	2 (6.7%)
SD: 18 (56.2%)	19 (59.4%)	16 (51.6%)	11 (36.7%)	5 (16.6%)
PD: 8 (25%)	8 (25%)	12 (38.7%)	16 (53.3%)	23 (76.7%)
Resection rate for locally advanced disease (LAPC): 2/32 (6.3%)				
Resection rate in case of radiologic regression: 2/6 (33.3%)				

Table 4 Change in the serum CA 19–9 levels of patients with partial regression (PR)

CA 19–9 level at diagnosis (U/ml)	Best CA 19–9 level after start of FOLFIRINOX (U/ml)
499	104
>1200	106
>1200	>1200
341	78
932	28
32	12

neutropenia. Another patient was hospitalized for a life-threatening septic condition leading to multiple organ failure caused by *Clostridium difficile* infection. Treatment was discontinued for toxicity in 6 patients (18.8%). Incidence rates of hematologic and non hematologic toxicity are summarized in Table 5.

Survival

PFS and overall survival were analysed. Median time to disease progression was 148 (IQR: 58–228) days in patients with disease progression. The probability of disease progression was 25% and 50% after 75 and 160 days with 88.4% of possibility of disease progression after 500 days. (Fig. 1.)

OS probability was 92.1, 71.5% and 49.5% at 180-, 365 and 540 days. Median time to death was 312 (IQR: 225–450) days (Fig. 2).

Discussion

The main finding of our present study was that FOLFIRINOX-based treatment regimen was associated with disease control in a high proportion of LAPC patients coupled with a survival benefit. However, the present data does not support the capability of FOLFIRINOX to render primary non-resectable cancer to resectable and it was associated with a high rate of adverse events.

Table 5 Hematologic and non hematologic toxicity associated with FOLFIRINOX

Non hematologic toxicity:				
Toxicity	Frequency		Gr. 3–4	
nausea	62.5%		18.8%	
fatigue	71.9%		12.5%	
vomiting	31.3%		18.8%	
neuropathy	28.1%		0%	
diarrhea	46.9%		12.5%	
alopecia	34.4%		NA	
Hematologic toxicity:				
neutropenia	Gr. 3–4 neutropenia	febrile neutropenia	anemia	thrombopenia
43.8%	28.1%	3.1%	25%	15.6%

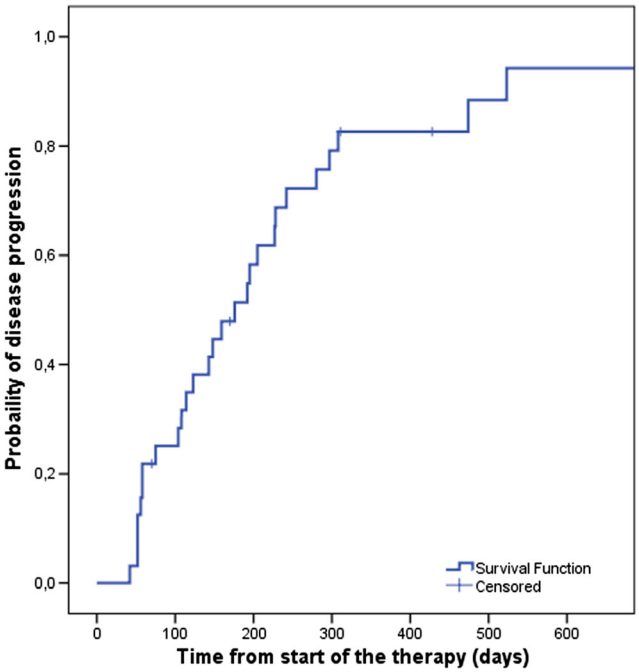

Fig. 1 Probability of disease progression

The management of LAPC remains controversial. It is questionable whether neoadjuvant treatment is capable to render primary non-resectable disease to resectable. The optimal strategy to perform neoadjuvant therapy is also unknown. Most studies evaluating the value of FOLFIRINOX in LAPC are coming from the US and Europe and have a small sample size and a retrospective design (Table 6.) Treatment results, such as objective response rate (range 12–50%), median progression free survival (range: 10.3–17.8 months), median overall survival (range: 14.8–26.6 months) and the rate of resection (6–44%) varied greatly between studies. A recent meta-analysis suggests, that FOLFIRINOX is more effective compared to gemcitabine in this setting [6].

We included 32 consecutive patients receiving FOLFIRINOX for LAPC at our department. Borderline resectable cases were excluded. The patients belonged to a younger age group and were all fit for chemotherapy (ECOG PS: 0/1). In more than half (56.2%) of the patients explorative laparotomy was performed and confirmed non-resectable cancer.

Considering the fact, that FOLFIRINOX can lead to significantly increased toxicity, a number of modified regimens are in use by different institutions. Modification can affect the dose of oxaliplatin and irinotecan, or the administration of bolus 5-FU can be omitted. Many publications report decreased rate of adverse events beside maintained efficacy, however only data from small series are available. [9]

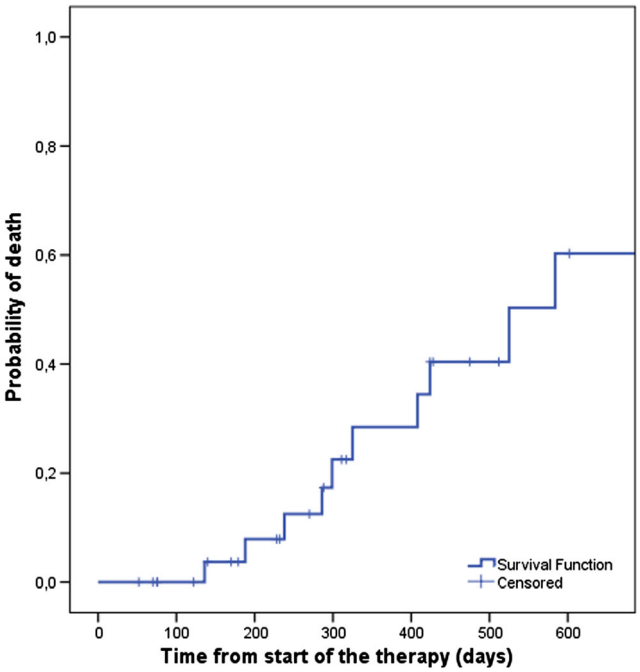

Fig. 2 Probability of death

Recently a prospective phase II study confirmed favourable safety and efficacy profile regarding modified FOLFIRINOX. [10] We applied a modified protocol; attenuated doses of oxaliplatin and irinotecan were given and no bolus 5-FU was used.

Folfirinox was used as first line therapy in the majority of patients (97%). Best response to therapy was SD or PR in 75% of the cases. The rate of progressive disease at 6 and 9 month after the beginning of FOLFIRINOX was 53.3% and 76.7% respectively. Probability of PFS was 75%, 50% and 11.6% after 75, 160 and 500 days. Marthey et al. reported the results of a multicenter cohort of 77 LAPC patients treated with FOLFIRINOX [[11].] Within the cohort, 1-year PFS rate was 59% and 1-year OS rate was 77%. Of note, the probability of OS at 1-year in the present study was 71.5%

Radiologic regression was detected in six (18.8%) patients however, surgical resection was feasible in only 2 cases. Both patients had previous explorative laparotomy revealing unresectability before starting FOLFIRINOX. After performing neoadjuvant treatment (8 and 12 cycles) R0 resection could have been achieved in both cases, in one case histology revealed a good pathologic regression with only a small residual tumor remaining. The rate of resection was 6.3%, which stays below the results reported in the literature. A systematic review evaluated the results of 292 patients with LAPC treated solely with FOLFIRINOX, the resection rate was 12% (70% R0), with 15.7 months median OS. [12].

The use of the CA19–9 tumor marker has been widely accepted in the management of PC. Clinical usefulness of CA 19–9 was reported in early diagnosis, assessment of resectability and monitoring progression of PC. [13] The level of CA 19–9 was elevated in 75% of our patients. The change in the value of the tumor marker correlated well with treatment response in our study.

Despite dose reduction of oxaliplatin and irinotecan significant rate of toxicity was detected. The most frequent grade 3/4 adverse events were nausea, fatigue and diarrhea, incidence rates were comperable with the results of the randomised trial conducted by Conroy et al. [5] Grade 2 alopecia occured in 34.4% of the patients which is more than reported previously. Due to the application of primary G-CSF prophylaxis, the incidence of grade 3/4 neutropenia was lower (28.1%) with only one documented case of febrile neutropenia. One patient was successfully treated for septic

Table 6 Efficacy of FOLFIRINOX in LAPC studies

References	Study design	n	CR %	PR %	SD %	PD (%)	ORR (%)	DCR (%)	Resection rate (%)	mPFS months	mOS months
Conroy [15]	phase II	11	NA	NA	NA	NA	27	na	na	na	na
Gunturu [16]	retrospective	16	6	44	44	0	50	94	na	na	na
Hosein [(17)]	retrospective	18	NA	NA	NA	NA	NA	NA	28	NA	NA
Faris [(18)]	retrospective	22	NA	NA	NA	NA	27.3	NA	22.7	11.7	NA
Peddi [(19)]	registry	18	6	28	50	17	34	84	NA	NA	NA
Marthey [(11)]	prospective database	77	NA	NA	NA	NA	28	84	36	NA	NA
Rombouts [20]	retrospective	18	NA	NA	NA	NA	12	NA	6	10.3	14.8
Blazer [21]	retrospective	26	NA	NA	NA	NA	NA	NA	44	0	0
Mahaseth [9]	retrospective	24	NA	NA	NA	NA	NA	NA	NA	13.7	17.8
Boone [22]	retrospective	13	NA	NA	NA	NA	NA	NA	10	NA	NA
Moorcraft [23]	retrospective	22	NA	NA	NA	NA	NA	NA	NA	12.9	18.4
Stein [10]	phase II	33	NA	NA	NA	NA	17.2	NA	41.9	17.8	26.6

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate, *DCR* disease control rate, *mPFS* median progression free survival, *mOS* median overall survival

Clostridium difficile infection associated with the use of FOLFIRINOX. Treatment had to be discontinued for toxicity in 18.8% of the patients.

In metastatic PC nanoliposomal irinotecan in combination with fluorouracil and folinic acid has been recently shown to prolong survival with a manageable safety profile in patients who previously received gemcitabine-based therapy. [14] Due to the favourable survival and toxicity data, the use of gemcitabine +/− nab-paclitaxel, followed by second line treatment with nanoliposomal irinotecan should be considered as treatment possibility also for locally advanced disease not eligable for surgical resection. Further investigation is needed to confirm the results also in the non-metastatic setting.

Conclusion

According to the high disease control rate and survival data found in our study, FOLFIRINOX might be an effective choice for first line therapy for LAPC patients. However, our data does not support the capability of FOLFIRINOX to render primary non-resectable cancer to resectable. Different patient selection or combination with radiotherapy might improve resection rates. Despite reduced chemotherapy doses, significant toxicity has been observed. Frequency of adverse events may prevent long term ulitization of FOLFIRINOX therapy. The use of primary G-CSF prophylaxis was effective to prevent febrile neutropenia. The clinical value of CA 19–9 determination was confirmed in our study. In conclusion, further investigations are needed to determine the role of FOLFIRINOX in LAPC.

Compliance with Ethical Standards

Conflict of Interest None.

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