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Neoadjuvant FOLFIRINOX followed by gemcitabine based chemoradiation as a treatment paradigm for Borderline resectable pancreatic adenocarcinoma

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SUMMARY

Background: The patient's outcome for Borderline Resectable Pancreatic Adenocarcinoma (BRPC) is dismal. We aimed to evaluate FOLFIRINOX efficacy/toxicity as a neoadjuvant chemotherapy followed by gemcitabine-based chemoradiation in (BRPC).

Methods: 23 chemotherapy/radiotherapy-naïve (BRPC) patients received six months of biweekly FOLFIRINOX chemotherapy. After FOLFIRINOX (12 times), protocol-based concurrent gemcitabine/IMRT external beam radiation therapy was delivered. Gemcitabine was administered on days (1/8/22 and 29). One month later, patients without progressive disease or unacceptable toxicity continued treatment for additional 2 cycles of gemcitabine infusions. The primary endpoint was R0 resection rates. Secondary endpoints were the Overall Response Rate (ORR), progression-free survival, overall survival, and toxicity.

Results: The ORR was 43.5% and the disease control rate was 82.1%. Nine patients had stable disease and 4 patients had disease progression. The resection rate was 60.9%, with R0 resections at 43.5%. Median PFS and OS were 16 and 23 months, respectively.1-year and 2-year OS rates were 74.7% and 49.6% respectively. 1-year and 2-year PFS rate was 54.9% and 35.3% respectively. Neutropenia (43.5%), was and Diarrhoea (17.4%), nausea (39.1%) were the most common grade (3-4) haematological and non-haematological toxicity, respectively.

Conclusion: FOLFIRINOX followed by gemcitabine-based chemoradiation, was a more efficient regimen with a manageable toxicity profile in (BRPC).

Key words: borderline resectable pancreatic cancer, FOLFIRINOX, gemcitabine based chemo radiation

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INTRODUCTION

Carcinoma of the pancreas is a lethal malignancy [1-3]. Over the last few decades, it has a markedly increased incidence and ranked as the 7th leading cause of cancer-related deaths [4]. In the United States, the estimated newly reported cases and deaths from pancreatic cancer were about 55,440 and 44,330 respectively, in 2018 [5]. Cancer of the exocrine pancreas has been traditionally associated with low resectability [6-9]. Poor prognosis [2, 3,10,11], rarely curable and has a 5-year overall survival rate of 8% and a 10-year Overall Survival (OS) of 3% for all the stages [2,12]. Improvements in imaging technology, including positron emission tomographic scans, endoscopic ultrasound examination, magnetic resonance imaging scans, spiral computed tomographic scans, and laparoscopic staging can help to diagnose and identify patients with diseases that are not prone to resection [2, 7, 10, 13].

Patients with pancreatic cancer, at any stage, would be considered as appropriate candidates for the clinical trials, due to the well documented inadequate response to the conventionally used therapeutic modalities including radiation therapy, surgery, and chemotherapy [1, 3, 6, 7, 12, 14].

Patients with Borderline Resectable Pancreatic Cancer (BRPC) and locally advanced unresectable pancreatic cancers are anatomically characterized by the involvement extent of major vessels, which is likely associated with positive resection margin [15]. Several clinical trials have proposed that preoperative chemoradiotherapy for potentially resectable tumours helps to improve local recurrence and survival in resected patients [1, 7, 12, 13]. The 5-year OS was (20%) for patients undergoing resection, which may be improved up to (32%) in patients achieving complete resection and (40%) in those with node-negative disease [12]. Thus, if the tumour is actually localized to the pancreas, the highest cure rate is recorded; however, unfortunately, only less than (20%) of patients are at this stage of the disease [14].

Several studies have recommended preoperative chemoradiotherapy for the locally advanced tumours, that were subsequently could be resected [1, 10, 12,13,16].

Previously, in a multi-institutional phase 2 study that was conducted on patients with pancreatic cancer to evaluate the

neoadjuvant oxaliplatin and gemcitabine together with radiation therapy in patients with pancreatic cancer. They reported a resection rate of 63% for all treated patients, with 53% for R0 resections. Kim and his colleagues reported median survival of (18.2) months for all patients and (27.1) months, for resected patients [15].

Recently, In 2020, in the phase 2 trial on patients with (BRPC), neoadjuvant FOLFIRINOX and Intensity-Modulated Radiation Therapy (IMRT) concurrent with fixed-dose/rate gemcitabine, significantly improved the median OS for resected patients, with a median value of (37.1) months [13].

There was an amazing improvement in the magnitude of median OS, but it came with a price. Notably, there was an increased exposure and duration to local therapy intensification and systemic treatment [13]. However, the clinical evidence of significant activity in (BRPC) stimulated us to conduct this exploratory study. In this study, we investigate the efficacy of neoadjuvant FOLFIRINOX followed by gemcitabine when used concurrently with IMRT external beam radiotherapy as first-line therapy in (BRPC) patients.

PATIENTS AND METHODS

Patient Eligibility Criteria

This phase II trial was carried out from January (2017) to January (2020). Twenty-three chemotherapy and radiotherapy-naïve patients with, confirmed measurable (BRPC) (BRPC stage has been defined by, the National Comprehensive Cancer Network [9], by quantification of the degree of tumour involvement with its surrounding arteries/ veins on imaging tumour involvement of or portal vein and the superior mesenteric more than (180°) without deformity, venous involvement less than (180°) with deformity, or short segment venous occlusion; celiac/superior mesenteric arteries contact of less than (180°), any common hepatic artery involvement, that is amenable to reconstruction; or direct abutment of the hepatic artery in absence of celiac axis extension) were enrolled.

Inclusion criteria

Includes Chemotherapy/radiotherapy-naïve, (18-70) years old patients; Eastern Cooperative Oncology Group (ECOG) performance status of (0-1); measurable borderline resectable disease; adequate bone marrow reserve (WBC count ≥3.5 × 10^9/L, ANC count ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and haemoglobin ≥ 10 g/dL), preserved renal functions (creatinine clearance ≥ 60 mL/min) and preserved liver functions (transaminases<(2) × upper normal limit, and serum bilirubin level< (1.5) mg/dL).

Exclusion criteria

Includes symptomatic heart failure, severe arrhythmia, peripheral neuropathy, prior chemotherapy or radiotherapy, pregnant or lactating mothers, active infection, previous history of hypersensitivity reactions, any other uncontrolled medical problems or other malignancy.

Design of the study

This is a single-arm prospective (phase II) study of a single institution. Protocol approval was given by the Ethics Committee. Prior to initiation of any treatment; an informed consent was signed by all patients.

Pre-treatment evaluation

Pre/on-treatment close monitoring consisted of detailed medical history, physical examination, routine laboratory studies, pelvic and abdominal ultrasound, CT-scan of the pelvis, abdomen, and chest and (CA19.9 and CEA) measurement. Prior treatment, histologic, or cytological evidence of the pancreatic adenocarcinoma was documented in all patients.

Treatment plan and dose modification

Eligible patients received biweekly FOLFIRINOX (oxaliplatin (85) mg/m^2 given as a 2-hour intravenous IV infusion, followed immediately by leucovorin 400 mg per square meter, given as a 2-hour IV infusion, with the addition, after 30 minutes, of irinotecan 180 mg per square meter, administered as a 90-minute IV infusion was followed immediately by fluorouracil 400 mg per square meter, administered by IV bolus, followed by a continuous IV infusion of 2400 mg per square meter over 46 hours, repeated every 2 weeks for 6 months of chemotherapy). Patients without Progressive Disease (PD) or unacceptable toxicity continued treatment up to 12 times over 6 months. Adequate hydration, anti-emetic therapy as well as steroids were secured for all patients. Antibiotics and growth factors, as a granulocyte-colony stimulating factor (G-CSF), were given to patients, guided by their continuous clinical evaluation.

Dose adjustment of FOLFIRINOX

Decisions were taken biweekly to modify the doses of chemotherapy, withhold treatment or progress with the schedule. Full biweekly doses of FOLFIRINOX regimen were given only if the absolute granulocyte count (AGC) was >1,000 cells/µl, platelets were > 100,000 cells/µl, and non-hematologic toxicities were ≤ grade 2. If the AGC ranged between (500-1,000) cells/µl or the platelet count ranged between (50,000-100,000) cells/µl, the FOLFIRINOX regimen dose was reduced by 25%. FOLFIRINOX regimen dose was reduced by 50% for grade 3 non-hematologic toxic effects. If the AGC was <500 cells/µl, the platelet count was <50,000 cells/µl and/or the non-hematologic toxic effects was grade 4, the FOLFIRINOX regimen dose was withheld, and the patient was reevaluated the following week.

Radiotherapy and gemcitabine administration

After 6 months of FOLFIRINOX, protocol-based concurrent gemcitabine IMRT external beam radiation therapy was delivered at 2.0 Gy per fraction, to a total dose of the mean planning target volume of 50.0 Gy if possible, in 25 fractions. Gemcitabine was administered on days 1, 8, 22, and 29 (1000 mg/m^2 infused over 100 minutes).

Patients were treated with IMRT external beam radiation therapy. The radiotherapy field for IMRT encompassed the

Gross Tumour Volume (GTV) included primary tumour and regional involved lymphatics identified on the pretreatment CT scan, including the porta hepatis, celiac axis, and superior mesenteric vessels (if involved). The Clinical Target Volume (CTV) included the GTV plus a 0.5 cm. The planning target volume (PTV) included the CTV plus 0.5 cm.

Evaluation during concurrent gemcitabine-IMRT external beam radiation therapy

During therapy, patients were assessed weekly *via* a directed history as well as physical examination. The occurrence and detailed nature of any adverse events, during treatment, were documented. Before each dose of gemcitabine, a full blood count was conducted. Other levels of blood chemistry were closely monitored as clinically indicated (alkaline phosphatase, bilirubin, aspartate transaminase, alanine transaminase, creatinine, blood urea nitrogen, calcium, phosphorus, glucose, albumin, total protein and electrolyte). One month after completion of protocol-based concurrent gemcitabine-IMRT external beam radiation therapy treatment monitoring consisted of a CT-scan and/or MRI of the abdomen and pelvis. Patients without PD or unacceptable toxicity continued treatment for another additional 2 cycles of gemcitabine infusions to complete neoadjuvant protocol.

Restaging

After treatment completion, all patients were re-evaluated by CT-scan and/or MRI of the abdomen and pelvis to radiographically document tumour response. Based on the assessment of CT images taken at the time of restaging, surgery was considered in patients whose disorder was assumed to be technically resectable after therapy completion.

PATIENT ASSESSMENT

Assessment of clinical benefit, and follow-up

Tumour response was assessed based on the Response Evaluation Criteria in Solid Tumors [17], with the overall response rate, including partial/complete response, while, the disease control rate, including partial response, complete response, and stable disease. Patients were evaluated, after treatment completion, by physical examination, abdominopelvic CT, and chest radiography, every 3-4 months. Biopsy from new recurrent disease sites was rarely carried out and was reported at the time of initial occurrence.

Assessment of toxicity

During therapy, all patients were carefully examined bimonthly via a directed history as well as physical examination. The occurrence/nature of any adverse events was reported. The toxicity grading was based upon standard terminology standards for adverse events (NCI-CTC, version 3.0) [18].

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint of this study was R0 resection rates, (as defined by the absence of both microscopic/gross involvements of tumour resection margins) in (BRPC) population. Secondary endpoints were the overall response rate, OS, progression-free survival and toxicity. Disease progression was assessed from the first chemotherapy dose, and it was defined as increase in the size of a previously present disorder as documented by serial axial CT, the appearance of new local/distant metastatic disorder.

Statistical analysis

Twenty-three patients were enrolled in the current study between January 2017 and January 2020. The date of this analysis was June 2021.

OS rates were calculated, by the Kaplan-Meier method [19], from the start of biweekly FOLFIRINOX to the time of the last follow-up visit or death, using SPSS (Statistical package, version 21.0). Progression-free survival was the time elapsed from the initiation date of biweekly FOLFIRINOX to the date of the first evidence of disorder progression or death in the absence of disease progression. OS and progression-free survival were compared by the Kaplan-Meier method [19] with statistical significance evaluated by the log-rank test. Mean and Standard Deviation (SD) were calculated from quantitative data. All P values were two-tailed; a value of ≤ 0.05 was considered significant.

RESULTS

Patient characteristics

Patient characteristics were listed in Table 1. The median age was 53 years (range, 36-68). Fourteen patients (60.8%) had performance status 1. Twelve patients (52.2%) had involved body and tail pancreatic sites. Three (13.1%) patients had a biliary stent. The median level of CA19.9 was 600 U/ml. The median maximum cross-sectional Tumour Area (TA) was 8.7 cm^2.

Treatment administration

A total of 114 FOLFIRINOX chemotherapy cycles were administered. Patients were treated with a median number of 4 cycles of FOLFIRINOX (range 3-6 cycles), with dose modifications (according to criteria of dose adjustment mentioned previously in patients and methods) in 48.2% (55/114) of all FOLFIRINOX cycles.

Four patients (17.4%) had >3 dose delay of gemcitabine during concurrent gemcitabine-IMRT external beam radiation therapy. Two (9%) patients had radiotherapy interruptions due to toxicity. Fifteen patients (65.2%) complete 2 cycles of gemcitabine post radiation therapy.

Patients' response to this regimen

The overall response rate (CR+PR) was 43.5% (10/23) of all patients and the disease control rate (CR+PR+SD) was 82.1% (19 patients). Nine patients (39.1%) had stable disease and 4 patients (17.4%) had disease progression (Table 2).

Tab.1. Baseline patient and tumour characteristics of the 23 patients with borderline resectable pancreatic cancer

Patient Characteristics	No.	%
Sex		
Male	15	65.2
Female	8	34.8
Age, years		
Median	53	
Range	36-68	
ECOG performance status		
0	9	39.1
1	14	60.9
Tumor location		
Head	9	39.1
Body and tail	12	52.2
Overlapped lesion	2	8.7
Biliary stent		
Yes	3	13.1
No	20	86.9
Presenting symptoms		
Jaundice	16	70
Fatigue	11	48
Abdominal pain	17	74
Change in bowel pattern	10	43.5
Back pain	9	39
Anorexia	7	30
Largest axial area on CT		
Median	8.7 cm^2	
Range	2.5 cm^2-37 cm^2	
Level of CA19.9, U/ml		
Median	600	
Range	0-101 0,66	

ECOG: Eastern Cooperative Oncology Group
CA19.9: Carbohydrate antigen

Tab.2. Tumour response of the 23 patients with borderline resectable pancreatic cancer

Evaluable patients	N=23	
	No.	%
Complete Response (CR)	0	0
Partial Response (PR)	10	43.5
Stable Disease (SD)	9	39.1
Progressive Disease (PD)	4	17.4

Pancreatic resection

Fourteen (60.9%) of the 23 patients who received this treatment protocol were thought to be candidates for pancreatic resection (either pancreaticoduodenectomy or distal pancreatectomy) based on CT images obtained four weeks after chemoradiation completion. The pre/post-treatment CT scans were reviewed to evaluate the lesion size and its relationship with the vessels before considering surgery. The resection rate in all treated patients was (60.9%), with R0 resections in 10 patients (43.5%). The median number of dissected regional lymph nodes was 10 (range, 5-15), and 9 patients (39.1%) had a positive metastatic nodal disease. No surgery-related mortality was reported.

Survival

All our patients had a regular follow up, with no one having lost follow-up in the current study. The median follow-up period was 24.5 months ± SE 1.01.

Median (OS) for all our patients was 23 months ± SE 8.451, (95% CI, 6.437-39.563) (Figure 1). The 1-year and 2-year OS rates for all our patients were 74.7% and 49.6% respectively (Figure 1). It was 13 months ± SE 2.336, (95% CI, 8.421-17.579) for unresected patients and 30 months (95% CI, not reached) for resected patients (Figure 2).

Median Progression-Free Survival (PFS) for all our patients was 16.000 months ± SE ± 4.440), (95% CI, 7.297-24.703) (Figure 3). The 1-year and 2-year PFS rate was 54.9% and

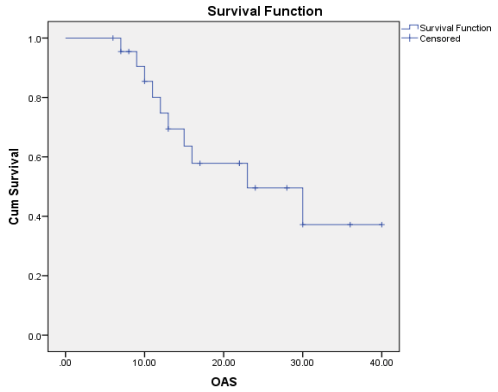

Fig. 1. Kaplan-Meier curve for overall survival time in all patients with borderline resectable pancreatic cancer

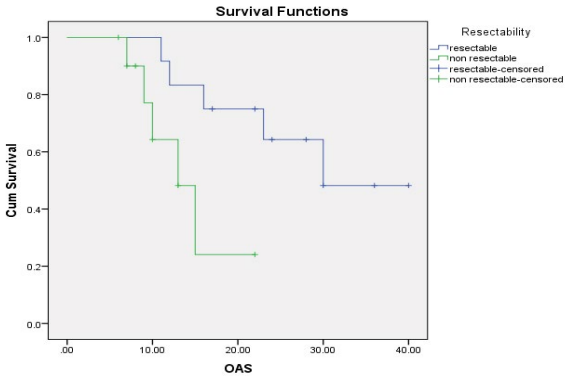

Fig. 2. Kaplan-Meier curves for overall survival time in resectable and unresectable pancreatic cancer patients

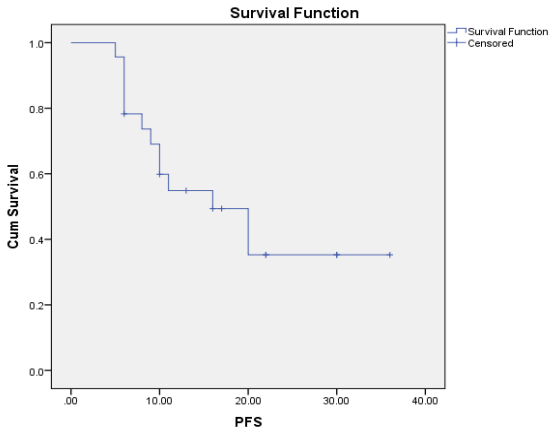

Fig. 3. Kaplan-Meier curve for progression-free survival time in all patients with borderline resectable pancreatic cancer

35.3% respectively, (Figure 3). It was 10.000 months, SE ± 2.942 (95% CI, 4.233-15.767) for unresected patients, and 20 months, ± 2.828 (95% CI, 14.456- 25.544) for resected patients (Figure 4).

Toxicity

To assess non-hematologic/hematologic toxicities (Table 3), all enrolled patients were evaluated for toxicity and adverse events by the common terminology criteria for adverse event (version 3.0; NCI-CTC) [18]. The most common grades (3-4) haematological toxicities were neutropenia in 10 patients (43.5%), with two patients (8.7%) suffering from febrile neutropenia, and another two patients (8.7%) developed grade (3-4) thrombocytopenia. Grade (3-4) diarrhoea in 4 patients (17.4%), nausea in 9 patients (39.1%) and mucositis in 2 patients (8.7%) were the most common Grade (3-4) non-haematological toxicity. Eight patients (34.8%) were started on prophylactic G-CSF concomitant with the first FOLFIRINOX cycle while additional nine patients (39.1%) had G-CSF support, which was added in later FOLFIRINOX cycles.

Four patients (17.4%) had >3 dose delay of gemcitabine during concurrent gemcitabine-IMRT external beam radiation therapy, and 2 (8.7%) patients presented with gastrointestinal bleeding with evidence of duodenal or gastric ulceration. Two (8.7%) patients had radiotherapy interruptions due to toxicity.

Due to treatment-related toxicity, ten (43.5%) of the 23 patients treated with this regimen were admitted to the hospital for

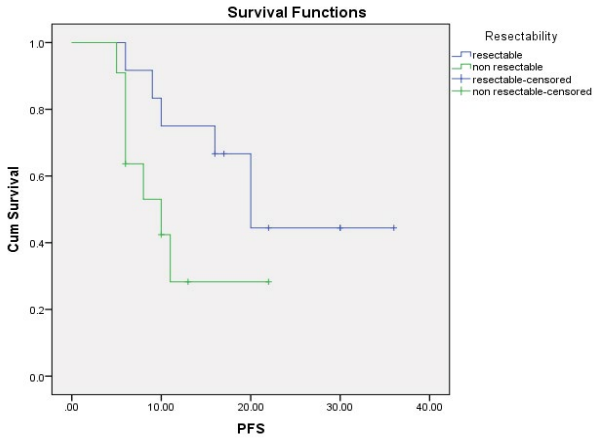

Fig. 4. Kaplan-Meier curve for progression-free survival time in resectable and unresectable pancreatic cancer patients

Tab.3. Hematologic and non-hematologic grade 3 and 4 toxicity of this regimen in the management of the 23 patients with borderline resectable pancreatic cancer

Enrolled patients	No.	%
Haematologic Toxicity		
Neutropenia	10	43.5
Febrile Neutropenia	2	8.7
Thrombocytopenia	2	8.7
Non-hematologic Toxicity		
Diarrhoea	4	17.4
Nausea/vomiting	9	39.1
Mucositis	2	8.7
Gastrointestinal bleeding	2	8.7

supportive care. The median stay was 4 days. Five of these 10 patients were admitted twice and 5 were admitted three times.

Late toxicity

Two episodes (8.7%) of severe late effects that might have been treatment-related occurred. The 2 patients had episodes of duodenal ulceration with bleeding. An endoscopic biopsy was negative for the tumour but showed severe reactive changes consistent with the impact of treatment.

DISCUSSION

Pancreatic cancer management remains a daunting challenge, often requiring a multidisciplinary approach to provide an efficient approach and, preferably, to optimise survival. The combination of local-regional approaches, such as surgery and radiotherapy, and systemic micrometastasis eradication therapies should also be considered for (BRPC) patients and those with locally advanced, unresectable disease [1,2,6].

BRPC has a poor prognosis with upfront surgery due to the high likelihood of microscopic and/or macroscopic residual tumours [20, 21]. However, neoadjuvant therapy may lead to improvement in R0 resection rates and long-term survival [7].

The integration of gemcitabine with radiation in a combined modality regimen may represent one strategy to improve outcomes in patients with pancreatic cancer, considering its activity as a single agent and laboratory studies that have demonstrated potent radiosensitization in human pancreatic cancer cell lines [12,13,15,16, 22].

FOLFIRINOX is clinically beneficial in both metastatic and non-metastatic pancreatic cancer patients, considering substantial rates of adverse effects and the use of dose modifications. The toxicity of the regimen did not distort overall response and survival [23-26]. In our institution, it is the standard systemic treatment for metastatic, BRPC and locally advanced disease in patients with good performance status.

These observations have led us to document the use of neoadjuvant FOLFIRINOX and gemcitabine-based chemoradiation and its efficacy and tolerance in BRPC patients.

Our treatment schedule was based on data from Tran, et al. study that concluded that the optimal therapeutic index, in BRPC patients, can be achieved with FOLFIRINOX administration followed by gemcitabine-based chemoradiation [13].

In our study, responses were observed in 43.5% (10/23) of patients which were similar to the results of the Tran, et al. study [13], in patients with BRPC published in 2020 (RR was 44%) [13]. However, our results were better than the results of a study carried out between May 2016 and March 2018, in which investigators at Asan Medical Center, Seoul, Korea treated 44 patients with BRPC with neoadjuvant modified FOLFIRINOX followed by postoperative gemcitabine [7] who developed response rates of 34.1%.

In the current study, the disease control rate (PR+CR+SD) of 82.1% (19 patients) was comparable to the results of the Tran, et al. trial on FOLFIRINOX followed by gemcitabine-based chemoradiation in (BRPC) (disease control rate of 88%) [13].

In retrospect, it is now obvious from clinical data that when gemcitabine is used simultaneously with radiotherapy, the size of irradiated normal tissue is a crucial variable. The recommended dose of 1000 mg/m^2 infused over 100 minutes on days 1, 8, 22, and 29 that we used with 50 Gy in 25 fractions to regional radiotherapy fields to most of the patients in our study is comparable to the dose given in prior study that used IMRT irradiation concurrently with gemcitabine[13]. While Sakamoto, et al. [27], suggest that because of its decreased toxicity, the low-dose gemcitabine infusion regimen can be consistently administered to patients with both locally advanced and systemically spreading pancreatic cancer, resulting in better life quality and an improved safety profile compared with the current care regimen for infusion.

The infusion rate of gemcitabine is a significant variable which has become evident from clinical data. Most studies assessing concomitant radiotherapy and gemcitabine were given at the manufacturer's recommended 30-minute as infusion rate for gemcitabine [28], which may not be ideal based on other clinical studies suggesting that a 10 mg/m^2/min infusion rate is more efficient [13,16,29, 30]. The rate of infusion we used could have been serendipitously optimal; however, the smaller radiation volume with the use of IMRT is probably more important and could, in part, explain why we can be able to use higher doses of gemcitabine with good tolerability with the ability to finish gemcitabine-based chemoradiation for all our patients.

It is now obvious that the fractionation/ volume of irradiated normal tissue affects the patients' tolerance with concomitant gemcitabine [1-3]. Omitting elective nodal irradiation is an obvious means of expanding the therapeutic ratio in the studies of concomitant gemcitabine and radiotherapy. This idea has been advocated by researchers at the University of Michigan in patients with irresectable diseases 30 and owing to the enhanced toxicity associated with elective nodal irradiation if gemcitabine is to be used in radiotherapy; it tends to be the most desirable technique. The objective progression rate of the primary tumour was so high, in patients receiving concurrent radiotherapy and gemcitabine, in their study of BRPC patients. Indeed, it is hard to believe that elective nodal irradiation may have been of any benefit. In our study, higher doses of the weekly administered gemcitabine have been tolerated as radiotherapy is delivered to gross disease and involved regional lymph nodes only by the use of IMRT.

Our patients who received neoadjuvant FOLFIRINOX followed by gemcitabine-based chemoradiation were selected carefully (the ECOG PS was ≤ 1, with 39.1% of patients having ECOG PS of 0), yet the rate of hospitalization was elevated due to frequently reported severe acute toxicity. Ten (43.5%) of the 23 patients treated with the current regimen were admitted to the hospital for supportive care due to treatment-associated toxicity, with a median stay period of 4 days. Five of these 10 patients were admitted twice, while 5 patients were admitted three times. Our rate of hospitalization for treatment-related toxicity was higher than the rate of hospitalizations due to adverse events in Peddi, et al. trial (34.4%) [26] and comparable with Faris, et al. trial

(41%) [31], most commonly for neutropenic fever, most of the patients in these two trials [26, 31], who displayed neutropenia (grades 3 or 4) had not received prophylactic growth factors with the start of treatment with FOLFIRINOX. Furthermore, the hospitalization rate in our study was higher than that reported in another retrospective single-institution series (14%) [32]. Differences in the rates of hospitalization for treatment-related toxicity between our trial and other trials may be due to the variations in the number of patients between these studies, the varying stages of pancreatic cancer included in these trials as well as the differences in the regimens of FOLFIRINOX- based treatment.

In our study 8 (34.8%) patients were started on prophylactical G-CSF concomitantly with the first treatment cycle while an additional 9 (39.1%) patients had G-CSF as supportive added in the later treatment cycles. Thus the 73.9% (17 patients) of our patients who received GCSF were comparable to the proportion of patients who received GCSF in Peddi, et al. [26] trial (73.9% *vs.* 77%, respectively). In the current study, neutropenia was reported as the most frequent grade (3-4) haematological toxicity in 10 patients (43.5%), compared to 40% in Tran, et al. study. In the ACCORD trial only 42% of patients in the FOLFIRINOX arm, received support with (G-CSF) resulting in a similar proportion of patients suffering from grade 3-4 neutropenia as in our study (45.7% *versus* 43.5% respectively). Consequently, 1 patient died from febrile neutropenia in the FOLFIRINOX group in the ACCORD trial [33], while, there was no treatment-related death in our study. Washington University physicians used a database to track the FOLFIRINOX efficacy and tolerance [32]. 48% of patients starting with the first cycle were given prophylactic growth factor support; 10% of patients started (G-CSF) in the subsequent cycles. Neutropenia (grades 3 and 4) has been reported in a lower proportion of patients (14%) [32]. Differences in rates of grades 3 and 4 neutropenia between our trial and other trials may be due to the variations in the number of patients in all these studies, the varying stages of included pancreatic cancers as well as the differences in the regimens of FOLFIRINOX-based treatment.

The severe non-haematologic toxicity rate in the present study was similar in patients treated with neoadjuvant FOLFIRINOX followed by gemcitabine-based chemoradiation and in those treated with the same regimen in Tran, et al. [13] study. Grade 3-4 nausea in 9 patients (39.1%) and diarrhoea in 4 patients (17.4%), were the most common Grade 3-4 non-haematological toxicity in our study. Similarly, the most frequently reported non-hematologic treatment-related adverse events in Tran, et al. trial [13] were nausea and vomiting in 40% and diarrhoea in 16%.

In our study, the dose was modified in 48.2% (55/114) of all cycles in response to adverse events. Researchers at Yale University have noted that oncologists were hesitant to use FOLFIRINOX, in a full dose, due to its toxicity profile [34]. A retrospective study has been conducted on pancreatic cancer patients, who were treated with FOLFIRINOX, at their institution between June (2010) and June (2011), to evaluate the possible effect of dose reduction on efficacy/toxicity. In the first cycle, only 17% of patients received a complete dose of FOLFIRINOX. The median relative doses of oxaliplatin, irinotecan, 5-FU bolus, and 5-FU infusion were 90%, 68%, 68%, and 100%, respectively. To track the tolerance and efficacy of FOLFIRINOX, Peddi, et al. used a registry [32]. In the majority of patients, the protocol was empirically altered because of concern about possible toxicities. In 48%, the 5-FU bolus was deleted. In 46%, the dosage of Irinotecan was reduced.

In our study, the median (OS) for all our patients was 23 months similar to that published in many other trials, in which the median OS of their population was in the range of 21.7-37.7 months [13, 24, 25]. In the current study, the 1-year and 2-year OS rates for all our patients were 74.7% and 49.6% respectively, compared with the 75.4% and 54.2%, respectively reported in the Tran, et al. trial [13].

The median OS survival reported in patients with the unresectable disorder, who were treated with this combination was similar to OS rate in patients treated with the same regimen in Tran, et al. [13] study, (13 months vs. 12.6 months respectively). These observations concluded a very narrow therapeutic index for the utility of neoadjuvant FOLFIRINOX followed by concurrent gemcitabine and radiotherapy administered in this way without tumour resection. In spite of the reported increased toxicity no clear significant increase in efficacy in patients not amenable for curative surgery. However, the OS of the resected cohort was more favourable. In our study, the median OS of the R0 resected patients is 30 months, approximately comparable to that mentioned in R0 resected patients of other studies treated with preoperative FOLFIRINOX followed by chemoradiation for BRPC [13,24,25].

Because curative therapeutic approaches in pancreatic cancer patients must include surgery, all therapies that increase resectability are of interest. A possible benefit of FOLFIRINOX followed by concurrent gemcitabine and radiotherapy in this study was the ability to perform surgery in 14 patients (60.9%) of (BRPC) patients. Ten patients (43.5%) receiving FOLFIRINOX followed by concurrent gemcitabine and IMRT external beam radiotherapy underwent margin negative pancreaticoduodenectomies.

The R0 resection rate in this study was observed to be 43.5% which is lower than the 52% mentioned in Tran, et al. [13] study using the same regimen of our study (FOLFIRINOX followed by concurrent gemcitabine and radiotherapy) and the 64% published in Katz, et al. phase 2, a multi-institutional trial using FOLFIRINOX followed by capecitabine concurrently with radiation in patients with BRPC [24] as well as the 65% R0 resection rate in Murphy, et al. using FOLFIRINOX followed by capecitabine concurrent with radiation in patients with (BRPC) [25]. However, this 43.5% R0 resection rate in our study was observed to be better than the R0 resection rate of 30% in Small, et al. [35] and Katz, et al. [36] studies. Differences in resection rates between our trial and other trials may be due to the small number of patients in all these studies, the varying definitions of (BRPC) as well as the variations in the experience of the surgeons.

According to the results achieved with FOLFIRINOX followed by gemcitabine and 50 Gy IMRT, both local and distant failure rates were significant problems in our patients, regardless of the used chemotherapy. Although the FOLFIRINOX followed by a combination of radiation and gemcitabine, is a potent cytotoxic intervention modality [22], we reported one-year and two-year PFS rates of 53% and 30% respectively. Median (PFS) for all our patients was 16 months, slightly more than the 13.1 months reported in the Tran et al [13] study using the same regimen of our study (FOLFIRINOX followed by concurrent gemcitabine and IMRT radiotherapy). We have used a radiotherapy dose of 50 Gy in 25 fractions. However, some may argue that higher radiation doses may be more appropriate for unresectable diseases with enhanced survival, but there is no compelling proof up till now [37]. In our experience, distant metastasis is the predominant cause of death. Thus, distant metastases are still the main limitation. This clarifies the need for ongoing research into novel systemic agents for this disease [38-40]. Thus far, major improvement in outcome for patients with BRPC has not been demonstrated with this therapy. The study of the impact of higher radiation doses does not seem to be a priority until more reliable systemic therapy is developed.

CONCLUSION

In conclusion, the FOLFIRINOX followed by concurrent gemcitabine and IMRT external beam radiotherapy regimen has gained increased acceptance due to its better efficacy as first-line therapy in patients with BRPC, improved response rate and median OS over that achieved with gemcitabine-based combination regimens in previous studies. The doses and schedules of concurrent gemcitabine and radiotherapy used in this study had a high toxicity rate than did treatment with other multiagent combinations including, gemcitabine and nab-paclitaxel and radiotherapy [41]. Thus, in spite of, the overall survival rate was significantly better for patients who received neoadjuvant FOLFIRINOX followed by concurrent gemcitabine and radiotherapy, this treatment program still has significant limitations. Considering the toxicity and efficacy, this regimen could be a viable therapeutic option in selected patients with a good PS only.

Further prospective trials should evaluate how to adjust doses to ameliorate the toxicity of this regimen. In addition, patients with BRPC should continue to be enrolled in prospective trials to explore potential formulations of concomitant radiotherapy with cytotoxic agents and/or biologic agents. Future prospective research should also be supported based on further knowledge of tumour biology, targeting different growth factor signalling pathways, and developing new technologies, including the discovery of biomarkers that predict the response to treatment.

DISCLOSURE STATEMENT

No potential conflict of interest was documented by the author(s).

REFERENCES

1. O'Reilly EM, Ferrone C. Neoadjuvant or Adjuvant Therapy for Resectable or Borderline Resectable Pancreatic Cancer: Which Is Preferred?. J Clin Oncol. 2020;38:1757-1759.
2. Silvestris N, Brunetti O, Bittoni A, Cataldo I, Corsi D, et al. Clinical practice guidelines for diagnosis, treatment and follow-up of exocrine pancreatic ductal adenocarcinoma: Evidence evaluation and recommendations by the Italian Association of Medical Oncology (AIOM). Cancers. 2020;12:1681.
3. Huart C, Chen JW, Le Calvé B, Michiels C, Wéra AC. Could Protons and Carbon Ions Be the Silver Bullets Against Pancreatic Cancer?. Int J Mol Sci. 2020;21:4767.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: cancer j clin. 2018;68:394-424.
5. Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, et al. Cancer statistics for hispanics/latinos, 2018. CA: cancer j clin. 2018;68:425-445.
6. Bacalbasa N, Balescu I, Vilcu M, Croitoru A, Dima S, et al. Pancreatoduodenectomy after neoadjuvant chemotherapy for locally advanced pancreatic cancer in the presence of an aberrant right hepatic artery. in vivo. 2020;34:401-406.
7. Yoo C, Lee SS, Song KB, Jeong JH, Hyung J, et al. Neoadjuvant modified FOLFIRINOX followed by postoperative gemcitabine in borderline resectable pancreatic adenocarcinoma: a phase 2 study for clinical and biomarker analysis. Br j cancer. 2020;123:362-368.
8. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology. 2015;15:8-18.
9. Valle V, Fernandes E, Mangano A, Aguiluz G, Bustos R, et al. Robotic Whipple for pancreatic ductal and ampullary adenocarcinoma: 10 years experience of a US single-center. Int J Med Robot Comput Assist Surg. 2020;1:1-7.
10. Oba A, Ho F, Bao QR, Al-Musawi MH, Schulick RD, et al. Neoadjuvant treatment in pancreatic cancer. Front oncol. 2020;10:245.
11. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. The Lancet. 2017;389:1011-1024.
12. Giovinazzo F, Soggiu F, Jang JY, Versteijne E, Van Tienhoven G, et al. Gemcitabine-based neoadjuvant treatment in borderline resectable pancreatic ductal adenocarcinoma: a meta-analysis of individual patient data. Front oncol. 2020;10:1112.
13. Tran NH, Sahai V, Griffith KA, Nathan H, Kaza R, et al. Phase 2 trial of neoadjuvant FOLFIRINOX and intensity modulated radiation therapy concurrent with fixed-dose rate-gemcitabine in patients with borderline resectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2020;106:124-133.
14. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395-2406.
15. Katz MH, Kim MP, Tzeng CW, Lee JE. Preoperative Chemoradiation for Borderline Resectable Pancreatic Cancer: The New Standard?. Ann Surg. 2018;268:223-224.
16. Kim EJ, Ben-Josef E, Herman JM, Bekaii-Saab T, Dawson LA, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. Cancer. 2013;119:2692-2700.
17. Therasse P, Arbuck SG, Eisenhauer EA. New guidelines to

evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205-216.

18. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, et al. CTCAE v3. 0: development of a comprehensive grading system for the adverse effects of cancer treatment. In Seminars in radiation oncology 2003;13:176-181.
19. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958;53:457-481.
20. Kang CM, Chung YE, Park JY, Sung JS, Hwang HK, et al. Potential contribution of preoperative neoadjuvant concurrent chemoradiation therapy on margin-negative resection in borderline resectable pancreatic cancer. J Gastrointest Surg. 2012;16:509-517.
21. Evans DB, Erickson BA, Ritch P. Borderline resectable pancreatic cancer: definitions and the importance of multimodality therapy. Ann Surg Oncol. 2010;17:2803-2805.
22. Van Laethem JL, Hammel P, Mornex F. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomized EORTC-40013-22012/FFCD-9203 /GERCOR phase II study. J Clin Oncol 2010; 28:4450-4456.
23. Kumar R, Herman JM, Wolfgang CL, Zheng L. Multidisciplinary management of pancreatic cancer. Surg Oncol Clin. 2013;22:265-287.
24. Katz MH, Shi Q, Ahmad SA, Herman JM, Marsh RD, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for clinical trials in oncology trial A021101. JAMA surgery. 2016;151:e161137.
25. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. JAMA oncology. 2018;4:963-969.
26. Peddi PF, Lubner S, McWilliams R, Tan BR, Picus J, et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. J Pancreas. 2012;13:497-501.
27. Sakamoto H, Kitano M, Suetomi Y, Takeyama Y, Ohyanagi H, et al. Comparison of standard-dose and low-dose gemcitabine regimens in pancreatic adenocarcinoma patients: a prospective randomized trial. J Gastroenterol. 2006;41:70-76.
28. Mukherjee S, Hurt CN, Bridgewater J. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): A multicentre, randomised, phase 2 trial. Lancet Oncol. 2013; 14:317-326.
29. Ben-Josef E, Schipper M, Francis IR, Hadley S, Ten-Haken R, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancerInt. J Radiat Oncol Biol Phys. 2012;84:1166-1171.
30. McGinn CJ, Zalupski MM, Shureiqi I, Robertson JM, Eckhauser FE, et al. Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2001;19:4202-4208.
31. Faris JE, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. The oncol. 2013;18:543.
32. Willenbrock F, Cox CM, Parkes EE, Wilhelm-Benartzi CS, Abraham AG, et al. Circulating biomarkers and outcomes from a randomised phase 2 trial of gemcitabine versus capecitabine-based chemoradiotherapy for pancreatic cancer. Br J Cancer. 2021;124:581-586.
33. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl j med. 2011;364:1817-1825.
34. Gunturu KS, Yao X, Cong X, Thumar JR, Hochster HS, et al. FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. Med Oncol. 2013;30:1-7.
35. Small Jr W, Berlin J, Freedman GM, Lawrence T, Talamonti MS, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. J Clin Oncol. 2008;26:942-947.
36. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206:833-846.
37. Allen AM, Zalupski MM, Robertson JM. Adjuvant therapy in pancreatic cancer: Phase I trial of radiation dose escalation with concurrent full-dose gemcitabine. Int J Radiat Oncol Biol Phys 2004;59:1461-1467.
38. Wei D, Li H, Yu J, Sebolt JT, Zhao Let, al. Radiosensitization of human pancreatic cancer cells by MLN4924, an investigational NEDD8-activating enzyme inhibitor. Cancer research. 2012;72:282-293.
39. Engelke CG, Parsels LA, Qian Y, Zhang Q, Karnak D, et al. Sensitization of pancreatic cancer to chemoradiation by the Chk1 inhibitor MK8776. Clin cancer res. 2013;19:4412-4421.
40. Cuneo KC, Morgan M, Schipper MJ, Maybaum J, Al-Hawary M, et al. Phase I study of definitive chemoradiation with gemcitabine and the WEE1 inhibitor AZD1775 in unresectable pancreatic cancer.
41. Von Hoff DD, Ervin T, Arena FP. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-1703.