Folfirinox Neoadjuvant Therapy for Locally Advanced and Borderline Resectable Pancreatic Cancer - A Retrospective Study

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ABSTRACT

Introduction: The management of borderline resectable pancreatic cancer has been heterogeneous and based on retrospective series. Historically, chemoradiotherapy had been used to reduce the risk of a positive margin, local recurrence, and metastatic progression. Study was aimed to assess clinical and pathologic efficacy of neoadjuvant FOLFIRINOX for locally advanced (LAPC) and borderline resectable pancreatic cancer (BRPC).

Material and Methods: In this retrospective study, patients received neoadjuvant FOLFIRINOX for LAPC and BRPC were included. Post-treatment patients achieving resectability were referred for surgery, whereas unresectable patients continued chemotherapy. Clinical and pathological data were retrospectively recorded.

Results: The neoadjuvant group consisted of 29 PDAC patients, 16 with LAPC and 13 with BRPC who received neoadjuvant FOLFIRINOX. Reasons for non-resectability following treatment included disease progression (10 patients), locally non-resectable disease (3 patients), and deterioration of patient performance status (1 patient). Tumors size was 1.87cm, the rate of lymphovascular invasion was 17.4%, the peripancreatic fat invasion was 52.2%, 22% of patients had lymph node metastases. R0 resection was achieved in all patients. Evaluation of treatment response grading (TRG) demonstrated complete response (TRG 0) in 2 (15%) patients, and marked response (TRG 1) in 2 (15%) patients.

Conclusion: Neoadjuvant FOLFIRINOX is an effective, well-tolerated regimen for patients with locally advanced and borderline resectable pancreatic cancer.

Keywords: Pancreatic cancer, Neoadjuvant FOLFIRINOX, Surgery

INTRODUCTION

Pancreatic cancer leads to an estimated death of 2,27,000 people annually across the world and is the fourth leading cause of cancer death in the United States.[1-6] The tumors involve the local structures and metastasize to the regional lymph nodes at a very early stage and the majority of the patients present with advanced disease at the time of presentation. For treatment and surgical purposes, the surgeons classify pancreatic cancer as Resectable, Borderline resectable (BRPC) and Unresectable (locally advanced or metastatic).[7] 30-35% of the cases are locally advanced pancreatic adenocarcinoma (LAPC). A non-randomized retrospective study by Suker et al suggests that the overall survival of patients with pancreatic cancer ranges from 10 to 32.7 months with a median of 24.2 months and the average progression-free survival (PFS) was between 3 and 20 months.[8] Systemic chemotherapy and chemoradiotherapy is the treatment option for LAPC and recent studies have been investigating the efficacy of FOLFIRINOX in those patients. Surgical resection is the possible long term curative treatment option in patients with resectable or borderline resectable disease.[9] But the challenge in surgery is that pancreatic tumors are surrounded by a dense stromal layer which makes access difficult. The prognosis is predicted by the presence of tumor marker CA 19-9 in the blood before and after surgery, a low CA 19-9 level indicates a better prognosis.

Even though FOLFIRINOX has significant adverse effects, it is one of the first line treatment options for advanced pancreatic cancer. Before 20 years gemcitabine was the mono-therapeutic gold standard for treatment of pancreatic cancer[10] but clinical trials proved that there were no significant improvement in the overall survival (OS) rates with combination gemcitabine therapy.[11,12] A Randomised Control Trial by PRODIGE/ACCORD demonstrated that the OS rate was better with the four combination regimen FOLFIRINOX than with gemcitabine (11.1 vs 6.5 months).[13] Apart from the survival benefits of FOLFIRINOX a controversy about the possible adverse effects and toxicities of this combination regimen still exists.[14] Patients who do not have metastatic spread after FOLFIRINOX can undergo subsequent radiotherapy (RT) to achieve local control.[15]

Neoadjuvant chemotherapy with or without chemoradiation for localized disease allows for systemic control and improves the chances of resection, particularly when the possibility of complete resection is unclear [e.g., for borderline resectable pancreatic cancer (BRPC) or locally advanced pancreatic cancer (LAPC)]. The optimal regimen in this setting is tolerable and offers both systemic and local control.

Study aimed to assess clinical and pathologic efficacy of

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neoadjuvant FOLFIRINOX for locally advanced (LAPC) and borderline resectable pancreatic cancer (BRPC).

MATERIAL AND METHODS

This retrospective study was conducted in the Department of Medical Oncology at Coimbatore Medical College and Hospital from June 2017 to May 2018.

All patients underwent triphase contrast-enhanced CT. Resectability was determined according to the guidelines of the NCCN. All pre-treatment imaging studies were reviewed by a single radiologist (GR) to categorize tumors as BRPC or LAPC. Chest CT and baseline measurements of CEA and CA 19.9 were done. A biopsy confirming the diagnosis of PDAC was required for all patients before commencing neoadjuvant therapy.

FOLFIRINOX was administered and response to treatment was evaluated every 2-3 months using clinical evaluation, chest and abdominal CT scans, and tumor markers. Patients showing the response to treatment and tolerable side effects completed 4-6 months of treatment. Surgery was performed within 6 weeks after stopping chemotherapy. Progression of disease, treatment intolerance, and deterioration of functional status was an indication to stop treatment and abort plans for curative surgery.

The operation started with laparoscopic exploration aimed to rule out peritoneal and liver metastases, followed by an open exploration and assessment of arterial involvement. Adherence of the tumor to the SMV-PV was an indication for resection and reconstruction of the vein in a standard fashion, and short segment involvement of the hepatic artery or celiac trunk lead to resection and reconstruction of these vessels. Arterial reconstruction was performed as end-to-end anastomosis, or using an autologous graft. Fibrotic encasement of the SMA was biopsied and sent for frozen section analysis (FSA). Presence of tumor cells in the tissue encasing vessels that were not amenable for resection was considered an indication to abort resection. Fibrotic arterial encasement with an FSA that was negative for cancer leads to skeletonization or resection of the vessel.

Postoperative complications were graded Operation started with laparoscopic exploration aimed to rule out peritoneal and liver metastases, followed by an open exploration and assessment of arterial involvement. Adherence of the tumor to the SMV-PV was an indication for resection and reconstruction of the vein in a standard fashion, and short segment involvement of the hepatic artery or celiac trunk lead to resection and reconstruction of these vessels. Arterial reconstruction was performed as end-to-end anastomosis, or using an autologous graft. Fibrotic encasement of the SMA was biopsied and sent for frozen section analysis (FSA). Presence of tumor cells in the tissue encasing vessels that were not amenable for resection was considered an indication to abort resection. Fibrotic arterial encasement with an FSA that was negative for cancer leads to skeletonization or resection of the vessel. Postoperative complications were graded

The histologic grade of the response to treatment was assessed by a single pathologist (EB). The response was graded according to the protocol of the American College of Pathologists. Details regarding the administration of adjuvant therapy were collected.

RESULTS

The neoadjuvant group consisted of 29 PDAC patients, 16 with LAPC and 13 with BRPC who received neoadjuvant FOLFIRINOX (table-1).

A mean number of cycles was 8 (range, 5-14). Eleven patients received between 8-12 cycles of treatment, and the mean interval from the start of neoadjuvant treatment to surgery was 115 days. One patient (6.25%) received radiation therapy. 2 patients (12.5%) had grade 3-4 toxicity, including severe thrombocytopenia (n=2), and fever requiring hospitalization for antibiotic treatment (n=1).

Following FOLFIRINOX treatment, 2 patients (12.5%) initially defined as LAPC were deemed surgical candidates. Reasons for non-resectability following treatment included disease progression (10 patients), locally non-resectable disease (3 patients), and deterioration of patient performance status (1 patient). Of 13 patients initially defined as BRPC, 11 (85%) were deemed surgical candidates. The reason for non-resectability in all 2 cases was systemic disease progression. No cases of local disease progression from BRPC to LAPC were identified.

Portal vein resection was performed in 6 (46.1%) of the patients. Arterial resection was performed in 3 (23%) of patients, including hepatic artery (n=1), SMA (n=1), and

Characteristics		BRPC	LAPC
Age (Mean)		52.4	61.2
Gender	Male	9	9
	Female	4	8
Tumor location	Head/uncinate	58%	61%
	body	42%	39%
Median CA 19-9		129	218
Achieving surgical exploration		11	2

Table-1: Baseline characteristics

Characteristics		Patients operated post neoadjuvant FOLFIRINOX (n=13)
Surgical procedure	Whipple	7
	Distal pancreatec-tomy	5
	Total pancreatectomy	2
Vein resection		6
Arterial resection	Hepatic artery	1
	Celiac trunk	1
	SMA	1
Operative time (hours)		10.28
Postoperative complication	Clavien 1-2	6
	Clavien 3-4	1
Reoperations		1

Table-2: operative procedures and perioperative outcomes

celiac trunk resection (n=1). Arterial reconstruction was required in three cases in which the SMA or the celiac artery and hepatic artery and GDA were resected. Reconstruction was performed as an end-to-end anastomosis in two cases, and using autologous splenic artery graft (from the resected distal pancreas, n=1). In one case the left HA and GDA were resected, and arterial supply was based on dominant replaced right HA (table-2). Notably, there were no cases of pancreatic leaks in the patients treated with FOLFIRINOX.

Tumors size was 1.87 cm, the rate of lymphovascular invasion was 17.4%, the peripancreatic fat invasion was 52.2%, 22% of patients had lymph node metastases. R0 resection was achieved in all patients. Evaluation of treatment response grading (TRG) demonstrated complete response (TRG 0) in 2 (15%) patients, and marked response (TRG 1) in 2 (15%) patients.

DISCUSSION

The incidence and the number of deaths caused by LAPC are gradually rising and pancreatic cancer is projected to be the second major cause of cancer deaths in 2030.[16] Despite the substantial progress made in the understanding of the biology of cancer, the 5-year survival rates of patients with pancreatic cancer after diagnosis is only 4% as more than one- third of the patients present with an advanced stage of unresectable disease during diagnosis.[17] This is why curative surgical options are limited in LAPC. FOLFIRINOX is emerging to be the first line of treatment in borderline resectable and LAPC because it has shown significant downstaging of the disease and further management with resection, chemotherapy or chemoradiotherapy seems to improve the OS and PFS rates. The 6-month and 1-year overall survival (OS) rates of locally advanced pancreatic cancer (LAPC) were 90.9% and 76.2% and progression-free survival (PFS) rates of LAPC were 81.5% and 48.5% respectively.[18]

Owing to the dose-related toxicity and adverse events associated with standard FOLFIRINOX like neutropenia, thrombocytopenia, febrile neutropenia, anemia, nausea, fatigue, vomiting, diarrhoea, neuropathy and increased ALT we chose to use the modified regimen to improve the tolerability and efficacy in our study. Modified FOLFIRINOX is more applicable for patients with poor performance status.

In BRPC the surgical oncologist may achieve a good R0 resection rate but with LAPC it is difficult due to the absence of clear tumor margins and localized invasion into the adjacent tissues and resectability is determined by the tumor extension into the superior mesenteric artery(SMA), coeliac artery, superior mesenteric vein(SMV),common hepatic artery and the portal vein. All these vascular extensions differ histopathologically and in CT.[19] In an uncontrolled study with BRPC, who received neoadjuvant therapy with FOLFIRINOX and deemed eligible for pancreatic resection, the survival rate was better than those who did not have pancreatectomy.[20] BRPC patients who require vein resections showed benefits from post-surgical adjuvant chemotherapy.[21] In LAPC where surgery is not possible or where aggressive resection was needed neoadjuvant therapy with FOLFIRINOX significantly downstaged the disease and resulted in better marginal performance status.

Previous studies have been conducted to demonstrate the better therapeutic benefits of FOLFIRINOX when compared to gemcitabine(GEM) monotherapy.[22] The one-year survival rate was much higher for FOLFIRINOX than with GEM even at low dosage intensity with an estimated 76.2% survival rate for LAPC with FOLFIRINOX and 18 to 37.2% with GEM therapy.[23] A prospective phase II study has been conducted for the assessment of adverse events which proved that modified FOLFIRINOX significantly reduced the occurrence of such adverse events.[24] And this hypothesis led the clinical strategy of reducing or stopping FOLFIRINOX chemotherapy in poorly tolerated patients.[25]

It was incurred that the modified FOLFIRINOX neoadjuvant therapy provides good survival benefits for patients with advanced stages of pancreatic cancer by increasing the OS and PFS significantly and also caused only a fewer adverse event. The findings suggest that the dosage attenuation of neoadjuvant FOLFIRINOX improves its tolerability with no compromise on its efficacy. Multiple combinations of the four drugs have been formulated and studied by different authors (for example removal of the 5-FU bolus) to identify the best combination for different ethnic groups and different health conditions and this still remains a subject of concern.[26]

CONCLUSION

The study concludes that FOLFIRINOX was a considerable neoadjuvant regimen in patients with LAPC and BRPC that offers a promising R0 resection rate and is also seen to increase the overall survival and progression-free survival rates of those patients, with minimal toxic drug reactions. Further treatment with surgical resection and adjuvant chemo and radiotherapy may increase the life span of the patient or benefit them positively.

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