JBUON 2020; 25(5): 2525-2527
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

SHORT COMMUNICATION

Initial experience with neoadjuvant FOLFIRINOX as first line therapy for locally advanced pancreatic cancer

Georgia-Sofia Karachaliou, Vasiliki Lazarou, Dimitrios Giannis, George Astras, Dimitrios Moris, Athanasios Petrou

Nicosia Department of Surgery/Div. HPB, 93 Agiou Nikolaou Street, Engomi, 2408, Nicosia, Cyprus.

Summary

The prevalence of pancreatic ductal adenocarcinoma (PDAC) is increasing in the western world, being currently on of the leading causes of mortality. Surgical resection provides best chances of cure but, unfortunately, less than 20% of the patients are eligible for curative intent surgery at the time of diagnosis. Chemotherapeutic agents such as FOLFIRINOX have been used in patients with metastatic or locally advanced disease showing survival benefit.

Methods: *In this pilot study, we present an early initial experience with neoadjuvant FOLFIRINOX as first line therapy for locally advanced and non resectable PDAC highlighting the toxicity and complete resection rates as well as overall survival.*

Results: *Roughly every patient experienced toxicity according to ECOG criteria with a median recorded event up to 6, most of them grade I and grade II. One third of the patients had downsizing of tumor, however only 43.3% of them ended up having resectable disease. A R0 resection was achieved in 10 of the patients (76.9%). Median follow up for the entire study was 14 months. Fourteen patients (46.6%) had stable disease and 7 (23.3%) had tumor-related death. Approximately 30% of the patients were in remission by the end of follow up. Considering the above results patients that had good response to FOLFIRINOX and underwent R0 surgical treatment had increased their median survival to 30 months compared to those who did not have oncological tumor resection (13 months).*

Conclusions: *FOLFIRINOX is an effective treatment regimen that manages to convert unresectable -at diagnosis PDAC- to resectable with increased survival. However, due to high toxicity, treatment is only feasible in selected patients and requires close monitoring.*

Key words: *pancreatic cancer, FOLFIRINOX, toxicities, survival*

Introduction

The prevalence of pancreatic ductal adenocarcinoma (PDAC) is increasing in the western world, being currently one of the leading causes of mortality, with complete resection of the tumor being the only chance of cure [1]. Unfortunately, this is only feasible in about 10-20% of the patients at the time of presentation and the rest of them are treated with chemotherapy and radiotherapy, with less than 20% overall survival [2]. Since 2011, a new combination of chemotherapeutic agents, FOLFIRINOX (bolus and continuous infusion 5-FU, leucovorin, oxaliplatin, irinotecan) was introduced for patients with metastatic PDAC [3]. The ACCORD trial demonstrated increased median overall survival with FOLFIRINOX (11.1 months) when compared to gemcitabine (6.8 months) [3]. These encouraging results led to a wider application of FOLFIRINOX in patients with locally advanced PADC [4].

Here, we present an early initial experience with neoadjuvant FOLFIRINOX as first line therapy

Corresponding author: Dimitrios Moris, MD, MSc, PhD. Nicosia Department of Surgery/Div. HPB, 93 Agiou Nikolaou Street, Engomi, 2408, Nicosia, Cyprus
Tel:+306073671665, Fax:+302106440590, Email: dimmoris@yahoo.com
Received: 11/03/2020; Accepted: 02/04/2020

for locally advanced and non resectable pancreatic cancer, highlighting the toxicity and complete resection rates as well as overall survival.

Methods

After approval from the Institutional Review Board we performed a retrospective analysis of all patients since 2011 with pancreatic cancer. All patients were diagnosed as locally advanced pancreatic cancer and underwent Whipple procedure. Disease-free survival and overall survival were reported since the date of diagnosis. All patients underwent a triple-phase contrast-enhanced CT scan in order to define resectability and tumor size. Biopsy-histology was obtained under CT or endosonographic guidance. Patients with occlusion of superior mesenteric or portal vein and invasion of superior mesenteric artery, hepatic artery or celiac trunk were considered as locally advanced and included in this study. Patients with borderline resectable tumors or with metastatic disease were not included in our analysis.

Demographic information, patient characteristics, preoperative procedures and regimen are presented in Table 1. Toxicity was documented according to the Eastern Cooperative Oncology Group (ECOG) toxicity criteria into 0 (none) up to 5 (life threatening-death). FOLFIRINOX regimen consisted of leucovorin 175 mg intravenous infusion followed by irinotecan at a dose of 180 mg/m^2 (90 min intravenous infusion) and a bolus dose 400mg/m^2 of fluorouracil. The treatment was followed by a continuous intravenous infusion of 600mg/m^2 per 11.5 hrs infusion (total dose 2400mg/m^2) over a 46-hour period. FOLFIRINOX cycle was administrated every 15 days. Additional dose adjustments, supportive care as well as therapy modifications were conducted by a medical oncologist.

Table 1. Demographics and patient characteristics

Characteristics	*Number (%)*
Gender	
Male	20 (66.6)
Female	10 (33.4)
Median age, years	62 (47-76)
Weight loss (kg)	12
Race	
Caucasian	26 (86.4)
Other	4 (13.3)
ECOG performance status	
0	12 (40)
1	18 (60)
Pancreatic tumor location	
Head	27 (90)
Uncinate process	3 (10)
Biliary stent	
Yes	7 (23.4)
No	23 (76.6)
Jaundice prior to treatment	
Yes	7 (23.5)
No	23 (76.5)
T stage (TNM)	
T3	9 (30)
T4	21 (70)
N stage (TNM)	
N0	8 (26.6)
N1	22 (73.3)

Results

Since 2011 a total of 30 patients with locally advanced pancreatic tumor were qualified from the multidisciplinary board to receive FOFLIRINOX. Twenty patients (66.6%) had tumor-related comorbidities at the time of diagnosis and 13 (43.3%) had dose reduction due to the aggressiveness and toxicity of treatment. Roughly, every patient experienced toxicity according to ECOG toxicity criteria with a median recorded event up to 6, most of them grade I and grade II. Two patients had grade III infection, and another had grade IV pulmonary toxicity, and all had to stop treatment.

Ten of thirty patients had downsizing of tumor though 13 of them were able to undergo resection (43.3%) some including also vascular reconstruction. One of the patients had local response with conversion of locally unresectable tumor to borderline but developed metastatic disease thus surgery was excluded as option of therapy. Two of the patients had progressive disease and the rest of them (14/30) had stable disease. Pancreaticoduodenectomy was the operation that all the patients received due to the localization of the tumor with median operative time longer than resectable tumors that did not receive neoadjuvant therapy. Three of 13 patients had vascular resection-reconstruction in order to obtain macroscopic oncological resection, all involving the superior mesenteric vein. A R0 resection was achieved in 10 of the patients (76.9%). Regarding the postoperative course, 2 of the patients had grade II respiratory infection and one of them grade II wound infection (Dindo-Clavien classification) [5]. No postoperative mortality was noted (within two weeks).

Median follow up for the entire study was 14 months. Fourteen patients (46.6%) had stable disease and 7 (23.3%) had tumor-related death. Approximately 30% (9/30) of the patients were in remission by the end of follow up. Patients with progressive disease passed away in 6 months, but patients with stable or partial remission disease lived up to 14 months. Considering the above results patients that had good response to FOL-

FIRINOX and underwent R0 surgical treatment had increased their median survival to 30 months compared to those who did not have oncological tumor resection (13 months).

Discussion

This retrospective study indicates that FOLFIRINOX can be considered as a new standard of care for patients with locally advanced pancreatic cancer since it is safe in patients with good performance status and potentially rendered locally advanced tumors into resectable. According to a meta-analysis, FOLFIRINOX treatment offers R0 resection rates of 64% in borderline and 23% in locally advanced pancreatic tumors [4]. This treatment combined with other chemotherapeutic regimens was very well tolerated with mild grade I and II toxicities and led to a temporary tumor control, with significant improvement of median survival.

Patients who received FOLFIRINOX in this study were fit and healthy, but the toxicities cannot be overlooked. Most of the patients experienced toxicity effects graded up to II with 6 median events and two of them had to quit therapy. Thus, the decision to initiate FOLFIRINOX treatment requires multidisciplinary consensus, appropriate selection of patients as well as supportive care during chemotherapy administration including antiemetics, growth factors or hydration, even dose reduction. Despite the high rates of toxicity, there was no effect of the patient suitability for surgical resection or even in postoperative morbidity or mortality.

Our study has limitations that should be mentioned. It is of retrospective nature and limited to a small number of patients with locally advanced pancreatic cancer. Even though, it is aligned with emerging literature demonstrating increasing response and resection rates as well as survival benefit in patients with locally advanced pancreatic cancer [6-8].

Conclusions

FOLFIRINOX is an effective treatment regimen that manages to convert unresectable -at diagnosis pancreatic cancer - to resectable with increased survival. However, due to high toxicity, treatment is only feasible in selected patients and requires close monitoring. Further clinical trials are required to provide evidence-based treatment recommendations, still FOFLFIRINOX will definitely influence the treatment of pancreatic cancer in future studies.

References

1. Moris D, Machairas N, Tsilimigras DI et al. Systematic Review of Surgical and Percutaneous Irreversible Electroporation in the Treatment of Locally Advanced Pancreatic Cancer. Ann Surg Oncol 2019;26:1657-68.
2. Petrou A, Soonawalla Z, Silva MA et al. Prognostic indicators following curative pancreatoduodenectomy for pancreatic carcinoma: A retrospective multivariate analysis of a single centre experience. JBUON 2016;21:874-82.
3. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
4. Rombouts SJ, Walma MS, Vogel JA et al. Systematic Review of Resection Rates and Clinical Outcomes After FOLFIRINOX-Based Treatment in Patients with Locally Advanced Pancreatic Cancer. Ann Surg Oncol 2016;23:4352-60.
5. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
6. Hosein PJ, Macintyre J, Kawamura C et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer 2012;12:199.
7. Strobel O, Berens V, Hinz U et al. Resection after neoadjuvant therapy for locally advanced, "unresectable" pancreatic cancer. Surgery 2012;152:S33-42.
8. Nanda RH, El-Rayes B, Maithel SK et al. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. J Surg Oncol 2015;111:1028-34.