Pancreatology 14 (2014) 425–430

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Case report

Complete pathological response after FOLFIRINOX for locally advanced pancreatic cancer. The beginning of a new era? Case report and review of the literature

S. Valeri [a], D. Borzomati [a], G. Nappo [a, *], G. Perrone [b], D. Santini [c], R. Coppola [a]

[a] Unit of General Surgery, Campus Bio-Medico University of Rome, Italy
[b] Department of Pathology, Campus Bio-Medico University of Rome, Italy
[c] Unit of Medical Oncology, Campus Bio-Medico University of Rome, Italy

ARTICLE INFO

Article history:
Available online 19 July 2014

Keywords:
FOLFIRINOX
Pancreatic cancer
Neoadjuvant treatment
Complete pathological response
Locally advanced pancreatic cancer
Neoadjuvant chemotherapy

ABSTRACT

Neoadjuvant treatments (chemo or chemoradiation therapy) are used for patients with locally advanced Pancreatic Ductal Adeno-Carcinoma (PDAC). FOLFIRINOX is now considered an effective treatment modality for patients with metastatic pancreatic cancer and a promising option for patients with locally advanced PDAC. Complete pathologic response after neoadjuvant therapies is anecdotic and its prognostic impact is completely unclear. We report the case of a complete pathological response after treatment with FOLFIRINOX in a patient affected by a locally advanced PDAC with a review of the literature regarding the use of FOLFIRINOX for locally advanced PDAC.

Introduction

Pancreatic Ductal Adeno-Carcinoma (PDAC) is the fourth leading cause of cancer-related death [1], with a 5-year overall survival rate of 2–6% [2]. Surgical resection is the only chance of cure for PDAC. However, at diagnosis, only 20% of patients fulfill the resectability criteria. At clinical presentation, 30–40% of patients are affected by a locally advanced cancer due to abutment of the celiac axis, aortic invasion or significant superior mesenteric artery encasement [3]. In spite of neoadjuvant treatments (chemotherapy- or chemoradiation therapy) are advocated for locally advanced PDAC there is no compelling evidence from randomized phase III trials of clinical benefit [4]. Complete pathologic response after neoadjuvant therapy is increasingly recognized as an important prognostic factor after surgical excision of malignancies, including gastric, breast and rectal cancer [5–7]. In case of locally advanced PDAC the evidence of a complete pathologic response after neoadjuvant therapies is anecdotic and its prognostic impact is unclear [8]. We herein report the case of a complete pathological response after neoadjuvant treatment with FOLFIRINOX in patient affected by a locally advanced PDAC.

Case report

A 73 year-old woman affected by a locally advanced pancreatic adenocarcinoma of the head was referred at our Institution (Fig. 1). CT-scan showed infiltration of the portal vein confluence (more than 180°), absence of portal thrombosis, infiltration of the hepatic artery, enlarged aorto-caval lymphnodes (sizing 5 cm in diameter). Laboratory exams were normal with only a slight increase of CA 19.9 (77.6 UI/mL, normal value < 37 UI/mL). Percutaneous US-guided biopsy of the lesion showed an undifferentiated carcinoma (Fig. 2). Immunohistochemistry revealed absence of sinaptofisin receptors and presence cytokeratine receptors, suggesting the epithelial origin of the lesion. Moreover, the negativity of CK 20 (expressed in the epithelium of intestinal cells), and the positivity of CK7 also confirmed the pancreatico-biliary origin of the tumor (Fig. 3). According to these results, the patient underwent 8 cycles of chemotherapy with FOLFIRINOX regimen (Irinotecan 180 mg/mq; Oxaliplatin 85 mg/mq; 5-Fluorouracil 400 mg/mq; Folinic acid 400 mg/mq) for a duration of 5 months. No dose reduction was required. Major toxicity during the whole treatment was not recorded (only grade 2 neutropenia and thrombocytopenia). Re-staging CT-scan showed the complete disappearance of the tumor (Fig. 4) with normal flow of the portal vein and of the superior mesenteric vein. The enlarged aorto-caval lymphnodes were no more visible (Fig. 5). Based on radiological downstaging, the patient was offered surgical exploration. At laparotomy, no hepatic or

* Corresponding author.
E-mail address: g.nappo@unicampus.it (G. Nappo).

http://dx.doi.org/10.1016/j.pan.2014.07.002

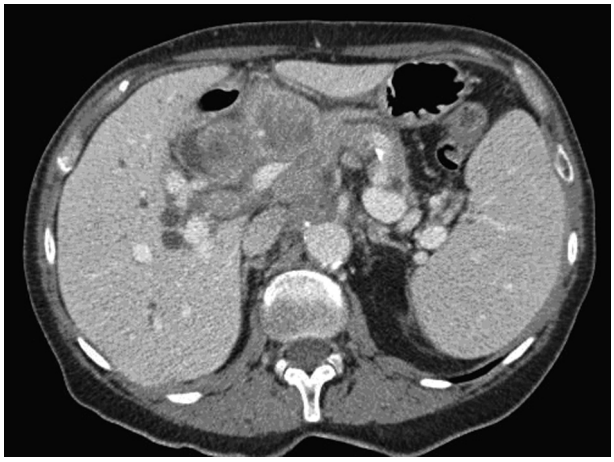

Fig. 1. CT-scan shows the presence of a large periampullary mass. This image is not able to discriminate if there was a lesion originating from the distal common bile duct or from the thead of the pancreas.

peritoneal metastases were found. Pancreaticoduodenectomy without vascular resections was performed. A relevant grade of fibrosis was observed during the dissection. Frozen sections of aorto-caval nodes, of transectional margins (biliary, duodenal, and pancreatic) and of the fibrotic tissue around the hepatic artery were negative. The post-operative course was uneventful and the patient was discharged on post-operative day 9. The pathological staging was pT0pN0 with absence of neoplastic cells both in the specimen and in all examined lymphnodes (Figs. 6 and 7). No adjuvant treatment was performed. Fourteen months after surgery, the patient is alive without evidence of local or distant disease recurrence. The length of overall survival (from time of diagnosis to present) is twenty-four months.

Discussion

Nowadays, only 20–25% of PDAC patients undergo surgical resection and adjuvant chemotherapy [9,10]. Unresectability is due to advanced-stage disease, with (50%) or without (30%) metastases [9,10]. Patients affected by locally advanced lesions are treated with "neoadjuvant treatments" (radiotherapy, chemotherapy or radiochemotherapy) [11–16]. The effectiveness of these treatments in this large subset of patients is still an argument of debate. Several papers have addressed this issue in clinical trials, implementing different radiation doses and regimens, radiation techniques, and combinations with various chemotherapeutic agents [14–16]. FOLFIRINOX is an aggressive therapeutic option for patient with metastatic PDAC. Conroy et al. [17] first reported impressive results in terms of efficacy and tolerability in a phase II study on 46 patients with unresectable pancreatic cancer (11 locally advanced, 35 metastatic). More recently, the same group compared FOLFIRINOX with gemcitabine in a randomized phase III trial in 342 metastatic PDAC patients [18]. This study showed a significant clinical impact for the FOLFIRINOX arm in terms of overall survival (11.1 months Vs 6.8 months), 1-year survival (48.8% vs 20.6%) and objective Response Rate (RR) (31.6% vs 9.4%). Based on these results, FOLFIRINOX is considered a very effective therapy for metastatic pancreatic cancer patients. However, due to toxicity, there is still reluctance to use full doses FOLFIRINOX. Moreover, in spite of improved oncological results given in the metastatic setting, there are limited data on its efficacy and tolerability in locally advanced pancreatic cancer.

MD Anderson criteria well defined the difference between the borderline and locally advanced pancreatic cancer [19]. Tumor abutment of less than or equal to 180° (< or =50% of the vessel circumference) of the superior mesenteric artery, short segment abutment or encasement (> or =50% of the vessel circumference) of the common hepatic artery (typically at the gastroduodenal artery origin), or segmental venous occlusion are used to categorize a pancreatic tumor as borderline resectable. Locally advanced pancreatic cancer is otherwise defined as a tumor abutment more than 180° (>50% of the vessel circumference) of the superior mesenteric artery, long segment abutment or encasement (>50% of the vessel circumference) of the common hepatic artery, or portal thrombosis.

Table 1 summarizes all the studies reporting the use of FOLFIRINOX in locally advanced pancreatic cancer. Disappointingly, the majority of these studies included borderline resectable and locally advanced patients with or without distant metastases.

In the above mentioned study by Conroy and Coll [17], authors report a series of 46 patients affected by metastatic (35 cases) and locally advanced (11 cases) treated with FOLFIRINOX. Treatment-related mortality was absent with 52% of patients experiencing grade 3 to 4 neutropenia. Grade 3 to 4 nausea (20%), vomiting (17%) and diarrhea (17%) and grade 3 neuropathy (13%) were also recorded. The response rate was 26%, including 4% of complete responses. Median time to progression was 8.2 months and median overall survival was 10.2 months. In the subset of patients with locally advanced (non metastatic) pancreatic cancer, the Response Rate (RR) was 27.3%, with a median Overall Survival (OS) of 15.7 months.

Mahaseth et al. [20] reported a series of 28 patients treated with FOLFIRINOX for locally advanced pancreatic cancer. Eight patients (29%) experienced grade 3/4 toxicities: nausea/vomiting (11%), diarrhea (11%), fatigue (11%), neuropathy (4%), neutropenia (4%), thrombocytopenia (4%), and sepsis-not related to neutropenia (4%).

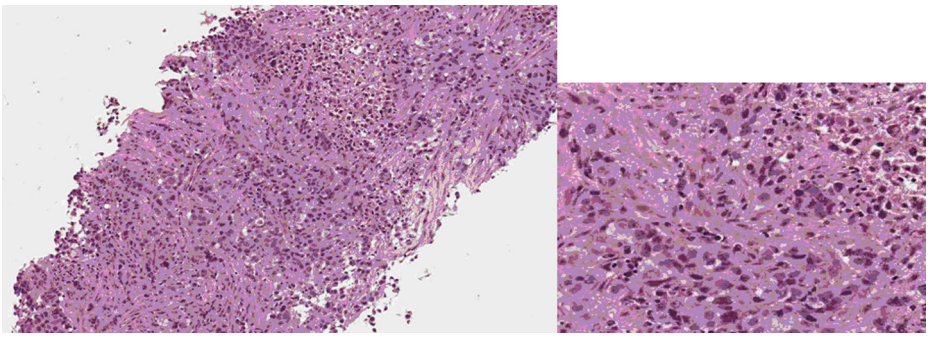

Fig. 2. The bioptic specimen shows the complete replacement of normal pancreatic parenchyma with infiltration of neoplastic cells, with severe atypiae, and fibrous tissue.