Case Series

Resection of Locally Advanced Pancreatic Neoplasms after Neoadjuvant Chemotherapy with Nab-Paclitaxel and Gemcitabine following FOLFIRINOX Failure

Sarah Hahn^a Ahmet Ayav^b Anthony Lopez^a

^aDepartment of Gastroenterology and Hepatology and Inserm U954, Nancy University Hospital, Lorraine University, Vandoeuvre-lès-Nancy, France;

^bDepartment of HPB Surgery, University Hospital Nancy Brabois, Lorraine University, Vandoeuvre-lès-Nancy, France

Keywords

Pancreas · Drug therapy · Surgery · Tumor

Abstract

The incidence of pancreatic cancer has dramatically increased over the past years, but the prognosis has not improved. Between 30 and 40% of tumors are considered locally advanced, essentially due to vascular involvement. In recent years, new chemotherapy protocols with high response rates have been developed. FOLFIRINOX seems to be an interesting option in this situation, but hematologic toxicity could be an obstacle to its prescription. Nab-paclitaxel and gemcitabine offer significant response rates with a reasonable safety profile. We report here a single-center experience of 2 cases with a locally advanced pancreatic cancer initially considered unresectable, progressive after first-line neoadjuvant FOLFIRINOX chemotherapy, and then treated with second-line nab-paclitaxel/gemcitabine chemotherapy.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Introduction

Pancreatic cancer is the second most frequent digestive neoplasm after colorectal cancer [1], and it is expected to be the second leading cause of cancer-related death by 2030 in the US [2]. With an overall survival of 7% at 5 years, the prognosis of pancreatic cancer has not improved over the past two decades [1]. Surgical resection is the only available potentially curative treatment, with a survival rate of 20% at 5 years, but only 15–20% of patients can benefit from it [3]. Locally advanced pancreatic cancer, either unresectable or borderline resectable, is often treated with systemic neoadjuvant chemotherapy, with the hope of surgical cure. This situation concerns between 30 and 40% of patients [1]. Due to the heterogeneity and small sample size of available retrospective series, it is difficult to recommend a specific schedule of treatment for these patients. Since 2011, chemotherapies with response rates between 20 and 30% are used in metastatic pancreatic cancer patients based on two phase III studies evaluating FOLFIRINOX [4] and nab-paclitaxel/gemcitabine [5]. We report here 2 cases with a locally advanced pancreatic cancer initially considered unresectable, progressive after first-line neoadjuvant FOLFIRINOX chemotherapy, and then treated with second-line nab-paclitaxel/gemcitabine chemotherapy.

Case 1

We present the case of a 44-year-old man with a history of glaucoma. He smoked about one pack of cigarettes a day during 25 years and stopped 1 year before his first visit at our institution. He suffered from persistent epigastric pain during 2 months that led to a gastroenterologist consultation in April 2015. Due to CA19-9 values four times the upper limit of normal, an endoscopic ultrasonography was performed, finding a mass of the pancreatic isthmus in contact with the superior mesenteric vein (SMV). The initial computed tomography (CT) scan demonstrated a mass of the pancreatic body in contact with the celiac axis (CA) and common hepatic artery (CHA) encasement $>180^\circ$, but without regional lymphadenopathy or distant metastasis (Fig. 1a). Given the contact with the CA and the CHA, the tumor was deemed locally advanced and nonresectable.

Based on the Eastern Cooperative Oncology Group (ECOG) status of 0, the patient began a systemic treatment with FOLFIRINOX (oxaliplatin 85 mg/m² of body surface area, leucovorin 400 mg/m², irinotecan 90 mg/m², and 5-fluorouracil 400 mg/m² given as a bolus followed by 2,400 mg/m² as a 46-h continuous infusion, every 2 weeks, with granulocyte colony-stimulating factor support). Four cycles of chemotherapy were administered without major toxicity.

After 2 months of treatment, the patient underwent a restaging CT scan, which showed partial regression of the tumor of about 10% and a persistent contact with the CA and the CHA $>180^\circ$ (Fig. 1b). The tumor was still not resectable after four cycles of first-line chemotherapy, so we initiated a second line of systemic chemotherapy with a nab-paclitaxel/gemcitabine regimen. Three cycles were administered (1,000 mg/m² of gemcitabine and 125 mg/m² of nab-paclitaxel on days 1, 8, and 15 every 28 days), without major toxicity. The patient underwent a new restaging CT scan after the three cycles of chemotherapy, which showed good tumoral response, with regression of the perivascular infiltration (Fig. 1c). We also noticed a decrease in the CA19-9 level (Fig. 2). According to the tumoral response on the CT scan and the young age of the patient, he was offered surgical exploration. The latter did not find any peritoneal carcinomatosis or liver metastasis, and intraoper-

ative frozen sections of tissue around the CHA showed no evidence of malignancy, so that a distal pancreatectomy was performed. The pathological tumor stage was ypT2N0. It was a R0 resection, with security margins >1 mm.

The patient received additional nab-paclitaxel/gemcitabine as adjuvant treatment for 3 months, considering efficacy of this regimen before surgery. Unfortunately, 2 months after the end of chemotherapy, CT scan showed local tumoral recurrence and signs of peritoneal carcinomatosis. At present he has been treated with palliative chemotherapy for 6 months.

Case 2

We present the case of a 62-year-old woman with a history of diabetes and arterial hypertension. She consulted a gastroenterologist because of a major weight loss during the past few months, over 10 kg in 6 months, associated with diarrhea (until 10–12 bowel movements a day). A CT scan was performed and a pancreatic head mass (15 × 25 mm) involving the SMV was diagnosed (Fig. 3a), with infracentimetric liver and pulmonary lesions considered aspecific by the local multidisciplinary tumor board. A liver magnetic resonance imaging (MRI) scan was performed, but the lesions were too small to draw a conclusion. Given the contact with the SMV, the tumor was deemed borderline.

Based on the ECOG status of 0, the patient began systemic treatment with a FOLFIRINOX regimen. Four cycles of chemotherapy were administered. During the treatment, the patient developed fatigue, but global tolerance was acceptable, with an ECOG status remaining between 0 and 1.

After 2 months of treatment, the patient underwent a restaging CT scan (Fig. 3b). It showed tumoral progression and involvement of the right side of the superior mesenteric artery (SMA). The tumor was considered unresectable, and we started palliative chemotherapy with nab-paclitaxel/gemcitabine.

Three cycles of chemotherapy were administered. The patient underwent a new restaging CT scan after the three cycles of chemotherapy, which showed significant tumoral response, with a 29% regression of the mass and a contact <180° with the SMA (Fig. 3c).

According to the regression of the tumor, the patient underwent surgical exploration. The surgeon found no irresectability criteria, so that the patient underwent total duodenopancreatectomy associated with splenectomy. The surgery led to no major complication except for mild malnutrition. As a consequence, enteral nutrition was administered for a few months.

The patient received adjuvant nab-paclitaxel/gemcitabine adjuvant chemotherapy, but only two cycles of chemotherapy were administered due to deterioration of her general health status, with an ECOG status of 3. After the end of chemotherapy, the performance status improved. Within 1 year of regular monitoring with physical examinations, laboratory tests, and CT scans, we have found no sign of tumor recurrence.

Discussion

The treatment of borderline/locally advanced pancreatic tumors is still controversial. There are different approaches, such as neoadjuvant chemotherapy followed or not by chemoradiation. A meta-analysis published in 2010 [6] showed that approximately one-third of tumor patients initially staged nonresectable would be expected to have resectable

tumors following neoadjuvant therapy, with a survival comparable to that of initially resectable tumor patients. In the same study, polychemotherapies were superior to monochemotherapies in terms of response and resection rates. Robust data about the role of neoadjuvant chemotherapy in case of locally advanced pancreatic cancer are scarce. In a monocentric study with 22 patients treated with FOLFIRINOX, 5 patients had a R0 resection, with a progression-free survival of 11.7 months [7]. However, this chemotherapy regimen is significantly associated with more hematologic toxicity than gemcitabine alone [4]. The safety profile of nab-paclitaxel/gemcitabine seems to be better [5], even if no direct comparison with FOLFIRINOX was made. Moreover, the nab-paclitaxel plus gemcitabine regimen seemed to be effective after FOLFIRINOX failure in a prospective multicenter cohort study in 57 patients with metastatic pancreatic adenocarcinoma [8].

Another key issue is to determine the eligibility for surgery in borderline/unresectable patients after neoadjuvant treatment. For the 2 described patients, we organized a CT scan after 2 months of chemotherapy. However, a retrospective cohort study showed that the sensitivity and specificity of CT and MRI to detect vascular involvement were only 71 and 58% after downstaging chemotherapy [9]. Vascular involvement on imaging was often tumor fibrosis rather than viable neoplastic cells. In these 2 cases, the CT scan overestimated the tumors, but the patients could still have a lifesaving R0 resection, which is one of the most significant factor for survival [10].

These 2 cases illustrate that locally advanced pancreatic cancer patients with a good performance status might undergo explorative laparotomy, even after two lines of chemotherapy, as achieving a R0 resection may still be possible in some cases. Moreover, local tumor extension tends to be overestimated by imaging procedures after neoadjuvant chemotherapy.

In these 2 cases, we first prescribed a FOLFIRINOX chemotherapy regimen as neoadjuvant treatment due to its good response rate. However, nab-paclitaxel/gemcitabine can be another valid option, with a better safety profile. A phase II randomized trial comparing nab-paclitaxel/gemcitabine and gemcitabine alone in locally advanced pancreatic cancer patients is ongoing (NCT02043730). Finally, chemoradiotherapy in patients with disease controlled after induction chemotherapy could be a promising treatment, but the available data are conflicting [11, 12]. A phase III study recently began comparing neoadjuvant mFOLFIRINOX with or without preoperative concomitant chemoradiotherapy in patients with borderline resectable pancreatic carcinoma (PANDAS-PRODIGE 44, NCT02676349).

Statement of Ethics

Informed consent was obtained for this case report.

Disclosure Statement

The authors have nothing to disclose.

Author Contributions

A. Lopez and S. Hahn wrote the manuscript. A. Lopez is the article guarantor. A. Ayav critically revised the manuscript. All authors approved the final manuscript.

References

- 1 Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
- 2 Rahib L, Smith BD, Aizenberg R, et al: Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74:2913–2921.
- 3 Garrido-Laguna I, Hidalgo M: Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. *Nat Rev Clin Oncol* 2015;12:319–334.
- 4 Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New Engl J Med* 2011;364:1817–1825.
- 5 Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *New Engl J Med* 2013;369:1691–1703.
- 6 Gillen S, Schuster T, Meyer zum Buschenfelde C, et al: Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267.
- 7 Faris JE, Blaszkowsky LS, McDermott S, et al: FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist* 2013;18:543–548.
- 8 Portal A, Pernot S, Tougeron D, et al: Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after FOLFIRINOX failure: an AGEO prospective multicentre cohort. *Br J Cancer* 2015;113:989–995.
- 9 Donahue TR, Isacoff WH, Hines OJ, et al: Downstaging chemotherapy and alteration in the classic computed tomography/magnetic resonance imaging signs of vascular involvement in patients with pancreaticobiliary malignant tumors: influence on patient selection for surgery. *Arch Surg* 2011;146:836–843.
- 10 Barugola G, Partelli S, Marcucci S, et al: Resectable pancreatic cancer: who really benefits from resection? *Ann Surg Oncol* 2009;16:3316–3322.
- 11 Huguet F, Andre T, Hammel P, et al: Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326–331.
- 12 Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al: Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA* 2016;315:1844–1853.

Fig. 1. CT scans of patient 1 at diagnosis (a), after FOLFIRINOX (b), and after nab-paclitaxel/gemcitabine (c).

Fig. 2. Evolution of CA19-9 levels in cases 1 and 2.

Fig. 3. CT scans of case 2 at diagnosis (a), after FOLFIRINOX (b), and after nab-paclitaxel/gemcitabine (c).