A case of successful resection after FOLFIRINOX in a patient with borderline resectable pancreatic adenocarcinoma

Yusuke Shimodaira¹ · Seiji Ohigashi¹ · Koyu Suzuki² · Gautam A. Deshpande³ · Keiichiro Ohta¹

Received: 2 March 2015 / Accepted: 2 April 2015 / Published online: 9 April 2015
© The Japan Society of Clinical Oncology 2015

Abstract Pancreatic adenocarcinoma (PAC), one of the most aggressive human neoplasms, continues to have an exceedingly poor prognosis. With the advance of diagnostic techniques, a distinct subset of pancreatic cancer labeled “borderline resectable pancreatic cancer” has emerged. Optimal treatment of this disease with a multidisciplinary approach including neoadjuvant and adjuvant therapy remains controversial. We describe a case of borderline resectable PAC treated with FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) followed by successful pancreaticoduodenectomy. CT scan demonstrated a pancreatic head tumor attached to the superior mesenteric artery, subsequent to which the patient received FOLFIRINOX. Follow-up images showed no lymph node involvement or metastatic disease, suggesting that radical surgery would be curative. The patient underwent pancreaticoduodenectomy with negative margins and was subsequently diagnosed as Stage III (T3N0M0). Though requiring precise case selection and toxicity management, recent literature suggests that FOLFIRINOX is an effective neoadjuvant regimen in the setting of borderline resectable PAC.

Keywords Neoadjuvant therapy · FOLFIRINOX · Borderline resectable pancreatic cancer · Pancreatic adenocarcinoma

Introduction

Despite advances in surgical technique, imaging technology, chemotherapy, and radiotherapy, pancreatic adenocarcinoma (PAC) still remains one of the most aggressive cancers, causing more than 20,000 deaths every year in Japan. The median 5-year survival is less than 5 % [1, 2]. Complete surgical resection remains the only treatment with curative potential, but only 10–20 % of patients with pancreatic cancer will be candidates for curative resection at diagnosis [3]. Here, we present a patient with borderline resectable PAC who underwent successful resection after neoadjuvant FOLFIRINOX therapy.

Case report

A 73-year-old man was diagnosed with a solid tumor at the pancreatic head after receiving transabdominal ultrasonography for sudden elevations in blood glucose. Histopathological findings from endoscopic ultrasound-guided fine-needle aspiration biopsy revealed PAC. Computed tomography (CT) demonstrated a solid tumor at the pancreatic head with an axial diameter of 3.0 cm, and attachment (<180°) to the superior mesenteric artery (SMA) without compromise of celiac axis (CA) or portal vein (Fig. 1). There was no evidence of lymph node involvement or metastatic disease. CA19-9 was elevated (1263.0 UI/mL). After diagnosis of borderline resectable PAC, the patient was administered 16 cycles of FOLFIRINOX (L-

✉ Yusuke Shimodaira
yshimodaira@mdanderson.org

¹ Department of Gastrointestinal Surgery, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan

² Department of Pathology, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan

³ Center for Clinical Epidemiology, St. Luke's Life Science Institute, 10-1 Akashi-cho, Chuo-ku, Tokyo 104-0044, Japan

Fig. 1 Computed tomography at the time of diagnosis showed the attachment ($<180^\circ$) of the tumor to the superior mesenteric artery (SMA) (arrow) and also suggested tumor attachment to the root of the right colic artery (RCA)

Fig. 2 Computed tomography after FOLFIRINOX showed no progression of disease and less compromise of SMA and RCA (arrow)

OHP 85, CPT-11 180, I-LV 200 mg/m² day 1, 5-FU 400 mg/m² bolus day 1, 5-FU 2400 g/m² on 46 h infusion every 2 weeks). Bolus 5-FU was discontinued because of the development of Grade 3 fatigue after 2nd cycle. After 7th cycle, he required 20 % dose reduction of L-OHP for Grade 3 peripheral sensory neuropathy, and after 13th cycle the dose had to be reduced by another 20 % due to Grade 3 neuropathy. CA19-9 decreased to 25.6 UI/mL by the end of treatment. Follow-up CT demonstrated no progression in local disease, obscuration of attachment to SMA, and no metastatic disease (Fig. 2). 18F-FDG positron emission tomography (PET) showed no evidence of increased FDG activity in the pancreas (Fig. 3). Ten

Fig. 3 Positron emission tomography (PET) after preoperative chemotherapy showed no evidence of increased FDG activity in pancreas head (arrow)

Fig. 4 Histopathology review demonstrated moderately differentiated adenocarcinoma consisted with irregular gland formation (arrow). Poorly differentiated adenocarcinoma was recognized in some portions. About 50 % variable residual carcinoma cells were identified

months after the initial diagnosis, after 6 weeks since last administration of FOLFIRINOX, the patient underwent a subtotal stomach-preserving pancreaticoduodenectomy (SSPPD). Histopathological analysis of the specimen showed a 2.0-cm moderately differentiated tubular adenocarcinoma, and the patient was assessed to be Stage III (T3N0M0) (Figs. 4, 5). Surgical margins were free of disease with all 18 examined lymph nodes being negative. Less than half of carcinoma cells in the focus were viable, and the pretreatment effect was considered to be grade IIb [4].

Postoperatively, he was discharged 3 weeks after surgery with no complications. Adjuvant chemotherapy with S-1 (80 mg/body, po bid, day 1–28 every 6 weeks) was

Fig. 5 Immunohistochemistry showed residual carcinoma which are infiltrating into pancreatic parenchyma

started 2 months postoperatively, but stopped due to a keratitis (Grade 3). Currently, the patient continues to do well with no evidence of recurrence after 5 months of follow-up.

Discussion

The overall 5-year survival rate of pancreatic cancer has remained very poor in spite of the combination of surgery, chemotherapy, and radiation therapies [5]. Although margin-free resection is the only potentially curative technique for managing PAC, most patients are diagnosed with advanced disease; as such, only 10–20 % patients are candidates for curable resection at the time of diagnosis [6]. Even with margin-free resection, however, the recurrence rate is extremely high compared with other solid cancers, and the median survival of patients who receive surgical treatment followed by adjuvant therapy is approximately 20 months [7]. The strongest prognostic indicators for long-term patient survival are negative margin status, tumor DNA content, tumor size, and absence of lymph node metastases [8].

With recent advances in imaging and surgical techniques, the distinct subset of “borderline resectable pancreatic cancer” has emerged [9]. How best to treat this group using a multidisciplinary approach including neoadjuvant and adjuvant therapy is a topic of great interest. Although individual institutions typically have their own defining criteria for borderline resectable tumors, among which there remain numerous subtle differences, there is a general consensus that this group of tumors includes those with encasement of a short segment of the hepatic artery, without evidence of tumor extension to the CA and/or tumor abutment of the SMA involving 180° or

less of the artery circumference. The relationship between tumor and superior mesenteric vein–portal vein (SMV-PV) varies by the guideline referenced. For example, the National Comprehensive Cancer Network and American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology guidelines both take a conservative view of the tumor–vein relationship, stating that any impingement or narrowing of the SMV-PV should be considered borderline resectable [9–12].

It still remains controversial whether patients with resectable disease should undergo surgery or preoperative chemotherapy first. Neoadjuvant therapy for borderline resectable PAC is being widely investigated as a potential strategy for down staging initially unresectable tumors, allowing for more successful margin-negative resection. Although there is no high-level evidence supporting neoadjuvant therapy for patients with borderline resectable disease, there is a general consensus in the USA that these patients, having the high possibility of radiographically occult metastatic disease, should not be taken directly to the operating theater without induction therapy, in order to prevent margin-positive outcomes. Preoperative therapy offers several potential benefits including delivery of pharmacotherapy to intact and well-vascularized tissues, tumor downsizing, and maximizing the potential for margin-negative resection. Neoadjuvant therapy also offers the benefit of higher rates of treatment completion, as a reported 24 % of post-operative patients never receive planned adjuvant therapy due to post-surgical complications [13]. Several groups have reported that patients completing preoperative regimens demonstrate lower incidence of margin-positive resection and local recurrence [14, 15]. An added putative benefit of neoadjuvant therapy is selection for surgery of those patients with more stable disease or disease that is more responsive to therapy. A potential risk involving surgical delay is disease progression during the period of preoperative therapy, which could result in a squandered opportunity for surgical intervention. However, it has also been shown that disease progression during the neoadjuvant therapy is less common than previously reported data in which less than 50 % of patients with borderline resectable disease completed whole therapy including successful surgery [12].

Currently, there is insufficient evidence to select specific neoadjuvant regimens, so optimal regimens in this setting remain unclear. Neoadjuvant therapy regimens are often similar to those used in locally advanced and metastatic disease. The results of the ACCORD4/Partenariat de Recherche en Oncologie Digestive (PRODIGE) 11 trial have had considerable influence on the management of patients with metastatic PAC [16]. These results suggest that effective preoperative therapy with FOLFIRINOX may be an important key to managing borderline resectable

Table 1 Summary of select clinical trials with neoadjuvant FOLFIRINOX

Reference	Type of study	<i>n</i>	Resection rate (%)	R0 resection rate (%)
Ferrone et al. [17]	Retrospective	47	85	88
Paniccia et al. [18]	Retrospective	20	85	100
Christians et al. [19]	Retrospective	18	67	100
Hosein et al. [20]	Retrospective	18	56	80

Fig. 6 Fibrotic changes identified around the SMA (arrow)

disease; several retrospective but promising clinical studies (Table 1) involving the application of neoadjuvant FOLFIRINOX have already been reported.

In this report, we have demonstrated that preoperative FOLFIRINOX followed by pancreaticoduodenectomy can be safely performed, and our experience suggests that it might improve treatment outcomes. Initially, we did not plan to perform surgery after chemotherapy, so FOLFIRINOX therapy administered in this case may not precisely be called neoadjuvant chemotherapy. Furthermore, we recognize that optimal number of cycles of preoperative treatment and timing of surgery remain debatable. However, similar to previously reported cases, our experience suggests that FOLFIRINOX is a useful preoperative treatment regimen in this setting as long as chemotherapy-related toxicity does not delay or compromise surgical resection. A common concern with FOLFIRINOX followed by surgery is the potential for cumulative toxicity. In our case, side effects were safely managed with antiemetic support and dose reductions. During surgery, we found fibrotic change and adhesions around the pancreatic head (Fig. 6). Although these warranted care, we felt that they did not make the procedure particularly more complicated or dangerous. Selecting appropriate cases, it seems feasible to use FOLFIRINOX as neoadjuvant therapy for borderline resectable disease. Further studies are needed to confirm whether FOLFIRINOX may have a role as a routine neoadjuvant agent.

In conclusion, we herein report a precious case of borderline resectable PAC that successfully underwent curative resection after preoperative FOLFIRINOX therapy.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Egawa S, Toma H, Ohigashi H et al (2012) Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. *Pancreas* 41:985–992
2. Ishii H, Furuse J, Boku N et al (2010) Phase II study of gemcitabine chemotherapy alone for locally advanced pancreatic carcinoma: JCOG0506. *Jpn J Clin Oncol* 40:573–579
3. Bond-Smith G, Banga N, Hammond TM, Imber CJ (2012) Pancreatic adenocarcinoma. *BMJ* 344:e2476
4. Evans DB, Rich TA, Byrd DR et al (1992) Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 127:1335–1339
5. Muller SA, Hartel M, Mehrabi A et al (2009) Vascular resection in pancreatic cancer surgery: survival determinants. *J Gastrointest Surg* 13:784–792
6. Li D, Xie K, Wolff R, Abbruzzese JL (2004) Pancreatic cancer. *Lancet* 363:1049–1057
7. Neoptolemos JP, Stocken DD, Friess H et al (2004) A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *New Engl J Med* 350:1200–1210
8. Sohn TA, Yeo CJ, Cameron JL et al (2000) Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 4:567–579
9. Varadhachary GR, Tamm EP, Abbruzzese JL et al (2006) Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 13:1035–1046
10. Tempero MA, Malafa MP, Behrman SW et al (2014) Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 12:1083–1093
11. Callery MP, Chang KJ, Fishman EK et al (2009) Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 16:1727–1733
12. Katz MH, Marsh R, Herman JM et al (2013) Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol* 20:2787–2795
13. Spitz FR, Abbruzzese JL, Lee JE et al (1997) Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 15:928–937
14. Pingpank JF, Hoffman JP, Ross EA et al (2001) Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. *J Gastrointest Surg* 5:121–130
15. Breslin TM, Hess KR, Harbison DB et al (2001) Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. *Ann Surg Oncol* 8:123–132

16. Conroy T, Desseigne F, Ychou M et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New Engl J Med* 364:1817–1825
17. Ferrone CR, Marchegiani G, Hong TS et al (2015) Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 261:12–17
18. Paniccia A, Edil BH, Schulick RD et al (2014) Neoadjuvant FOLFIRINOX application in borderline resectable pancreatic adenocarcinoma: a retrospective cohort study. *Medicine (Baltimore)* 93:e198
19. Christians KK, Tsai S, Mahmoud A et al (2014) Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 19:266–274
20. Hosein PJ, Macintyre J, Kawamura C et al (2012) A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 12:199