Int Surg 2015;**100**:287–291
DOI: 10.9738/INTSURG-D-13-00193.1

Case Report

Radical Resection of a Primarily Unresectable Pancreatic Cancer After Neoadjuvant Chemotherapy Using Gemcitabine, TS-1, and Nafamostat Mesilate; Report of a Case

Yuki Fujiwara, Hiroaki Shiba, Tadashi Uwagawa, Yasuro Futagawa, Takeyuki Misawa, Katsuhiko Yanaga

Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

A 58-year-old male visited his primary physician for epigastric and back pain. Abdominal-enhanced computed tomography (CT) revealed a hypovascular pancreatic tumor measuring 17 × 11 mm in the uncinate process of the pancreas extending into the superior mesenteric plexus for greater than 180°. With a diagnosis of unresectable pancreatic cancer, the patient received gemcitabine and TS-1 with arterial infusion of nafamostat mesilate. After 3 courses of chemotherapy, enhanced CT revealed a decrease in size of the pancreatic tumor with no lymph node and distant metastasis and improved invasion of the superior mesenteric plexus down to 120°. The patient underwent R0 pancreaticoduodenectomy. The patient made a satisfactory recovery without complications and was discharged on postoperative day 10. We herein report the first curative resected case of a primarily unresectable pancreatic cancer after neoadjuvant chemotherapy using gemcitabine, TS-1, and nafamostat mesilate.

Key words: Nafamostat mesilate – Neoadjuvant chemotherapy – Unresectable pancreatic cancer – Down-staging

Pancreatic cancer is one of the most common malignant cancers worldwide, with an overall 5-year survival rate of only 1 to 4%, because of advanced stage at the time of diagnosis, rapid tumor growth, and high potential for distant metastasis.[1] For insufficiency of chemotherapy and radiation against pancreatic cancer, resection rate for primary unresectable pancreatic cancer

Corresponding author: Yuki Fujiwara, MD, PhD, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan.
Tel.: +81-3-34331111 ext. 3401; Fax: +81-3-34334140; E-mail: sheetan@jikei.ac.jp

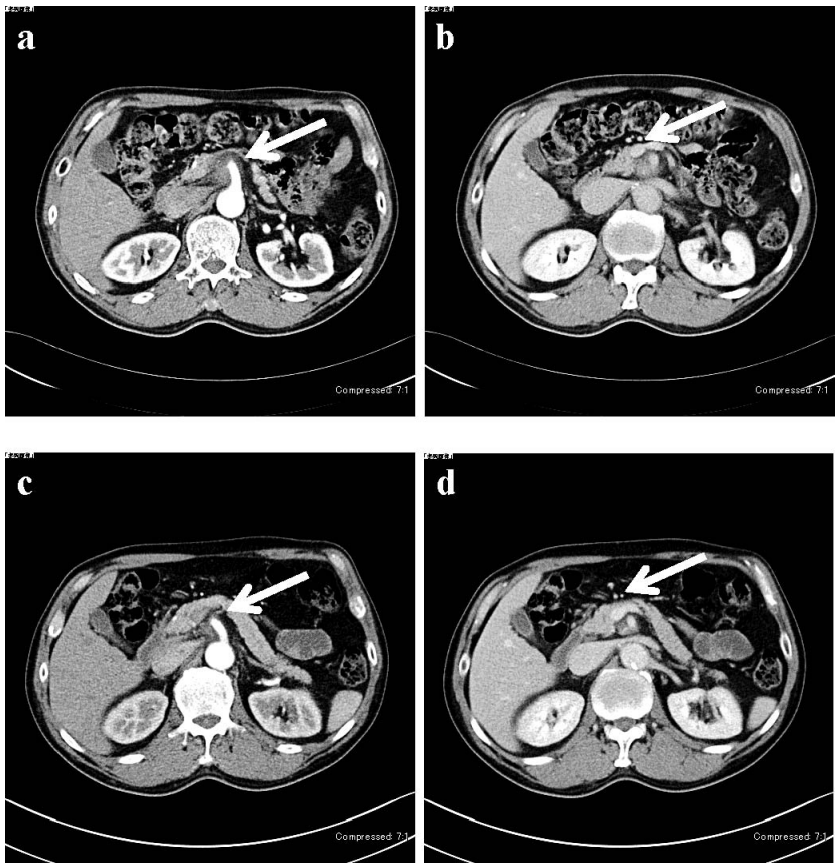

Fig. 1 Abdominal-enhanced CT image of the pancreatic lesion. A pancreatic mass of the uncinate process measuring 1.7 × 1.1 cm extended to surround the root of the superior mesenteric artery (a: arrow). However, there was not directly superior mesenteric vein involvement by the tumor (b: arrow). After neoadjuvant chemotherapy with gemcitabine and TS-1 in combination with regional arterial infusion of nafamostat mesilate, disease extension along the superior mesenteric artery improved (c: arrow) and no invasion of superior mesenteric vein (d: arrow).

remains very low.[2] We started the phase II trial of gemcitabine and TS-1 in combination with regional arterial infusion of nafamostat mesilate for patients with unresectable pancreatic cancer. We herein reported a successful R0 resection of a patient with primarily unresectable pancreatic cancer after neoadjuvant chemotherapy using gemcitabine, TS-1, and nafamostat mesilate.

Case Report

A 58-year-old male visited his primary physician for epigastric and back pain. He had no family history of pancreatic cancer. Abdominal-enhanced computed tomography (CT) revealed a hypovascular pancreatic tumor of the pancreatic uncinate process measuring 17 × 11 mm that extended into a neural and lymphatic invasion around the superior mesenteric plexus for greater than 180° (Fig. 1A). However, there was not directly superior mesenteric vein involvement by the tumor (Fig. 1B). There was no evidence of distant metastasis. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of the pancreatic tumor was compatible with adenocarcinoma (class V). Complete blood count and serum bilirubin, transaminases, amylase, lipase, and carcinoembryonic antigen (CEA) were within normal limits. Serum carbohydrate antigen 19-9 (CA19-9) was up to 45 U/mL (reference range: 0–37 U/mL). With a diagnosis of unresectable pancreatic cancer due to invasion of the superior mesenteric plexus for greater than 180°,[3] the patient received gemcitabine (1000 mg/m^2 intravenously for 30 minutes on days 1, 8, and 15) and TS-1 (120 mg/day per oral from days 1 to 14), together with nafamostat mesilate (4.8 mg/kg continuous regional

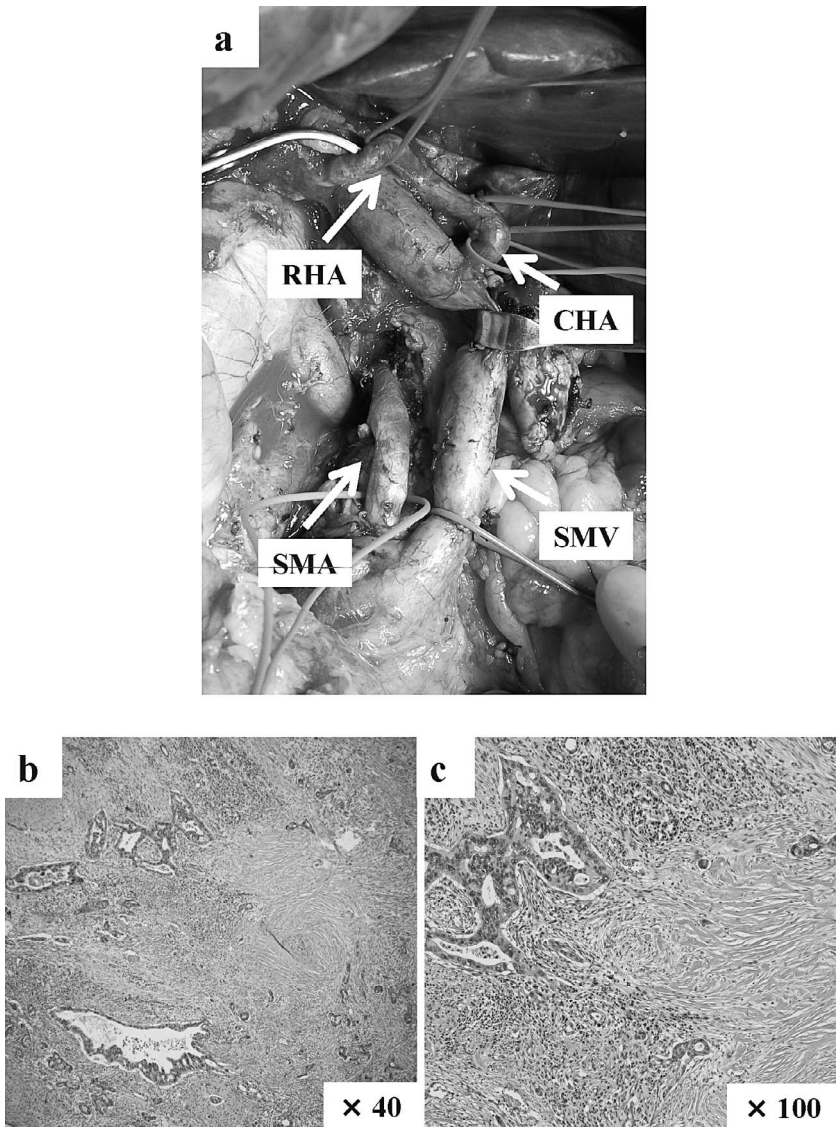

Fig. 2 Intraoperative findings during pancreaticoduodenectomy. (a) Arrows indicate right hepatic artery, common hepatic artery, superior mesenteric artery, and superior mesenteric vein, respectively. In microscopic views, residual variable tumor cells in the pancreatic uncinate process was detected with proliferation of fibroblast cells in the framework. Pathological features in H&E stain ×40 (b) 100 (c).

arterial infusion for 24 hours through a port-catheter system on days 1, 8, and 15). This regimen was repeated at 28-day intervals. After 3 courses of neoadjuvant chemotherapy, enhanced CT revealed a decrease in size of the pancreatic tumor (10 × 10 mm) with no evidence of lymph node or distant metastasis, and improved invasion of the superior mesenteric plexus down to 120° (Fig. 1C) and no invasion of superior mesenteric vein (Fig. 1D). Since such a condition satisfied criteria for respectability of pancreatic cancer, the patient underwent pancreaticoduodenectomy (Fig. 2A). In laparotomy findings, there were no ascites, peritoneal dissemination, or liver metastasis of pancreatic cancer. We reconstructed digestive tracts by modified child's method with a retrocolic gastrojejunostomy. Operation time and intraoperative bleeding were 415 minutes and 1415 mL, respectively. Perioperative transfusion was not used. The excited tissue showed a solid tumor with the diameter of 20 × 11 × 18 mm in the pancreatic uncinate process.

On histopathological evaluation, residual viable tumor cells in the pancreatic uncinate process were detected by hematoxylin and eosin staining (H&E) with proliferation of fibroblast cells in the framework (Figs. 2B and 2C). The tumor invasion of the superior mesenteric plexus was not detected. Final pathological staging was moderately differentiated invasive ductal adenocarcinoma of the pancreas without lymph node metastasis (Japan Pancreatic Society classification 10th edition; pT_1, pN_0, pM_0, stage I, Union International Control Cancer classification of malignant tumors 6th edition; pT_1, pN_0, pM_0, stage I, R0). The margins of the tumor that were pancreatic cut end margin, bile duct cut end margin, and dissected peripancreatic tissue margin were negative for cancer involvement in all margins. The patient made a satisfactory recovery without complications and was discharged on postoperative day 10. The patient will start to receive the novel adjuvant chemotherapy with gemcitabine and continuous regional arterial infusion of nafamostat mesilate, which were approved for phase II trial of the Jikei University School of Medicine.

Discussion

Currently, chemotherapy with gemcitabine is the one of most effective and standard treatments for patients with locally advanced or metastatic pancreatic cancer.[4] In Japan, TS-1 is another useful chemotherapeutic agent for pancreatic cancer resistant to gemcitabine. However, cases converted from unresectable to resectable pancreatic cancer after neoadjuvant gemcitabine or TS-1 alone have been very rare. Actually, there were few patients converted from unresectable to resectable pancreatic cancer after neoadjuvant gemcitabine alone, TS-1 alone, or combination gemcitabine with TS-1 in GEST study, which is a randomized control phase III trial for patients with unresectable pancreatic cancer in Japan and Taiwan.[5] Assifi *et al* reported that 36% of their cases were converted to resectable in patients with borderline or unresectable pancreatic cancer after neoadjuvant treatment.[6] However, 85% of patients in the studies received neoadjuvant radiotherapy. One of the possible reasons for insufficiency of combined chemotherapy with gemcitabine or TS-1 in patients with unresectable pancreatic cancer is that both agent-induced antitumor effects have been suppressed by the activation of nuclear factor-kappa B (NF-κB).[7] NF-κB plays an important role in the regulation of cell apoptosis, inflammation, and oncogenesis, including invasion and angiogenesis.[8] Nafamostat mesilate, a serine-protease inhibitor, has been widely used for treatment of pancreatitis and disseminated intravascular coagulation for hemodialysis in Japan.[9] We have previously demonstrated that nafamostat mesilate inhibited NF-κB activation and induced antitumor effects in pancreatic cancer.[10–12] Furthermore, we have proved that nafamostat mesilate enhanced antitumor effects of several chemotherapeutic agents by inhibition of NF-κB activation induced by these agents.[13–16] On the basis of the results from these translational research studies, combined chemotherapy with gemcitabine and nafamostat mesilate was designed in patients with an unresectable advanced pancreatic cancer that would inhibit gemcitabine-induced NF-κB activation.

For intra-arterial infusion of nafamostat mesilate, the tip of the catheter was inserted into the common hepatic artery, and a side hole of the catheter was placed in the celiac artery to deliver nafamostat mesilate to all areas of the pancreas. The recommended dose of nafamostat mesilate (continuous regional arterial infusion for 24 hours through a port-catheter system on days 1, 8, and 15) in combination with gemcitabine (1000 mg/m^2 intravenously for 30 minutes on days 1, 8, and 15) was 4.8 mg/kg from our phase I study in patients with unresectable pancreatic cancer.[17] In addition, we carried out a phase II study with combination gemcitabine with nafamostat mesilate for patients with unresectable pancreatic cancer. The median survival time of all the patients was 10.0 months and the 1-year survival rate was 40.0%. Response rates (both complete response and partial response) were 17.1%.[18] Adverse effects of combination gemcitabine and nafamostat mesilate in our previous phase I and II studies were comparable to those of gemcitabine alone for patients with unresectable pancreatic cancer.

Acknowledgments

The authors thank Dr. Shunichi Sadaoka (Department of Radiology, The Jikei University School of Medicine, Tokyo, Japan) for support of our study. The authors declare no conflicts of interest.

References

1. Evans DB, Abbruzzesse JL, Willett CG. Cancer of the pancreas. In: De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer-Principles*

and Practice of Oncology. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins, 2001:1126–1161
2. Niederhuber JE, Brennan MF, Menck HR. The National Cancer Data Base report on pancreatic cancer. *Cancer* 1995;**76**(9):1671–1677
3. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson AB 3rd, Casper ES *et al*. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2012;**10**(6):703–713
4. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR *et al*. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;**15**(6):2403–2413
5. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N *et al*. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 2013;**31**(13):1640–1648
6. Assifi MM, Lu X, Eibl G, Reber HA, Li G, Hines OJ. Neoadjuvant therapy in pancreatic adenocarcinoma: a meta-analysis of phase II trials. *Surgery* 2011;**150**(3):466–473
7. Arlt A, Gehrz A, Müerköster S, Vorndamm J, Kruse ML, Fölsch UR *et al*. Role of NF-κB and Akt/PI3K in the resistance of pancreatic carcinoma cell lines against gemcitabine-induced cell death. *Oncogene* 2003;**22**(21):3243–3251
8. Chen F, Castranova V, Shi X. New insights into the role of nuclear factor-κB in cell growth regulation. *Am J Pathol* 2001;**159**(2):387–397
9. Iwaki M, Ino Y, Motoyoshi A, Ozeki M, Sato T, Kurumi M *et al*. Pharmacological studies of FUT-175, nafamostat mesilate. V. Effects on the pancreatic enzymes and experimental acute pancreatitis in rats. *Jpn J Pharmacol* 1986;**41**(2):155–162
10. Uwagawa T, Li Z, Chang Z, Xia Q, Peng B, Sclabas GM *et al*. Mechanisms of synthetic serine protease inhibitor (FUT-175)-mediated cell death. *Cancer* 2007;**109**(10):2142–2153
11. Furukawa K, Iida T, Shiba H, Fujiwara Y, Uwagawa T, Shimada Y *et al*. Anti-tumor effect by inhibition of NF-κB activation using nafamostat mesilate for pancreatic cancer in a mouse model. *Oncol Rep* 2010;**24**(4):843–850
12. Fujiwara Y, Furukawa K, Haruki K, Shimada Y, Iida T, Shiba H *et al*. Nafamostat mesilate can prevent adhesion, invasion and peritoneal dissemination of pancreatic cancer through nuclear factor kappa-B inhibition. *J Hepatobiliary Pancreat Sci* 2011;**18**(5):731–739
13. Uwagawa T, Chiano PJ, Gocho T, Hirohara S, Misawa T, Yanaga K. Combination chemotherapy of nafamostat mesilate with gemcitabine for pancreatic cancer targeting NF-kB activation. *Anticancer Res* 2009;**29**(8):3173–3178
14. Fujiwara Y, Furukawa K, Shimada Y, Iida T, Shiba H, Uwagawa T *et al*. Combination paclitaxel and inhibitor of nuclear factor κB activation improves therapeutic outcome for model mice with peritoneal dissemination of pancreatic cancer. *Pancreas* 2011;**40**(4):600–607
15. Furukawa K, Ohashi T, Haruki K, Fujiwara Y, Iida T, Shiba H *et al*. Combination treatment using adenovirus vector-mediated tumor necrosis factor-alpha gene transfer and a NF-κB inhibitor for pancreatic cancer in mice. *Cancer Lett* 2011;**306**(1):92–98
16. Fujiwara Y, Shiba H, Iwase R, Haruki K, Furukawa K, Uwagawa T *et al*. Inhibition of NF-κB enhances the anti-tumor effect of combination treatment with tumor necrosis factor-alpha (TNF-α) gene therapy and gemcitabine for pancreatic cancer in mice. *J Am Coll Surg* 2013;**216**(2):320–332
17. Uwagawa T, Misawa T, Sakamoto T, Ito R, Gocho T, Shiba H *et al*. A phase I study of full-dose gemcitabine and regional arterial infusion of nafamostat mesilate for advanced pancreatic cancer. *Ann Oncol* 2009;**20**(2):239–243
18. Uwagawa T, Misawa T, Tsutsui N, Ito R, Gocho T, Hirohara S *et al*. Phase II study of gemcitabine in combination with regional arterial infusion of nafamostat mesilate for advanced pancreatic cancer. *Am J Clin Oncol* 2013;**36**(1):44–48