Multiple-line Chemotherapy for a Patient with Unresectable Mucinous Cystic Neoplasm of the Pancreas

Haruo Miwa, Kazuya Sugimori, Tomohiro Ishii, Akihiro Funaoka, Hiromi Tsuchiya, Yoshimasa Suzuki, Makoto Sugimori, Masaki Nishimura, Yuichiro Tozuka, Satoshi Komiyama, Takeshi Sato, Takashi Kaneko, Kazushi Numata and Shin Maeda

Abstract:
A 74-year-old woman with a cyst in her pancreatic tail was referred to our hospital. Computed tomography confirmed a large cystic lesion with irregular wall thickening, abdominal lymph node swelling, and ascites. We diagnosed her with an unresectable mucinous cystic neoplasm, since ascites cytology revealed adenocarcinoma. The patient received chemotherapy up to the fifth line for 55.2 months. Gemcitabine plus nab-paclitaxel and modified FOLFORINOX achieved a partial response with a progression-free survival time of 12.1 and 20.4 months, respectively. The overall survival time from the beginning of first-line chemotherapy was 69.4 months.

Key words: antineoplastic combined chemotherapy protocols, palliative therapy, pancreatic cancer, pancreatic cyst

Introduction
Mucinous cystic neoplasms (MCNs) are rare disease, representing about 20% of all resected pancreatic cysts, and are known to occur in the pancreatic body and tail in women (1, 2). Although MCNs are considered to have malignant potential, unresectable cases due to metastases or local invasion have rarely been reported. Palliative chemotherapy has been recommended for unresectable MCN in some reports (3, 4); however, no clinical evidence has been established about the efficacy of such treatment.

In recent years, the efficacy of palliative chemotherapy for metastatic pancreatic ductal adenocarcinoma (PDAC) has evolved. Combination regimens, such as FOLFIRINOX or gemcitabine plus nab-paclitaxel (GnP), have been reported to achieve a high response rates and an improved overall survival (5, 6). However, there are few reports on the efficacy of these combined chemotherapy regimens in unresectable MCN (7).

We herein report a patient with unresectable MCN who achieved a long-term survival under multi-line chemotherapy.

Case Report
A 74-year-old woman with a cystic lesion in her abdominal cavity was referred to the Yokohama City University Medical Center. During the physical examination, a soft, fist-sized mass was palpable in her left upper abdomen. Her serum tumor marker levels were normal (carcinoembryonic antigen: 3.6 ng/mL and carbohydrate antigen 19-9: 29 U/mL). Contrast-enhanced computed tomography (CECT) showed a cystic of 9 cm in diameter with enhanced irregular wall thickening in the pancreatic tail (Fig. 1). There were enlarged lymph nodes along the hepatic artery (No. 12a) and on the anterior surface of the pancreas (No. 17). Ascites and tiny nodules around the mesentery were also observed. Contrast-enhanced transabdominal ultrasonography showed an enhanced septum inside the cyst (Fig. 2). Endoscopic ul-
A 74-year-old woman with a mucinous cystic neoplasm of the pancreas. Contrast-enhanced computed tomography shows a 9-cm cystic lesion in the pancreas tail. Wall thickening is visible at the right side of the cyst (arrow). Swollen lymph nodes can be observed along the hepatic artery (black arrowhead) and in front of the pancreatic body (white arrowhead). Ascites is present around the liver and spleen.

![Figure 1](image1.png)

**Figure 1.** A) Conventional transabdominal ultrasound shows a cystic lesion with wall thickening and hyperechoic content. B) Contrast-enhanced ultrasound reveals an enhanced septum inside the cyst (arrows). The thickened wall shows blood flow (arrowheads).

Trasonography did not reveal a connection between the cyst and the main pancreatic duct. Ascites cytology revealed an adenocarcinoma (Fig. 3); therefore, we made a diagnosis of MCN with an associated invasive carcinoma with peritoneal dissemination and lymph node metastases. We considered palliative chemotherapy to be the best option for the patient. First-line chemotherapy consisting of 1,000 mg/m² gemcitabine (GEM) on day 1, 8, and 15 every 4 weeks was started. At the beginning of treatment, the patient’s performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) was Grade 0. After 3.9 months, CECT showed enlarged lymph nodes, indicating progressive disease.
of wall thickening of the cyst. Modified FOLFIRINOX was remarkable shrinkage of the lymph nodes and improvement cycle. After 1.9 months (3 cycles), a PR was achieved with notecan were reduced to 60% of the initial dose by the ninth assessed as Grade 2, until cycle 2. Both oxaliplatin and irinotecan were reduced to 80% of the initial dose of 5-FU over a 46-h period, every 2 weeks. The dosing regimen for fourth-line chemotherapy, consisting of 65 mg/m² of oxaliplatin, 120 mg/m² of irinotecan, and 300 mg/m² of leucovorin, followed by a continuous infusion of 2,400 mg/m² of 5-FU over a 46-h period, every 2 weeks. The dosage of oxaliplatin and irinotecan was reduced to 80% of the initial dose because of the elderly age of the patient. She experienced fatigue and peripheral sensory neuropathy, assessed as Grade 2, until cycle 2. Both oxaliplatin and irinotecan were reduced to 60% of the initial dose by the ninth cycle. After 1.9 months (3 cycles), a PR was achieved with remarkable shrinkage of the lymph nodes and improvement of wall thickening of the cyst. Modified FOLFIRINOX was continued with treatment interruption for three months and one month because of heart failure (Grade 3) and herpes zoster (Grade 2), respectively. After 20 cycles, CECT showed progression of the wall thickening of the cyst and enlargement of the lymph nodes, which were considered to reflect PD. The PFS under modified FOLFIRINOX was the longest among all regimens at 20.1 months. The ARDI of the 3 drugs-oxaliplatin, irinotecan, and 5-FU was 35% (Fig. 4).

We suggested the patient finish palliative chemotherapy; however, she strongly preferred to continue anti-cancer therapy. Therefore, fifth-line chemotherapy with 1,000 mg/m² of GEM on day 1 and 80 mg/day of S-1 from day 1 to 7 was administered every 3 weeks, and the PFS was 5.1 months. After 9.4 months, best supportive care was provided, but the ascites increased, and her general condition deteriorated to ECOG PS 2.

Another seven months later, the patient was hospitalized for one week due to an infection inside the cyst, but conservative therapy with antibiotics was effective in resolving this. Eventually, she died as a consequence of the primary tumor after 14.1 months of best supportive care. The overall survival from the beginning of first-line chemotherapy was 69.4 months, including 55.2 months receiving palliative chemotherapy (Table) (Fig. 5).

**Discussion**

MCN of the pancreas is a rare tumor that occurs predominantly in middle-aged women (8). When diagnosing MCN, it is important to differentiate it from branched-type intraductal papillary mucinous neoplasm (IPMN) (9). MCN is histologically diagnosed based on the existence of an ovarian-type stroma (10, 11). If a surgical specimen is not available, the clinical diagnosis is made based on the characteristics of a unilocular or septated macrocystic lesion without connection to the pancreatic duct, enhancing mural nodules on CECT, and wall thickening (12, 13). A cytological analysis after endoscopic ultrasound-guided fine-needle aspiration can detect malignant cystic lesions. However, it is difficult to differentiate between IPMN and MCN with a small specimen (14). We did not aspirate any contents of the cyst; however, the cytology of the patient’s ascites revealed an adenocarcinoma. In the present case, the diagnosis of MCN was confirmed by the characteristics of a cyst with irregular wall thickening and no connection to the main pancreatic duct.

Although MCN is considered to have malignant potential, there are only a few reports describing the rate of malignancy. Postlewait et al. (2), reported that 14.9% of 349 patients with resected pancreatic MCN had adenocarcinoma or high-grade dysplasia. Among them, lymph node metastasis was observed in about one-third. Due to this low incidence of metastasis, the prognosis of malignant MCN was better than that of PDAC, with a 3-year survival rate of 59%. However, regarding unresectable MCN, the prognosis is sig-

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Figure 3. Ascites cytology shows adenocarcinoma containing mucus-like structures in the cytoplasm (arrows).
alone in patients with metastatic PDAC. However, these remarkable increases in the survival compared with GEM GnP (5, 6). These combined chemotherapies have resulted in outcomes of chemotherapy for PDAC have radically im-
treatment had been selected in accordance with the recom-
moment MCN and observed a median survival time of 11
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regimen for unresectable MCN. Werner et al. (4). reported 5
there is currently no evidence guiding the best choice of
resectable or recurrent cystic lesions of the pancreas (14),
Although palliative chemotherapy is recommended for un-
resectable or recurrent cystic lesions of the pancreas (14),
Effect of chemotherapy was evaluated by RECIST guideline
FOLFIRINOX is consist of oxaplatin, irinotecan, 5-FU, and leucovorin, RECIST: Response evalu-
Table. Results of Systematic Chemotherapy.
| Regimen            | Best Response | PFS         | ARDI |
|--------------------|---------------|-------------|------|
| 1st line           | Gemcitabine   | SD          | 3.9 months | 100% |
| 2nd line           | S-1           | SD          | 6.6 months | 88%  |
| 3rd line           | Nab-paclitaxel plus Gemcitabine | PR  | 12.1 months | 40%  |
| 4th line           | Modified-FOLFIRINOX | PR  | 20.4 months | 35%  |
| 5th line           | Gemcitabine plus S-1 | SD  | 5.1 months  | 44%  |

significantly worse than that of surgically treated cases (8, 15, 16).

Although palliative chemotherapy is recommended for unre-
resectable or recurrent cystic lesions of the pancreas (14),
there is currently no evidence guiding the best choice of regimen for unresectable MCN. Werner et al. (4). reported 5 patients who received palliative chemotherapy for unre-
sectable MCN and observed a median survival time of 11
months (range: 4-37 months). In that report, GEM-based
treatment had been selected in accordance with the recom-
mended palliative chemotherapy of PDAC. However, the
outcomes of chemotherapy for PDAC have radically im-
proved with the advent of two regimens: FOLFIRINOX and
GnP (5, 6). These combined chemotherapies have resulted in remarkable increases in the survival compared with GEM alone in patients with metastatic PDAC. However, these
regimens also increase the frequency of severe adverse events; therefore, they are not recommended for use in pa-
patients with a poor general condition or an old age. At the
time of initiating treatment for the present patient, GnP was
not yet covered by national health insurance in Japan, and we did not have adequate experience regarding the clinical use of FOLFIRINOX. In addition, there were no reports concerning the use of GnP or FOLFIRINOX for MCN at the
time. Therefore, we selected a less toxic monotherapy of
gemcitabine with the findings of lymph nodes shrinkage. G, H, I) After 20 cycles (13 months), enlarg-
ment of the lymph nodes along the hilar artery (black arrowheads) and wall thickening (arrows) confirm progressive disease. J, K, L) A partial response is visible after three cycles (two months) of modified FOLFIRINOX. M, N, O) After 20 cycles (20.4 month), the enlargement of the lymph nodes along the hilar artery (black arrowheads) demonstrates progressive disease.
tropenia (Grade 3) in the fourth cycle. However, after the fifth cycle, no severe adverse events were observed. The ARDI of GnP was lower than the values noted in previous reports (6, 17); however, our patient was able to continue treatment for up to 12.1 months while maintaining a good PS. Brunetti et al. (7) reported the overall survival time of patients with unresectable MCN treated with GnP and FOLFIRINOX as 13 months and 9-14 months, respectively. Among these patients, 2 received both regimens, and their overall survival times were 9 and 14 months, respectively. Compared with these cases, the present case achieved a long survival.

Despite the fact that our patient has already received GEM monotherapy, GnP achieved PR, with the antitumor effect lasting for one year. This result may be due to the fact that nab-paclitaxel increases intratumoral GEM levels. Frese et al. (18) reported that paclitaxel reduced the levels of cytidine deaminase protein, which is associated with the metabolization of GEM, in mice. This synergistic effect may be the reason for the tumor reduction under GnP, although the ARDI was as low as 40%.

It may be considered controversial to administer modified FOLFIRINOX as the fourth-line chemotherapy because the patient was 76 years old at the time. Furthermore, there were no clinical reports that modified FOLFIRINOX was effective in patients with unresectable MCN. However, the patient’s good general condition (ECOG-PS 0) and her strong preference supported the decision to choose modified FOLFIRINOX. After three cycles, the thickness of the cyst wall had remarkably regressed on CECT, and the regimen was continued with intermissions for 20 cycles. Modified FOLFIRINOX had to be stopped because of heart failure (Grade 3) for 3 months after 8 cycles and because of herpes zoster (Grade 2) for 1 month after 10 cycles. However, we were able to restart the same regimen with dose reductions.

Several studies investigated the efficacy of modified FOLFIRINOX in patients with GEM-refractory PDAC (19-21). Sawada et al. reported the efficacy and good tolerability of modified FOLFIRINOX as second-line therapy after GnP (22). Although FOLFIRINOX poses a risk of serious adverse events, these studies have shown that it can be safely administered when doses are reduced. In this case, both oxaliplatin and irinotecan were first reduced to 80% of the initial dose and ultimately to 60%. Considering the interruptions in the administration, the ARDI reached 35%. Nevertheless, modified FOLFIRINOX was continued without tumor progression for 20.4 months. Peripheral neuropathy is the most important adverse event associated with the crossover therapy of GnP and modified FOLFIRINOX. Our patient suffered Grade 2 peripheral neuropathy in the course of modified FOLFIRINOX that did not require treatment interruption.

In conclusion, unresectable MCN is rare, and there is little clinical evidence supporting its treatment with combined chemotherapy. In our patient, only GnP and modified FOLFIRINOX achieved PR among the five regimens used. Although further large-scale prospective studies are required to confirm the efficacy and feasibility in patients with unresectable MCN, we recommend GnP and modified FOLFIRINOX to prolong the survival under palliative chemotherapy.

The authors state that they have no Conflict of Interest (COI).

Funding: The present study did not receive any funding support.

Funding: This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
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