Abstract. Background: Although chemoradiotherapy with full-dose gemcitabine as a strategy for locally advanced pancreatic cancer was expected to optimize local tumor control and prevent distant metastasis, the volume of the radiation field is the critical factor related to toxicities. We are currently developing a novel therapeutic technique to conduct neoadjuvant treatments of intra-arterial chemoinfusion prior to chemoradiotherapy with the aim of tumor volume reduction. Case Report: In two patients with locally invasive pancreatic cancer, the pancreatic blood supply was altered under angiographic guidance, and an intra-arterial catheter with a subcutaneous port was left in place for the administration of 5-fluorouracil (5-FU) 1,000 mg/m². After shrinkage of the tumor, chemoradiotherapy with gemcitabine 1,000 mg/m² was delivered. In both patients, the full-dose gemcitabine was administered concurrently with radiation therapy without severe complications. The patients responded to the treatment with survival times of 42 and 38 months. Conclusion: Intra-arterial chemoinfusion followed by chemoradiotherapy with full-dose systemic gemcitabine might prove to be a promising therapeutic approach for locally advanced pancreatic cancer. Large prospective Phase II trials of this combination regimen are warranted.

The standard treatments for locally advanced pancreatic cancer are chemoradiotherapy using 5-fluorouracil (5-FU) or systemic chemotherapy with gemcitabine. However, the reported therapeutic outcomes include response rates of 0-20% and median survival times of 9-16 months (1). Previous trials of radiotherapy for locally advanced disease resulted in limited survival due to the early development of distant metastases, thus combination with systemic treatment is now recognized to be essential (2). For ideal treatment of advanced pancreatic cancer, it is vital to optimize local tumor control and to prevent distant metastasis. Chemoradiotherapy (intravenous chemotherapy administered during radiotherapy sessions) with gemcitabine had been expected to accomplish both goals. However, in previous Phase I and Phase II trials the dose of gemcitabine had to be reduced to avoid toxicity and the tolerated doses of gemcitabine are unlikely to be effective against systemic disease (3, 4). To the best of our knowledge, only one study has indicated that full-dose gemcitabine with concurrent radiotherapy was tolerable, although the radiation dose of 36 Gy was delivered only to patients with resectable or borderline-resectable lesions (5).

The volume of the radiation field is one of the critical factors related to chemoradiotherapy toxicity. Therefore, the development of neoadjuvant treatments that could achieve tumor volume reduction prior to chemoradiation might prove beneficial. Although pancreatic cancer is widely regarded as “the chemoresistant cancer,” showing a response rate of 0-10% for standard systemic chemotherapies (6), several previous studies in patients with unresectable tumors have demonstrated that intra-arterial chemoinfusion resulted in much higher response rates of 70-80%, perhaps due to pharmacological advantages of direct infusion into arteries feeding the tumor (7-10). We hypothesized that initial administration of intra-arterial chemoinfusion would reduce the tumor volume, so that subsequent chemoradiotherapy could be delivered to a smaller targeted lesion and be combined with the full dose of gemcitabine. Here our first two patients, both having pancreatic body cancer, who responded to this combination therapy are described, and the possible advantages of this treatment approach are discussed.
Case 1

The first patient was a 62-year-old man with a 4.5 cm-diameter lesion of the pancreatic body that was invading the superior mesenteric, common hepatic and splenic arteries (Figure 1A). The patient underwent a percutaneous sonography-guided biopsy, and the tumor was diagnosed as adenocarcinoma. The serum tumor marker CA-19-9 level was elevated to 302 U/ml. An intravenous contrast enhanced CT revealed no lung, liver or distant nodal metastases, and no peritoneal metastases were found on laparoscopic examination. Because of the involvement of the superior mesenteric artery, this tumor was judged unresectable.

According to a previously reported technique for intraarterial chemoinfusion (11), the peri-pancreatic arteries arising from the superior mesenteric were embolized using metallic coils, and an indwelling catheter (W-Spiral catheter, Piolax Medical Devices, Yokohama, Japan) was placed in the celiac artery (Figure 1B). The proximal end of the catheter was connected to an implanted port (Celsite Port, Toray Medical, Urayasu, Japan). CT scanning during arterial infusion of contrast material revealed that the majority of the tumor was supplied through the port. However, contrast distribution to the tumor invading the superior mesenteric artery was not contrast enhanced.

Using a continuous infusion device (Dosi-Fuser 65H5, Toray Medical), a 1,000 mg/m² dose of 5-FU was administered during a 5-hour period through the port, while 1,000 mg/m² gemcitabine was simultaneously given in a 30 min intravenous infusion, on days 1, 8 and 15 of every 28 days for 6 cycles. CT scanning following this neoadjuvant therapy revealed that the tumor had decreased to 2.5 cm in diameter, even though the portion around the superior mesenteric artery, in which arterial drug distribution had been poor, had increased in size (Figure 1C). In addition, the serum CA19-9 had been reduced to 68 U/ml.

Chemoradiotherapy was performed with a stereotactic body radiotherapy system (Novalis Shaped Beam Surgery System, BrainLAB AG, Heimstetten, Germany) using the dynamic conformal arc technique (12). The clinical target volume (CTV) covered the gross tumor volume (GTV) (the residual tumor visualized after intra-arterial therapy), as well as the surrounding area extending 5 mm in a 3-dimensional fashion. The planning target volume (PTV) included the CTV plus a 2- to 6 mm margin along the medial, lateral, ventral and dorsal sides, plus a 5- to 10 mm margin on the cranial and caudal sides to accommodate respiratory motion. Normalization for the plan was calculated with the pencil beam algorithm so that, using the system software (BrainSCAN® v5.3, BrainLAB, AG), the 80% isodose line completely covered the PTV (Figure 1D). A total dose of 54 Gy was delivered in 18 fractions over 3.6 weeks. Systemic gemcitabine 1,000 mg/m² was concurrently administered during the radiotherapy (on days 1, 8 and 15). No adverse events were observed. Although CT scanning after chemoradiotherapy revealed no remarkable changes in tumor size, the serum CA19-9 dropped to normal levels (34 U/ml). Subsequently, the patient received systemic gemcitabine maintenance chemotherapy. After 24 months, because the serum CA19-9 increased slightly, the systemic chemotherapy agent was changed to paclitaxel. The patient survived for 42 months after presentation.

Case 2

The second patient was a 60-year-old woman with an advanced pancreatic body lesion 5.0 cm in diameter, invading the superior mesenteric artery. The tumor was adenocarcinoma, diagnosed by cytological examination of a sonographically guided biopsy specimen. The serum CA19-9 level was 178 U/ml. The pancreatic blood flow was altered by the same method used for the first patient, and a catheter-port system was placed. CT scanning during arterial infusion of contrast material revealed that the majority of the tumor was supplied through the port. However, contrast distribution to the tumor invading the superior mesenteric artery was poor.

Five cycles of intra-arterial 5-FU chemotherapy combined with systemic gemcitabine were administered, as described for the first patient. Although neutrocytopenia (Grade 2) and a state of depression (Grade 2) occurred, the therapy was accomplished on an outpatient basis. CT scanning after the neoadjuvant chemotherapy revealed that the tumor had decreased to 3.2 cm in diameter, even though the portion around the superior mesenteric artery had increased in size. The serum CA19-9 was reduced to 47 U/ml.

For the residual tumor, chemoradiotherapy was performed using the Novalis System. In this patient, intensity-modulated radiotherapy was performed using 5 co-planar beams of 0, 72, 144, 216 and 288 degrees. The GTV and PTV were 10.9 cm³ and 104.3 cm³, respectively. Normalization for the plan was calculated with the pencil beam algorithm so that the 90% isodose line completely covered the PTV. A total dose of 50 Gy was delivered in 25 fractions over a 5-week period. Full-dose gemcitabine (1,000 mg/m², on days 1, 8 and 15 every 28 days) was administered concurrently. Although neutrocytopenia (Grade 2) was observed, chemoradiotherapy was continued without postponement. The serum CA19-9 dropped to within the normal range (25 U/ml). Subsequently, the patient received maintenance systemic gemcitabine chemotherapy. Twenty-six months after the initiation of therapy, tumor progression was observed and the chemotherapy agent was changed to S1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan) which is an orally active combination of tegafur, gimeracil and oteracil. This patient survived for 38 months after presentation.
Discussion

The intra-arterial 5-FU administration to those two patients resulted in tumor shrinkage. Consequently, subsequent chemoradiotherapy with full-dose gemcitabine was successfully accomplished without severe adverse events, despite the fact that a total radiation dose of 50-54 Gy was delivered to a field wide enough to cover the CTV.

It may be that the additional chemoradiotherapy provided by this combination regimen somewhat overcomes the limitations of intra-arterial chemoinfusion alone, during which drug distribution does not extend to tumor spreading into the mesentery (11). In these two patients, the tumor around the superior mesenteric artery increased in size after intra-arterial therapy due to poor drug distribution.

Although evaluation CT after chemoradiotherapy revealed no remarkable changes in tumor size, the serum CA 19-9 dropped to normal levels. Systemic full-dose gemcitabine might effectively prevent the development of distant metastases. Hospitalization times for these patients were
extremely short and were necessary only for the few days required to place the indwelling catheter-port system. Furthermore, long survival times of 42 and 38 months were achieved, exceeding the median survival time obtained with successful surgical resection.

These patients were our first two on which this combination therapy was attempted. In our institution, chemoradiotherapy with a reduced dose of gemcitabine (300-600 mg/m²) has been used for locally advanced pancreatic cancer. When intra-arterial chemotherapy is performed, eligibility criteria have been limited to tumors which have not spread significantly into the mesentery. However, results obtained from these two patients suggest that this combination approach could become a new, well-tolerated therapeutic strategy for locally invasive pancreatic cancer. This combination therapy would be of limited use in patients who do not respond to the initial intraarterial chemoinfusion.

In summary, intra-arterial chemoinfusion followed by chemoradiation with full-dose systemic gemcitabine has a theoretical advantage, and this strategy might prove to be a promising therapeutic approach for locally advanced pancreatic cancer. Large prospective Phase II trials of this combination regimen are warranted.

References


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