Four Cases of Pancreatic Acinar Cell Carcinoma Treated with Gemcitabine or S-1 as a Single Agent

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Pancreatic acinar cell carcinoma (ACC) is a comparatively rare tumor and account for ~1% of all cases of pancreatic cancer. Clinical presentation is usually related to either local spread or metastasis. The clinical features, especially those related to the prognosis and treatment outcomes, have not yet been fully clarified. There are no established treatments for unresectable pancreatic ACC. We administered gemcitabine monotherapy to four patients with ACC; however, the results were not satisfactory. Disease control without obvious tumor shrinkage was observed in one patient. Another patient showed severe renal damage caused by gemcitabine. On the other hand, fluoropyrimidine-based chemotherapy may have some activity against this tumor, because one of the three patients who received S-1 as second-line chemotherapy showed a partial response. Prospective clinical trials are necessary to confirm the effectiveness of fluoropyrimidine for the treatment of pancreatic ACC.

Key words: GI-pancreas – GI-pancreas-med – GI-pancreas-radoncol – chemo-GI tract

INTRODUCTION

Pancreatic acinar cell carcinoma (ACC) is a rare tumor. According to a survey conducted by the National Pancreatic Cancer Registry in Japan (1982–2002), pancreatic ACC accounted for 93 (0.4%) of all the 25,582 cases of resectable pancreatic cancer (1). In the USA, Cubilla and Fitzgerald (2) reported that ACC accounted for ~1.2% of all cases of resectable pancreatic cancer. ACCs are defined as carcinomas in which the neoplastic cells show acinar differentiation and pancreatic enzyme production. On microscopic examination, these tumors are composed of cells arranged in nests and acinar structures, often showing lobulation, with thin strands of fibrovascular stroma. Periodic acid-Schiff staining with diastase digestion reveals fine zymogen granules in the cytoplasm of the tumor cells (3,5,6). All patients with ACC show positive staining with one or both of the stains available for pancreatic enzymes, namely trypsin and chymotrypsin. In case reports, ACCs are described as poorly defined, dense masses, well-defined masses with central necrosis, cystic masses surrounded by a thick hypervascular wall, well-defined hypodense masses with a thin, enhancing capsule, or well-defined, hypervascular solid masses on computed tomography (3). The radiological differential diagnosis of ACCs includes ductal adenocarcinoma, neuroendocrine tumor, solid and pseudopapillary tumor, pancreatic blastoma, mutinous cystic neoplasm and pseudocyst. It is important to differentiate among these neoplasms, because their treatments and prognoses differ significantly (3,4). However, with regard to the treatment of ACCs, no successful chemotherapeutic regimens have, unfortunately, been established yet. Therefore, there is clearly a need to establish effective treatment strategies for patients with recurrent or advanced unresectable disease. In this article, we report four patients with ACC of the pancreas who were treated with gemcitabine, which is regarded as the standard drug for the treatment of pancreatic ductal adenocarcinoma, and discuss potential treatment strategies for this disease.

CASE REPORTS

The clinical characteristics of the four patients are summarized in Table 1.

CASE 1

A 48-year-old man with a large palpable abdominal mass in the epigastriac region was referred to us. Dynamic computed tomography showed a huge, lobulated mass encircling the splenic artery, the splenic vein and the superior mesenteric
vein confluence in the pancreatic head and body (Fig. 1). Pancreaticoduodenectomy with excision of the tumor was performed in August 2005. Three metastatic nodules were found during the surgery and removed from the liver surface. The histological diagnosis was pancreatic ACC. After the operation, the patient received no chemotherapy, and 3 months later, multiple liver metastases were detected. Dynamic computed tomography showed metastases in the S6 segment of the liver. Chemotherapy was initiated with gemcitabine, which was administered by intravenous injection over 30 min at the dose of 1000 mg/m² on days 1, 8 and 15 of each 28-day cycle, for 6 months. After a long interval with stable disease (SD), progression of the liver metastases was confirmed and partial hepatectomy was performed at the patient’s request. Although all the metastatic liver tumors were resected, a new metastatic lesion was found in the left upper quadrant of the abdomen at 3 months after the operation. Therefore, surgical resection for the recurrent tumor and the tumor extension to the small intestine and transverse colon was performed. Nonetheless, multiple liver metastases were confirmed again 7 months after the final resection, and oral chemotherapy was initiated with S-1 at the dose of 40 mg/m² twice a day from day 1 to day 28 of each 42-day cycle. However, the chemotherapy of S-1 was judged to be ineffective, because progression of the liver metastases was noted during the second course. The treatment plan was then switched to best supportive care.

**CASE 2**

A 67-year-old man visited us with the chief complaint of epigastric discomfort of 6-month duration. He had received medical treatment for functional dyspepsia, because there were no abnormal findings on abdominal ultrasonography or

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**Table 1. Profiles of our four patients**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>UICC-TNM</th>
<th>Stage</th>
<th>Performance status</th>
<th>Surgery</th>
<th>First-line chemotherapy</th>
<th>Second-line chemotherapy</th>
<th>PFS for first-line chemotherapy with GEM</th>
<th>Survival time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48/M</td>
<td>T3N0M0</td>
<td>II</td>
<td>0</td>
<td>Pancreatectomy and partial hepatectomy</td>
<td>GEM, 6 cycles SD</td>
<td>S-1, 1 cycle PD</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>76/M</td>
<td>T4N0M0</td>
<td>III</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>NE</td>
</tr>
<tr>
<td>3</td>
<td>67/M</td>
<td>T3N1M1</td>
<td>IV</td>
<td>0</td>
<td>—</td>
<td>GEM, 1 cycle PD</td>
<td>S-1, 8 cycles PR</td>
<td>PD</td>
<td>S-1, 1 cycle PD</td>
</tr>
<tr>
<td>4</td>
<td>61/F</td>
<td>T4N0M0</td>
<td>III</td>
<td>0</td>
<td>—</td>
<td>GEM, 6 cycles SD</td>
<td>S-1, 1 cycle PD</td>
<td>—</td>
<td>S-1</td>
</tr>
</tbody>
</table>

PFS: progression-free survival; GEM: gemcitabine; S-1: tegafur-0.4 M gimestat-1 M otastat potassium; SD: stable disease; PD: progression disease; NE: not evaluable; PR: partial response.

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**Figure 1.** Abdominal computed tomography of Case 1 before treatment. The tumor appeared to be composed of cystic and solid components.
upper gastrointestinal (GI) endoscopy. However, since the patient showed no improvement, re-evaluation by abdominal ultrasonography was performed. The ultrasonography showed abdominal lymphadenopathy and multiple liver tumors and the patient was referred to our hospital for further examination. A final diagnosis of pancreatic tail cancer with liver, bone and lymph node metastases was made (Fig. 2). Histological diagnosis by needle aspiration biopsy confirmed the diagnosis of pancreatic ACC. Chemotherapy with gemcitabine was initiated in September 2007, the drug administered by intravenous injection over 30 min at the dose of 1000 mg/m² on days 1, 8 and 15 of each 28-day cycle. After the first chemotherapy cycle, progression of the ACC was noted, along with Grade 3 creatinine elevation. Thus, renal damage occurred suddenly and remained irreversible until the patient was discharged in November 2007. As gemcitabine was ineffective and had adverse effects, the patient was started on best supportive care.

**CASE 3**

A 67-year-old man with chronic hepatitis C was referred to our hospital with elevation of the serum α-fetoprotein level. Dynamic magnetic resonance imaging revealed a focal uniformly dense hypovascular mass in the pancreatic body. Surgical treatment was considered to be contraindicated because the tumor was found to invade the superior mesenteric artery confluence (Fig. 3). The histological diagnosis made by needle aspiration biopsy was pancreatic ACC, and some tumor cells showed focally positive staining for α-fetoprotein. Therefore, we surmised that the elevation of serum α-fetoprotein level might be caused by secretion from the ACC. Chemotherapy was initiated with gemcitabine administered by intravenous injection over 30 min at the dose of 1000 mg/m² on days 1, 8 and 15 of each 28-day cycle. After two courses of chemotherapy with gemcitabine, dynamic computed tomography revealed tumor progression. After discontinuation of the chemotherapy with gemcitabine, oral chemotherapy was started with S-1 administered at the dose of 40 mg/m² twice a day from day 1 to day 28 of each 42-day cycle. The tumor size decreased by 34.1% [classified as a partial response (PR)] by the end of four courses of treatment. The serum α-fetoprotein level decreased from 5386 to 1367 ng/ml. After eight courses of chemotherapy with S-1, however, tumor progression was noted again. Therefore, chemotherapy was discontinued and the patient was started on best supportive care.

**CASE 4**

A 61-year-old woman presented to us with high-colored urine. Physical examination revealed no abnormal findings. Upper GI endoscopy revealed deformation of the duodenal bulb, leading to the suspicion of. Dynamic computed tomography showed an irregularly lobulated mass in the pancreatic head encircling the splenic artery, the splenic vein and the superior mesenteric vein confluence (Fig. 4). The possibility of surgical treatment was ruled out because of tumor invasion into the superior mesenteric artery. The histological diagnosis made by needle aspiration biopsy was ACC of the pancreas. Chemotherapy was initiated with gemcitabine administered over 30 min at the dose of 1000 mg/m² on days 1, 8 and 15 of each 28-day cycle. The best overall response was SD through six courses. After six courses of chemotherapy, computed tomography revealed multiple liver metastases. Oral chemotherapy was started with S-1 administered at the dose of 40 mg/m² twice a day from day 1 to day 28 of each 42-day cycle. However, the multiple liver metastases continued to progress even after the start of S-1 treatment, and the patient was switched to best supportive care.
DISCUSSION

Surgical management remains the only curative therapy for patients with localized and resectable disease. Those who were treated by surgical resection were reported to show a median survival of longer than 30 months (7,8). This compares favorably with the data for patients with ductal adenocarcinoma of the pancreas; published reports on survival after resection have indicated a median survival of 12–18 months (10). More than 70% of the patients who undergo surgical resection are eventually confirmed to show recurrent disease (9). These results suggest that micrometastases are present even in cases where the disease is apparently localized to the pancreas (9).

In addition, most patients with pancreatic ACC present with unresectable locally advanced disease or obvious metastases. For patients at this stage of the disease, no adequate treatment strategies have been established yet (10,11), because no randomized controlled trials have been performed to confirm the efficacy of treatments. There are only a few reports on the use of single-drug chemotherapy, combination chemotherapy (9), chemoradiotherapy (10) or hepatic arterial injection chemotherapy (12–14) (Table 2). To the best of our knowledge, gemcitabine has never been demonstrated to show efficacy against ACC, although the drug has been widely used as the standard agent for the treatment of pancreatic adenocarcinoma. We administered chemotherapy with gemcitabine for patients with pancreatic ACC, and two of these patients showed SD without obvious tumor shrinkage. In addition, severe renal damage caused by gemcitabine was observed in one of our patients. Therefore, in our impression, chemotherapy with gemcitabine is not very promising for pancreatic ACC, although the true efficacy can only be determined by randomized controlled trials.

Some case studies have reported tumor shrinkage with fluoropyrimidine-based treatments. Holen et al. reviewed 22 chemotherapy regimens administered to 18 different patients and reported that there were no complete responses, only two PRs and seven SDs. The PRs were seen for combinations of irinotecan, 5-fluorouracil and leucovorin and also cytarabine, cisplatin and caffeine (9). It is noteworthy that ACCs of the pancreas tended to respond to 5-fluorouracil-based chemotherapies. The three patients showing PR reported in different case series had received combination therapies. Two of the patients had received 5-fluorouracil-based chemotherapy, and one patient had received combination therapies based on capecitabine (Table 2). In addition, we also observed good response to chemotherapy with S-1, a type of fluoropyrimidine. Further research is needed to clarify whether administration of fluoropyrimidine might improve the unsatisfactory results of chemotherapy for this disease.

For patients with unresectable, yet locally confined disease, radiotherapy may be one of the treatment options, as focal disease control may be expected. Holen et al. (9) also reported that all of the eight patients who were treated by radiation showed either PR or SD. Lee and Kim (10) reported two PR cases among locally advanced cases of ACC of the pancreas treated by concurrent capecitabine and radiation therapy. To obtain control of not only localized disease, but also of distant metastatic disease, radiotherapy combined with chemotherapy may be a potentially useful treatment strategy, but there are only a few reports of its use until date.

In conclusion, randomized controlled trials are needed to establish effective treatment strategies for unresectable...
pancreatic ACC. However, it is not easy to recruit patients for trials, as pancreatic ACC is a very rarely occurring tumor. Multicenter and multinational cooperative trials are necessary to establish treatments to improve the dismal prognosis of patients with this disease.

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Conflict of interest statement

None declared.

References