Paclitaxel-Based Chemotherapy for Advanced Pancreatic Cancer after Gemcitabine-Based Therapy Failure: A Case Series of 5 Patients

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Abstract
Background/Objectives: Gemcitabine (GEM) is a gold-standard chemotherapy agent for advanced pancreatic cancer. Because of the malignant character of the disease, nearly all patients show disease progression despite treatment with GEM-based chemotherapy; therefore, second-line chemotherapy may be beneficial for these patients. We report a retrospective analysis of 5 patients with advanced pancreatic cancer, treated with a paclitaxel-containing regimen as second-, third- or fourth-line chemotherapy after various therapies, such as a GEM-based regimen, S-1 regimen, and chemoradiation. We retrospectively analyzed the efficacy and adverse events, and evaluated the paclitaxel-containing regimens. A review of the literature is also discussed.
Results: The median overall survival from the start of salvage therapy was 10.7 months. The disease control rate of the paclitaxel-containing regimen according to RECIST criteria was 60%, including complete response in 0 patients, partial response in 3, and stable disease in 2. Two patients had malignant ascites at the start of this salvage therapy, and in both of them

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the ascites and clinical complaints improved. Grade 3 and 4 hematological adverse events were observed in 2 patients and 1 patient, respectively.

Conclusion: Salvage paclitaxel-based therapy could be beneficial to advanced pancreatic cancer patients who maintain good performance status after several chemotherapy failures.

Introduction

Pancreatic cancer is the fifth highest cause of cancer-related death in Japan [1]. Because pancreatic cancer is often diagnosed late in the course of the disease with metastatic spread, the development of effective medical therapy is needed. Gemcitabine (GEM) is a gold-standard chemotherapy agent for advanced pancreatic cancer; it shows a more significant improvement of clinical symptoms and a modest survival benefit as compared with 5-fluorouracil (5-FU) [2]. With the malignant character of advanced pancreatic cancer, most patients show disease progression despite treatment with GEM-based chemotherapy. The median progression-free survival (PFS) and median overall survival (MST) have been reported as 2–4 and 4.9–8.2 months, respectively [3].

Second-line chemotherapy after GEM treatment failure may be beneficial for patients with good performance status (PS) and tolerability of additional chemotherapy. Although a number of phase II and III second-line chemotherapy trials have been completed, sufficient evidence for efficacy has not been obtained [2]. In Japan, S-1, an oral agent containing a mixture of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxalate, has been approved for pancreatic cancer treatment [4]. Furthermore, the results of several phase II studies using S-1 as a second-line chemotherapeutic regimen after GEM failure have been reported [3, 5].

Paclitaxel is a semisynthetic taxane that interferes with mitotic spindles, inhibits the depolymerization of microtubules and blocks the mitotic cell cycle [6]. Recently, 3 reports of second-line chemotherapy using paclitaxel for advanced pancreatic cancer refractory to GEM or GEM-based regimens have been published, 2 with weekly administration of paclitaxel [7, 8], and 1 with a 5-FU/paclitaxel combination [9].

In this study, we treated 5 patients with advanced pancreatic cancer with paclitaxel-containing regimens as second-, third-, or fourth-line chemotherapy after various therapies, including GEM-based regimens, S-1 regimens, and chemoradiation. We retrospectively analyzed the efficacy and adverse events, and evaluated these paclitaxel-containing regimens.

Patients and Methods

This study included 5 patients with inoperable advanced pancreatic cancer who underwent paclitaxel therapy at our hospital or a related institution between November 2005 and January 2010. All patients had adenocarcinoma diagnosed by biopsy or cytology. They had been previously treated with various therapies as described below, and those patients in whom cancer was exacerbated or in whom the tumor tended to increase and tumor marker levels were elevated according to the Response Evaluation Criteria in Solid Tumors (RECIST criteria) underwent paclitaxel-based therapy. Informed written consent was obtained. Eastern Cooperative Oncology Group PS of the patients ranged from 0 to 2, and their bone marrow, hepatic and renal functions were good.

Previously, the patients had undergone GEM therapy, S-1 therapy, chemoradiotherapy (CRT), a combination of GEM and tegafur-uracil (UFT), and/or a combination of GEM and S-1 according to their symptoms. The patients who could not continue or were refractory to these therapies received paclitaxel-based chemotherapy. The therapeutic protocols were as follows: (1) GEM therapy: GEM (1,000 mg/m^2) was administered on days 1, 8, and 15, followed by a 1-week rest; this was defined as one course of treatment. (2) S-1 therapy: S-1 [80 mg/(m^2·day)] was administered for 4 weeks followed by a 2-week rest; this was defined as one course of treatment [4]. Alternatively, S-1 [80 mg/(m^2·day)] was administered for 2 weeks followed by a 1-week rest; repeated every 21 days. (3) GEM/UFT combination (GF) therapy: GEM (1,000 mg/m^2) was administered on days 1 and 8, and UFT [400 mg/(m^2·day)] was administered for 2 weeks (days 1–14), and both drugs were discontinued in week 3; this was defined as one course of treatment [10]. (4) GEM/S-1 combination (GS) therapy: GEM (1,000 mg/m^2) was administered on days 1 and 8, and S-1 [80 mg/(m^2·day)] was administered for 2 weeks (days 1–14), followed by a 1-week rest; this was defined as one course of treatment [11]. (5) CRT: as reported by our department, 2.0 Gy/day was administered for 5 days, for a total of 40–50 Gy. GEM (40 mg/m^2) was administered twice a week as a sensitizer [12]. The above-mentioned regimens were the basic protocols, and the dosages and schedules were adjusted according to the development of adverse reactions.

Paclitaxel/cisplatin/S-1 combination (PCS): Paclitaxel (60 mg/m^2), cisplatin (7 mg/m^2), and S-1 [60 mg/(m^2·day)] were administered on day 1, days 1 and 5, and days 1–5, respectively, for 3 weeks followed by a 1-week rest; this was defined as one course of treatment.

Tumor response was defined according to the RECIST criteria. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Results

Table 1 shows patient characteristics. The median age at the first visit was 65 years (range 41–70). The female-to-male ratio was 2:3. The Union for International Cancer Control (UICC) classifications at the first visit were stage III in 2 patients and stage IV in 3 patients. Symptoms at diagnosis included abdominal pain and jaundice in 1 patient, abdominal pain in 2 patients, ileus in 1 patient, and weight loss and diabetes exacerbation in 1 patient. The median period from initial chemotherapy to the start of paclitaxel therapy was 13.1 months (range 6.5–19.5). **Table 2** shows the prior therapies of the 5 patients; all 5 patients received multiple prior therapies. PS at the initiation of PCS was 0 in 2 patients, 1 in 2 patients and 2 in 1 patient. Reasons for starting PCS were as follows: development of malignant ascites in 2 patients, appearance of distant metastases to the liver in 2 patients and progression of primary site in 1 patient (**table 3**). The disease control rate of paclitaxel therapy according to the RECIST criteria was 60%, including complete response in 0 patients, partial response (PR) in 3 patients, and stable disease in 2 patients. Malignant ascites improved in the 2 affected patients, and subjective symptoms, such as abdominal pain, improved in all 3 affected patients. The median survival after the start of PCS was 10.7 months (range 9.1–27.6), and the MST from the start of initial chemotherapy was 25.2 months (range 11.6–47.1). All subjects developed alopecia and myelosuppression of grade 2 (2 patients), grade 3 (2 patients), or grade 4 (1 patient) as adverse reactions.

Case Report
Case 1 was a 70-year-old man with a history of alcoholic liver cirrhosis. A tumor 3.4 cm in diameter, associated with invasion of the superior mesenteric artery and found in the pancreatic head, was determined as UICC stage III pancreatic cancer (**fig. 1**a). GF therapy was started, but the size of the tumor increased; therefore, GF therapy was replaced with GS therapy. However, grade 3 thrombocytopenia developed, so GEM was administered every other week. Due to thrombocytopenia, GEM could not be continued; therefore, it was replaced with S-1 therapy 8 months after the start of

initial chemotherapy (fig. 1b). Thereafter, abdominal pain gradually increased, which required a higher dose of narcotic. The tumor size further increased, and 10 months after the start of initial chemotherapy, ascites developed (fig. 1c). Cytodiagnosis of ascites revealed adenocarcinoma cells; therefore, malignant ascites was diagnosed. Ascites improved and tumor size decreased after 1 course of PCS therapy, and the dose of narcotic was decreased by 20% of the maximal dose. An abdominal CT 6 months after the start of PCS (fig. 1d) showed complete resolution of ascites and PR of the tumor. The patient died 19.2 months after the start of PCS, which was 30.1 months after the start of initial chemotherapy.

Discussion

For more than 10 years, GEM has been the standard chemotherapy for advanced pancreatic cancer; however, the response rate is low, and chemoresistance occurs early. There have been very few randomized trials in GEM-refractory patients, and there is no widely accepted standard of care [13]. To obtain a better prognosis for advanced pancreatic cancer, effective second-line chemotherapy should be developed for patients with good PS after GEM failure.

In Japan, S-1 has been commonly used as second-line chemotherapy for patients with advanced pancreatic cancer after GEM failure. Morizane et al. [5] performed a phase II study of this agent in a second-line setting in patients with GEM-refractory metastatic pancreatic cancer. The response rate was 16%, the median PFS and MST were 2.0 and 4.5 months, respectively, and the 1-year survival rate was 14%. Furthermore, Todaka et al. [3] reported a retrospective study of 84 patients who received S-1 monotherapy as second-line treatment after GEM failure. Fifty-two patients were selected for the analysis, and the median PFS and MST were 2.1 and 5.8 months, respectively.

There have been several reports of paclitaxel as a second-line chemotherapeutic agent in patients with advanced pancreatic cancer refractory to GEM or GEM-based regimens. Oettle et al. [14] reported that weekly administration of paclitaxel at 50 mg/m^2, increasing up to 85 mg/m^2, in advanced pancreatic cancer patients after pre-treatment with GEM and/or in combination with 5-FU and folinic acid, was effective with a low toxicity profile. In this study, the disease control rate was 33.3%, including complete response in 1 patient, and the MST was 17.5 weeks [14]. Recently, Kim et al. [9] reported a phase II study of another second-line paclitaxel-containing regimen in 28 pancreatic cancer patients after GEM-based regimen failure. On days 1, 2 and 3, 5-FU (1,000 mg/m^2) was infused, and on day 1, paclitaxel (175 mg/m^2) was administered every 4 weeks. Of the 20 evaluated patients, 10% obtained PR, 20% had stable disease, and the MST was 7.6 months. Maeda et al. [8] presented results from a retrospective study of weekly administration of paclitaxel (80 mg/m^2 a week for 3 weeks followed by a 1-week rest) as second- or third-line treatment in patients with GEM-based regimen-refractory pancreatic cancer. Thirty patients were retrospectively analyzed, and the MST was 6.7 months. The response rate was 10% and the disease control rate was 46.7%. The authors found a significant correlation between the disease control rate and tumor marker decline within 2 months of paclitaxel treatment (p = 0.01) [8].

In this study, we evaluated 5 patients with advanced inoperable pancreatic cancer after various therapies such as chemotherapy using GEM, GF therapy, GS therapy, and S-1 monotherapy, or CRT. The median time from initial chemotherapy to the start of

paclitaxel therapy was 10.1 months. The idea for using a PCS regimen, a weekly paclitaxel regimen combined with low-dose FP (5-FU/cisplatin), came from a previous case series in Japan [15]. The background of each patient in this study differed at the initiation of paclitaxel therapy, the number of patients was small, and it was just a retrospective evaluation; therefore, the actual effectiveness of this regimen requires further investigation. However, it is possible that PCS could be a salvage chemotherapy candidate for patients with advanced inoperable pancreatic cancer with good PS after pretreatment failure.

The prognosis of patients with advanced pancreatic cancer refractory to GEM is poor due to metastases to the liver, lung, and bone, or peritoneal dissemination. Peritoneal dissemination causes massive ascites resulting in abdominal pain, fullness, constipation and/or malnutrition, and these patients' quality of life becomes poor. Recently, Shukuya et al. [7] reported the effectiveness of weekly paclitaxel after GEM failure in pancreatic cancer with malignant ascites in a retrospective study. They evaluated 23 patients who received weekly paclitaxel (80 mg/m^2 administered on days 1, 8, and 15 every 4 weeks); ascites decreased in 30% of the patients, and the ascites control rate was 61% [7]. In our study, 2 patients harbored malignant ascites at the initiation of paclitaxel therapy, and ascites and clinical complaints improved in both of them. Therefore, a chemotherapeutic regimen including paclitaxel after GEM failure could also provide a clinical benefit for pancreatic cancer patients with peritoneal dissemination.

Conclusion

In conclusion, for patients with advanced pancreatic cancer after several chemotherapy failures, including GEM, salvage paclitaxel-based therapy could be a candidate for second-, third-, or fourth-line chemotherapy, especially in patients maintaining good PS. However, a more detailed randomized study is required for further evaluation.

Disclosure Statement

The authors have no potential conflicts of interest.

Table 1. Patient profiles at the diagnosis of advanced pancreatic cancer

Case No.	Age years	Sex	UICC stage	Symptom at diagnosis
1	70	M	III	Abdominal pain
2	65	M	IV	Abdominal pain, jaundice
3	41	M	III	Ileus
4	68	F	IV	Weight loss, diabetes exacerbation
5	65	F	IV	Abdominal pain

Table 2. Prior therapy regimens

Case No.	Contents of prior therapy
1	GF, GS, S-1
2	GF, GS, CRT, S-1
3	Bypass surgery, GEM, GS, CRT, S-1
4	GF, GS
5	GEM, GS

Table 3. Patient profiles at the start of paclitaxel therapy and results

| Case No.	Time from initial chemotherapy to start of PCS therapy, months	PS at PCS therapy	Reason for introducing PCS therapy	Survival after initiation of PCS, months
1	10.9	1	Appearance of malignant ascites	19.2
2	13.1	1	Appearance of distant metastases	9.1
3	19.5	0	Progression of primary site	27.6
4	14.5	0	Appearance of distant metastases	10.7
5	6.5	2	Appearance of malignant ascites	5.1

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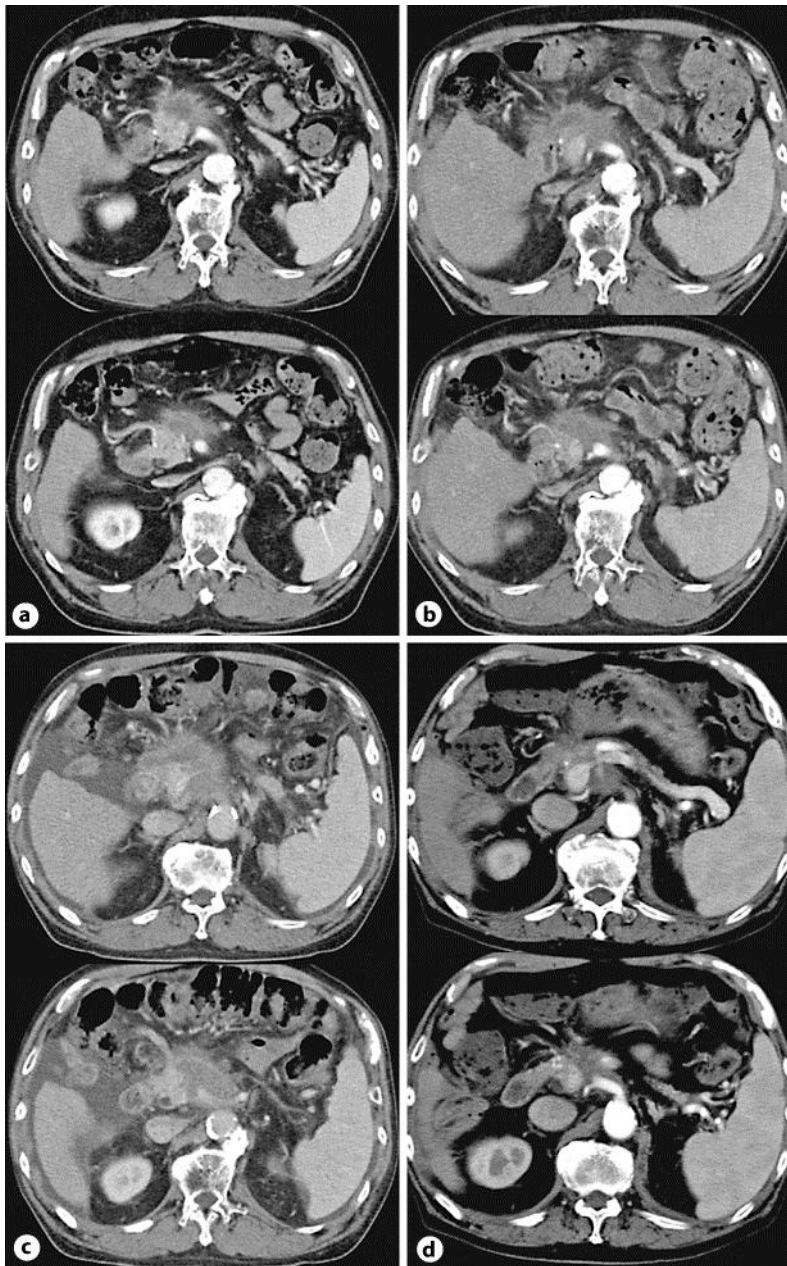
Fig. 1. Abdominal CT findings of case 1. **a** CT at admission. **b** CT 8 months after initial treatment. **c** CT 10 months after initial treatment. **d** CT 6 months after introduction of PCS regimen.

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