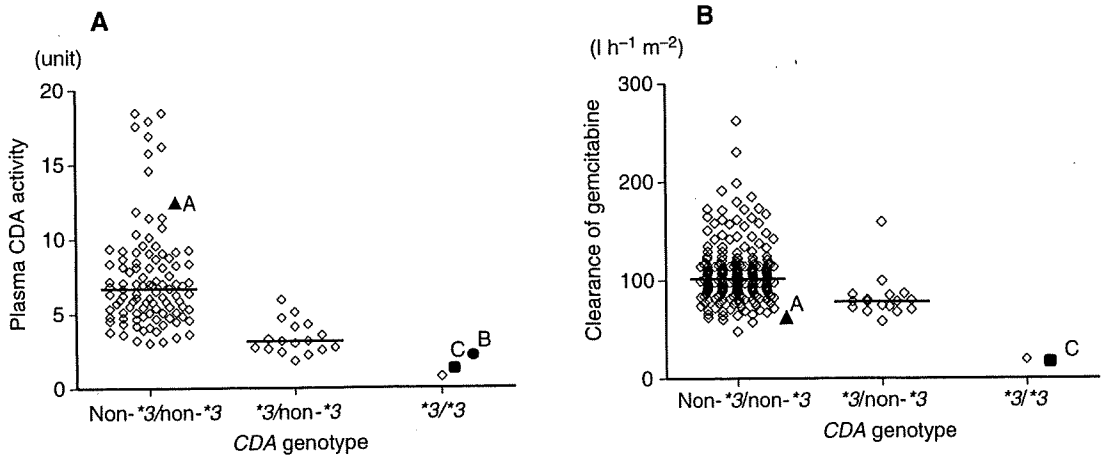

Figure 1 Effects of *CDA*3* on (**A**) plasma CDA activity towards gemcitabine and (**B**) gemcitabine clearance. The data obtained earlier (Sugiyama *et al*, 2007) are expressed as open diamonds, and those obtained in this study are as closed symbols. A, B, and C represent patients A, B, and C, respectively. Lines represent median values for non-*3/non-*3 patients and *3/non-*3 patients.

C received 1000 mg m^{-2} of gemcitabine, C_{max} and AUC values similar to those observed in the earlier reported *CDA*3/*3* patient were obtained. The value of gemcitabine clearance in patient C (*CDA*3/*3*) was less than one-fifth of the median value obtained earlier from *CDA*3*-negative patients. The clearance observed in patient A, who did not have *CDA*3*, was within the range obtained earlier from patients without *CDA*3* (Figures 1B).

DISCUSSION

We found two (patients B and C) of the three patients who experienced life-threatening adverse reactions to be homozygous for *CDA*3* and to have an extremely low CDA activity. Taken together with our earlier observations (Yonemori *et al*, 2005; Sugiyama *et al*, 2007), these life-threatening adverse reactions appear to have been caused by reduced deamination activity of CDA because of *CDA*3/*3* homozygosity. Sustained plasma gemcitabine elevations are most likely responsible for these severe adverse reactions. To date, we have had three *CDA*3/*3* patients, including one reported earlier (Yonemori *et al*, 2005; Sugiyama *et al*, 2007), and all experienced life-threatening severe adverse reactions. As genotyping of *CDA* was not carried out in the remaining 239 patients, we may have overlooked patients with *CDA*3/*3* who did not develop severe toxicities in this study. However, as the frequency of homozygous *CDA*3* in the Japanese population was estimated to be 0.14% in an earlier study (Sugiyama *et al*, 2007), the possibility of missing any such patients would be very low. Thus, *CDA*3/*3* is a potentially important biomarker for Japanese patients and for at least one African ethnic group (Fukunaga *et al*, 2004) for predicting severe gemcitabine-mediated adverse reactions including myelotoxicities.

We do not have sufficient pharmacokinetic data on *CDA*3/*3* to determine the optimal dose for this fraction of the patient population. However, the clearance and AUC values for the earlier reported patient (Sugiyama *et al*, 2007) and for patient C (dose adjusted), and the final dose for patient C (270 mg m^{-2}) suggest that a 75% reduction in the gemcitabine dose, at treatment initiation, may be appropriate for *CDA*3/*3* patients.

Patient A was given combined chemotherapy with oral S-1 (Table 1). As she could not tolerate gemcitabine monotherapy at the standard dose as shown in Table 2, gemcitabine itself appears to have been responsible for the life-threatening toxicities in this patient. Her gemcitabine clearance was within the range observed in patients without *CDA*3* (Sugiyama *et al*, 2007). Therefore, we concluded that there was no involvement of altered CDA activity in the severe neutropaenia experienced by patient A. Further investigation of gemcitabine pathway genotypes is needed to clarify factors contributing to this patient's adverse reactions.

In conclusion, in the Japanese population, *CDA*3/*3* is a major cause of gemcitabine-mediated life-threatening adverse reactions including myelosuppression. A substantial gemcitabine dose reduction is necessary for patients who are homozygous for *CDA*3*.

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Conflict of interest

Dr Saijo reported receiving honoraria from Eli Lilly. None of the other authors reported financial interest.

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Expression of carbonic anhydrase IX suggests poor outcome in rectal cancer

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The aim of the study is to assess the value of carbonic anhydrase isozyme IX (CA IX) expression as a predictor of disease-free survival (DFS) and disease-specific survival (DSS) in rectal cancer treated by preoperative radio- or chemoradiotherapy or surgery only. Archival tumour samples from 166 patients were analysed for CA IX expression by three different evaluations: positive/negative, proportion of positivity and staining intensity. The results of immunohistochemical analysis were confirmed by demonstrating CA IX protein in western blotting analysis. Forty-four percent of the operative samples were CA IX positive, of these 34% had weak and 66% moderate/strong staining intensity. In univariate survival analysis, intensity of CA IX expression was a predictor of DFS ($P = 0.003$) and DSS ($P = 0.034$), both being markedly longer in tumours with negative or weakly positive staining. In multivariate Cox model, number of metastatic lymph nodes and CA IX intensity were the only independent predictors of DFS. Carbonic anhydrase isozyme IX intensity was the only independent predictor of DSS, with HR = 9.2 for dying of disease with moderate-intense CA IX expression as compared with CA IX-negative/weak cases. Negative/weak CA IX staining intensity is an independent predictor of longer DFS and DSS in rectal cancer.

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Keywords: rectal cancer; CA IX; prognosis; predictive factor; radiotherapy; chemotherapy

Colorectal cancer (CRC) is a common malignancy in Western countries and the incidence is rising: there were nearly 372 000 new cases of CRC in Europe in 2002 (Ferlay *et al*, 2004). The most important prognostic factors of rectal cancer are the type of surgery, depth of invasion and nodal status. Other prognostic factors have been widely tested (Bendardaf *et al*, 2006, 2007) but as yet have not achieved an established role in the management of CRC.

Angiogenesis and tumour hypoxia have been widely studied during the past decades to develop better treatment modalities and prognostic factors. Angiogenesis favours tumour growth and metastasis, whereas hypoxia renders a tumour resistant to radiation and often to chemotherapy as well (Brizel *et al*, 1996). Hypoxic regions are common in various solid cancers due to their rapid growth. Tumour cells adapt to hypoxic conditions by stabilising the hypoxia-inducible transcription factor (HIF-1α), which leads to upregulation of several genes involved in cell proliferation and angiogenesis (Harris, 2002; Semenza, 2003). One of the upregulated genes is *CA9* (Opavsky *et al*, 1996). *CA9* encodes the carbonic anhydrase isozyme IX (CA IX) (Wykoff *et al*, 2000; Niemelä *et al*, 2007). Carbonic anhydrase isozyme IX is shown to be strongly inducible by hypoxia in tumour cells (Wykoff *et al*, 2000).

In earlier studies, the pattern of membranous CA IX expression is seen in malignant cells and only rarely in normal or benign cells (Pastorek *et al*, 1994; Kivelä *et al*, 2001). Colorectal tumours show an abnormal CA IX expression, which is especially seen in areas of high proliferation (Saarnio *et al*, 1998). More diffuse staining is seen in carcinomas than in benign lesions (Saarnio *et al*, 1998). Carbonic anhydrase isozyme IX is involved in maintaining the extracellular pH (Ivanov *et al*, 2001) by catalysing the reversible chemical reaction in which carbon dioxide is hydrated to carbonic acid and further to bicarbonate (Wykoff *et al*, 2000; Brennan *et al*, 2006). Thus, it is an important enzyme for cancer cells in hypoxic and normoxic conditions (Wykoff *et al*, 2000; Robertson *et al*, 2004) in the regulation of acid–base balance (Hilvo *et al*, 2007). Interestingly, in CRC samples studied by cDNA microarray (Talvinen *et al*, 2006), *CA9* was found to be the most upregulated gene.

This study was designed to assess the prognostic and predictive value of CA IX in rectal cancer treated by either short- or long course of radiotherapy (RT) with or without chemotherapy. Operative samples obtained from non-irradiated patients were used as controls. Carbonic anhydrase isozyme IX expression was studied in relation to histopathological features and clinical data pertinent to disease-free survival (DFS) and disease-specific survival (DSS).

PATIENTS AND METHODS

Study population

This study consists of archival operative tumour samples of 166 consecutive patients with rectal cancer, treated according to the

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ORIGINAL ARTICLE

A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer

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Abstract
Purpose Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. After disease progression, there is no standard regimen available. In a previous phase II trial, S-1 has been reported to show considerable efficacy, achieving a response rate of 37.5% in chemo-naïve patients with pancreatic cancer. This study evaluated the efficacy and toxicity of S-1 in patients with gemcitabine-refractory metastatic pancreatic cancer.
Methods Eligibility criteria were histologically proven pancreatic adenocarcinoma with confirmation of progressive disease while receiving gemcitabine-based first-line chemotherapy, 20–74 years of age, Karnofsky performance status of 80–100 points, with measurable metastatic lesions, adequate hematological, renal and liver functions, and written informed consent. S-1 was administered orally at 40 mg/m^2 twice daily for 28 days with a rest period of 14 days as one course. Administration was repeated until the appearance of disease progression or unacceptable toxicity. The primary endpoint of this study was an objective response, and secondary endpoints included toxicity, progression-free survival (PFS) and overall survival, as well as clinical benefit response in symptomatic patients.
Results Forty patients from two institutions were enrolled between September 2004 and November 2005. The most common adverse reactions were fatigue and anorexia, although most of those adverse reactions were tolerable and reversible. One patient developed grade 3 pneumonitis without neutropenia and recovered with appropriate antibiotic treatment. Although no complete response was seen, partial response was obtained in six patients (15, 95% confidence interval, 3.9–26%). Stable disease was noted in 17 patients (43%), and progressive disease in 15 patients (38%). Out of 19 evaluable patients, a clinical benefit response was observed in four patients (21%). The median PFS was 2.0 months, and the median survival time was 4.5 months with a 1-year survival rate of 14.1%.
Conclusion S-1 as monotherapy had marginal anti-tumor activity with tolerable toxicity in patients with gemcitabine refractory metastatic pancreatic cancer.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Salvage

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Background

The prognosis of patients with pancreatic carcinoma is extremely poor because of difficulty in the early detection of this disease, the high incidence of postoperative recurrence, and ineffectiveness of nonsurgical treatments. Gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU [3]. However, the benefit provided was inadequate, with an objective response rate of less than 15% and a median survival of 5–7 months. To improve the prognosis of patients with pancreatic cancer, one of the strategies is to develop the effective first-line chemotherapy including

gemcitabine combinations. Among various combinations with gemcitabine plus other agents as a first-line chemotherapy, only a few regimens have shown any survival benefit over single-agent gemcitabine [6, 20, 25], although the worldwide consensus regarding the results of these studies has not been established. Another strategy is to develop an effective second-line chemotherapy regimen after disease progression during first-line chemotherapy. However, despite the fact that several studies have investigated second-line chemotherapy in pancreatic cancer, the therapeutic results have been disappointing with poor response rate and survival [1, 2, 4, 5, 7, 14, 16, 18, 19, 21, 26, 27, 33, 34, 36, 38] Effective treatment in patients failing gemcitabine-based chemotherapy is eagerly awaited.

S-1 is a novel orally administered drug that is a combination of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and oteracil potassium (Oxo) in a 1:0.4:1 molar concentration ratio [31]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and acts to maintain efficacious concentrations of 5-FU in plasma and tumor tissues [35]. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, reducing the serious gastrointestinal toxicity associated with 5-FU [32]. The antitumour effect of S-1 has already been demonstrated in a variety of solid tumors such as advanced gastric cancer [15, 30], colorectal cancer [23], non-small-cell lung cancer [13], head and neck cancer [11], and breast cancer [29].

Concerning pancreatic cancer, a recent late phase II study of S-1 for chemo-naïve advanced pancreatic cancer patients demonstrated promising results with a response rate of 37.5% and a favorable toxicity profile [24]. Furthermore, clinical studies have reported activity of gemcitabine in pancreatic cancer patients with refractoriness to 5-FU [28], suggesting the lack of crossresistance between the gemcitabine and fluorinated pyrimidine, including S-1. Therefore, we conducted the present phase II study to investigate the feasibility and efficacy of S-1 in patients with advanced pancreatic adenocarcinoma in a progressive state under gemcitabine-based first-line chemotherapy.

Patients and methods

Patients

All patients were required to show histologically proven pancreatic adenocarcinoma with measurable metastatic lesions. Additional criteria included the following: progressive disease under gemcitabine-based first-line chemotherapy, post operative recurrence or metastatic disease before the start of first-line chemotherapy, 20–74 years of age, Karnofsky performance status (KPS) of 80–100 points, more than 3 weeks intervals between the last administration of the prior chemotherapy regimen and study entry, adequate bone marrow function (white blood cell count $\geq$ 3,000/mm^3, neutrophil count $\geq$ 1500/mm^3, platelet count $\geq$ 100,000/mm^3, haemoglobin level $\geq$ 9.0 g/dl), adequate renal function (serum creatinine level $\leq$ 1.5 mg/dL), and adequate liver function (serum total bilirubin level $\leq$ 2.0 mg/dL, transaminases level $\leq$ 2.5 times the upper limits of normal). Patients who had obstructive jaundice or liver metastasis were considered eligible if their transaminases levels could be reduced to within 5 times the upper normal limit of normal after biliary drainage. The exclusion criteria were as follows: regular use of phenytoin, warfarin or frucitocin, history of fluorinated pyrimidine use, severe mental disorder, active infection, ileus, interstitial pneumonia or pulmonary fibrosis, refractory diabetes mellitus, heart failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, brain metastasis, active concomitant malignancy. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center in Japan.

Treatments

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily after breakfast and dinner. Three initial doses were established according to the body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA < 1.50 m^2, 100 mg/day; and 1.50 m^2 $\leq$ BSA, 120 mg/day. S-1 was administered at the respective dose for 28 days, followed by a 14-day rest period; this treatment course was repeated until the occurrence of disease progression, unacceptable toxicities, or the patient's refusal to continue. When a grade 3 or greater haematologic or grade 2 or greater nonhaeamatologic toxicity occurred, either the temporary interruption of the S-1 administrations until the toxicity decreased to grade 1 or less, or dose reduction by 20 mg/day (minimum dose, 80 mg/day) was recommended. If no toxicity occurred, the rest period was shortened to 7 days or the dose was gradually escalated in the next course (maximum dose, 150 mg/day), or both were permitted according to the judgment of the individual physicians. If a rest period of more than 28 days was required because of toxicity, the patient was withdrawn from the study. Patients were not allowed to receive concomitant radiation therapy, chemotherapy, or hormonal therapy during the study. Patients maintained a daily journal to record their intake of S-1 and any signs or symptoms that they experienced.

Response and toxicity evaluation

The response after each course was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Primary pancreatic lesions were not considered to be measurable lesions because the dimensions of such lesions are difficult to measure accurately. Physical examinations, complete blood cell counts, biochemistry tests, and urinalyses were performed at least weekly. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Clinical benefit response

The clinical benefit response (CBR) was evaluated using the KPS and pain score, as described below [3]. The KPS was recorded weekly by the attending physician. Pain was evaluated by measuring the change from the baseline pain intensity and the daily dose of morphine or morphine-equivalent (doses of analgesic agents were converted to morphine-equivalent doses, i.e., 10 mg oxycodone = 15 mg morphine). The pain intensity was graded from 0 (no pain) to 100 (worst pain) using a visual analog scale and was recorded on a pain assessment card every day. Patients who fulfilled at least one of the following criteria were defined as eligible CBR analysis: (1) baseline pain intensity $\geq$20, or (2) baseline morphine consumption $\geq$10 mg/day. Moreover, all the patients underwent a 'pain stabilization period' for 2 days to ensure that the baseline values were stable before treatment: when the variation in the morphine consumption between 2 days was within 10 mg and the variation of the pain intensity was within 20, the patient was considered eligible for inclusion in the CBR analysis. For pain intensity, a positive response occurred when the score was improved by $\geq$50% from baseline, sustained for $\geq$4 weeks. For analgesic consumption, a positive response occurred when the weekly consumption was reduced by $\geq$50% from baseline, maintained for $\geq$4 weeks. A positive response for KPS was defined as an improvement of $\geq$20 points from baseline, sustained for at least 4 weeks. Any worsening from baseline, sustained for 4 weeks, was considered a negative response for each of the three domains. All the other results were considered stable. Pain intensity and analgesic consumption were compared to give a composite pain score. Each patient was classified positive, stable or negative for each of the primary measures (pain and KPS). In order to achieve a positive clinical benefit response, patients had to be positive for at least one parameter without being negative for any of the others for a minimum of 4 weeks. Patients who were stable in the two primary measures were classified as stable.

Statistical design

The primary endpoint of this study was objective response rate. The secondary endpoint of this study was clinical benefit response; toxicity; progression-free survival; and survival. The number of patients to be enrolled was planned using a SWOG's standard design (attained design) [8, 9]. The null hypothesis was that the overall response rate would be $\leq$5% and the alternative hypothesis was that the overall response rate would be $\geq$20%, the α error was 5% (one-tailed) and the β error was 10% (one-tailed). The alternative hypothesis was established based on the preferable data from previous reports [7, 16, 27, 36, 38]. Interim analysis was planned when 20 patients were enrolled. If none of the first 20 patients had a partial response or complete response, the study was to be ended. If a response was detected in any of the first 20 patients studied, an additional 20 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. If the lower limit of the 90% confidence interval exceeded the 5% threshold (objective response in seven or more of the 40 patients), S-1 was judged to be effective and we would proceed to the next large-scale study.

The progression-free survival was calculated from the date of study entry to the date of documented disease progression or death due to any cause (whichever occurred first); and overall survival time was calculated from the date of study entry to the date of death or the last follow-up. The median probability of the survival period and progression-free survival were estimated using the Kaplan–Meier method. The relative dose intensity of S-1 was calculated according to the Hryniuk method [10].

Results

Patients

Forty consecutive patients with metastatic pancreatic cancer which was progressing under gemcitabine-based first-line chemotherapy were enrolled in this study between September 2004 and November 2005. The patient characteristics are shown in Table 1. Thirty-six of the forty patients showed a KPS of $\geq$90. Prior treatment was gemcitabine monotherapy in all patients. Thirty-six of the forty patients (90%) received gemcitabine as a standard 30 min infusion, and the remaining four patients (10%) received gemcitabine administered by fixed dose rate infusion. Of 40 patients, 4 patients (10%) showed a partial response, 21 patients (53%) showed stable disease, and 12 (30%) patients showed progressive disease in first-line gemcitabine therapy. Three patients had received first-line chemotherapy at another hospital and accurate data about

Table 1 Patient characteristics ($n = 40$)

Age	
Median (range)	62 (36–74)
Gender	
Male	21
Female	19
KPS	
100	17
90	19
80	4
Biliary drainage	
(+)	6
Prior pancreatectomy	
(+)	7
Location of primary tumor	
Head	17
Body	14
Tail	9
Sites of metastasis	
Liver	33
Lymph node	16
Lung	3
Peritoneum	4
Prior chemotherapy	
Gemcitabine[a]	36
FDR-GEM[b]	4
TTP of prior treatment (months)	
Median (range)	2.8 (0.7–13.5)
CEA (ng/ml)	
Median (range)	14.9 (1.1–1,187)
CA19-9 (U/ml)	
Median (range)	4,673 (0.1–2,960,000)

KPS Karnofsky performance status, *TTP* time to progression, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9

[a] Gemcitabine as a standard 30-min infusion

[b] FDR-GEM: gemcitabine as a fixed dose rate infusion

treatment response could not be obtained. The median time to progression in the prior treatment was 2.8 months (range 0.7–13.5 months).

Treatments

A total of 94 courses were administered to the 40 patients with a median of two courses per patient (range 1–12). The initial administered dose of S-1 was 80 mg/day in 1 patient, 100 mg/day in 18 patients, and 120 mg/day in 21 patients. Treatment interruption was necessary in 18 patients, due to fatigue (grade 3: one patients, grade 2: one patient, grade 1: two patients), nausea (grade 2: three patients, grade 1: one patient), diarrhea (grade 3: two patients, grade 1: two patients), drainage tube related problem (two patients), grade 3 appetite loss (1), grade 1 leukocytopenia (1), grade 2 hand-foot skin reaction (1), and grade 1 pneumonitis (1). Dose reduction was required in three patients because of grade 3 diarrhea (1), grade 2 fatigue (1), and grade 1 nausea (1). The relative dose intensity was 94.7%. The reasons for discontinuation of treatment were radiologically confirmed progressive disease (PD) in 31 patients, clinical PD without radiological PD in 6 patients, at the patients request due to unacceptable toxicities in 2 patients (grade 2 fatigue and grade 3 anorexia), and loss to follow up in one patient.

Toxicity

All 40 eligible patients were assessable for adverse events. The treatment-related adverse reactions are listed in Table 2. One patient developed grade 3 pneumonitis without neutropenia and required hospitalization, but she recovered from the pneumonitis with antibiotic treatment. As to other grade 3 non-hematological toxicities, aspartate aminotransferase elevation (two patients), alanine aminotransferase elevation (2), fatigue (2), anorexia (2), diarrhea (2) were noted. Regarding hematological toxicities, grade 3 anemia was noted in one patient. No other severe or unexpected adverse reactions were noted. The most common adverse reactions were fatigue (78%) and anorexia (73%), although most of those adverse reactions were tolerable and reversible. Although five patients died within 4 weeks after discontinuation of treatment due to rapid disease progression, no treatment-related deaths were observed.

Efficacy

Out of the total of 40 eligible patients, 38 patients were assessable for response. Two patients discontinued chemotherapy at their request due to unacceptable toxicities (grade 2 fatigue and grade 3 anorexia) and moved to another hospital before tumor assessment. Although no complete response was seen, partial response was obtained in six patients (15, 95%, confidence interval 3.9–26%). Stable disease was noted in 17 patients (43%), and progressive disease in 15 patients (38%). Tumor responses to second-line S-1 therapy are classified according to tumor responses to first-line gemcitabine in Table 3. The serum CA 19-9 level was reduced to less than half in 8 (23%) of 35 patients with a pretreatment serum CA19-9 level of the upper limit of normal or greater. At the time of enrollment, nineteen of forty (47.5%) patients were eligible for the evaluation of clinical benefit response. Out of nineteen evaluable patients, a clinical benefit response was observed in four patients (21%). The median progression free survival time was 2.0 months, and the median survival time was 4.5 months (range 1.2–14.3+) with a 1-year survival rate of 14.1% (Fig. 1).

Table 2 Treatment-related adverse events ($n = 40$): worst grade reported during treatment period

	Grade				Grade 1–4	Grade 3–4
	1	2	3	4	*n* (%)	*n* (%)
Hematological toxicity						
Leukocytes	8	2	0	0	10 (25)	0 (0)
Neutrophils	3	2	0	0	5 (13)	0 (0)
Hemoglobin	5	13	1	0	19 (48)	1 (3)
Platelets	9	0	0	0	9 (23)	0 (0)
Non-hematological toxicity						
Aspartate aminotransferase elevation	13	1	2	0	16 (40)	2 (5)
Alanine aminotransferase elevation	8	1	2	0	11 (28)	2 (5)
Total bilirubin elevation	4	3	0	0	7 (18)	0 (0)
Fatigue	21	8	2	0	31 (78)	2 (5)
Nausea	18	6	0	0	24 (60)	0 (0)
Vomiting	5	1	0	0	6 (15)	0 (0)
Anorexia	22	5	2	0	29 (73)	2 (5)
Stomatitis	11	3	0	0	14 (35)	0 (0)
Diarrhea	8	4	2	0	14 (35)	2 (5)
Rash	3	0	0	0	3 (8)	0 (0)
Pigmentation	6	1	–	–	7 (18)	–
Hand-foot skin reaction	1	1	0	–	2 (5)	0 (0)
Pneumonitis without neutropenia	0	0	1	0	0 (0)	1 (3)

Table 3 Objective tumor response (RECIST criteria) ($n = 40$)

Response (2nd line)	*n* (%)	Response (1st line)			
		PR	SD	PD	NE
CR	0 (0%)	0	0	0	0
PR	6 (15%)	1	4	0	1[a]
SD	17 (43%)	2	9	5	1[a]
PD	15 (38%)	1	6	7	1[a]
NE	2 (5%)	0	2	0	0
Total	40 (100%)	4	21	12	3

Treatment response to second-line S-1 therapy is tabulated according to treatment response to first-line gemcitabine

[a] Three patients received first-line chemotherapy at another hospital and accurate data about treatment ressponse was unobtainable

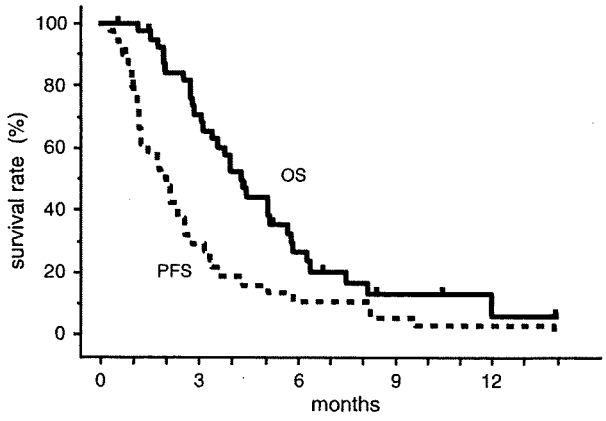

Fig. 1 Survival ($n = 40$). Progression free survival (*dashed line*), and overall survival time (*solid line*) curves of patients with gemcitabine refractory pancreatic cancer receiving systemic chemotherapy with S-1

Discussion

Over the last several years, many studies have been designed to establish effective treatment for gemcitabine-refractory pancreatic cancer patients. So far, the results of two randomized phase III studies had been reported. Jacobs et al. reported on a phase III study comparing Rubitecan, a new topoisomerase I inhibitor, versus "physicians' choice" in 409 pretreated patients. The study was unable to indicate any statistically significant survival benefit in the Rubitecan arm (3.7 months vs. 3.1 months, $P = 0.626$), although progression-free survival was significantly improved in Rubitecan arm (1.9 months vs. 1.6 months, $P = 0.001$) [12]. On the other hand, Oettle et al. [22] reported on phase III study comparing a combination of oxaliplatin, 5-FU and folinic acid with best supportive care (BSC). The BSC arm closed to accrual after 46 out of 165 planned patients were enrolled because physicians deemed it unethical. The median survival of second-line therapy was 21 weeks compared to 10 weeks for the BSC group ($P = 0.0077$). However, a worldwide consensus regarding this result has not been established because of the small number of patients in

this study. Other studies have investigated the feasibility and activity of second-line treatments in phase II studies [1, 4, 7, 17, 19, 26, 27, 33, 36, 38]. Compared with monotherapy, combination regimens exhibited superior activity in these studies. Fluoropyrimidine-, Irinotecan- or oxaliplatin-based combinations indicated relatively preferable activity with objective responses rate of about 20% and a median survival of 5–6 months in this setting [7, 17, 27, 36, 38]. The safety profiles of such combination regimens require further careful evaluation, and well-designed, larger randomized controlled studies are needed.

In the current study, S-1 produced a response rate of 15%, which was superior to the rates obtained for other reported single agents, including paclitaxel (5.5%) [21], raltitrexed (0%) [38], rubitecan (7%) [4]. However, this response rate failed to reach the pre-established boundary of 17.5% required for the agent to be considered effective. Furthermore, the progression-free survival (median 2 months) and the overall survival (median 4.5 months) were still extremely poor in this study. Although S-1 seems to have some degree of anti-tumor activity in patients with gemcitabine refractory metastatic pancreatic cancer, monotherapy may be insufficient to prolong survival. This limitation may be due to the strong chemo-resistance and heterogeneity of the tumors caused by the nature of the disease and acquired from previous chemotherapy regimens.

The toxicity of S-1 was acceptable and no life-threatening toxicities were observed. Although a population with an extremely poor prognosis was targeted in this study and the general condition of the participating patients was expected to be unstable, the toxicities were similar to the results of previous clinical studies for S-1 in chemo-naïve patients with pancreatic cancers [24, 37]. The safety profile of this study suggests that S-1 can be safely administered to pancreatic cancer patients even in a second-line setting, at least in selected populations.

We conclude that S-1 as monotherapy had marginal anti-tumor activity with tolerable toxicity in patients with gemcitabine refractory metastatic pancreatic cancer. In view of the favorable toxicity profile, its combination with other agents might have potential to improve therapeutic results.

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Do Recurrent and Metastatic Pancreatic Cancer Patients Have the Same Outcomes with Gemcitabine Treatment?

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Key Words
Gemcitabine · Metastatic · Outcomes · Pancreatic cancer · Recurrent · Survival

Abstract
Background: Whether recurrence after surgery and primary metastatic pancreatic cancer should be included in the same category when conducting gemcitabine-based clinical trials remains controversial. ***Objective:*** To clarify the outcomes of recurrent and metastatic pancreatic cancers. ***Methods:*** 326 patients who received gemcitabine monotherapy as a first-line treatment for advanced pancreatic cancer between 2001 and 2007 were reviewed. Multivariate analysis was performed to determine the prognostic relevance of recurrence or metastasis in relation to other factors possibly influencing treatment outcomes with respect to overall survival. Differences in response to chemotherapy, drug delivery and adverse events were also analyzed. ***Results:*** There were 65 recurrent and 261 metastatic cancer patients. Recurrent cancer patients had a significantly longer time to treatment failure and survival (respective medians 138 and 77 days, p = 0.017) than the metastatic patients (respective medians 270 and 185 days, p = 0.0003). Multivariate analysis revealed poor Karnofsky performance status (<80), presence of liver or peritoneal metastasis, elevated lactate dehydrogenase (>220 U/l), elevated alkaline phosphatase (>330 U/l) and elevated C-reactive protein (>1.0 mg/dl) to be significantly correlated with short survival, while neither recurrent nor metastatic status were related to survival (hazard ratio 0.76, 95% CI 0.53–1.09, p = 0.14). The response rates and dose intensities of gemcitabine were similar in these groups, although leukopenia was more frequently observed in the recurrence group (p = 0.008). ***Conclusion:*** When conducting clinical trials, it appears to be acceptable to treat recurrent pancreatic cancer after surgery and pancreatic cancer with primary metastasis under the same category.

Introduction

Pancreatic cancer is the fifth most common cause of cancer death in Western countries and Japan [1]. Advanced pancreatic cancer patients have a dismal prognosis, and the median survival time of symptomatic patients is no longer than 6 months. More than 80% of patients present at an advanced stage at diagnosis, and of those offered surgical resection, nearly 90% develop local and/or metastatic recurrence [2]. Gemcitabine is now considered to be the standard agent for advanced pancreatic cancer since it produced a modest increase in sur-

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vival as compared with fluorouracil (median 5.6 vs. 4.4 months, respectively) and has significant clinical benefit [3]. However, the efficacy of gemcitabine is limited because no more than 15% of patients can be expected to respond, and median survival is only approximately 6 months with gemcitabine treatment. Recently, various agents have been investigated in combination with gemcitabine but most have failed to improve survival as compared with gemcitabine monotherapy [4–16]. Erlotinib added to gemcitabine showed superiority in survival as compared with gemcitabine alone but the majority of oncologists still regard gemcitabine monotherapy as the standard approach because the survival benefit of adding erlotinib has little clinical significance [17].

Most clinical trials of chemotherapy for advanced pancreatic cancer involve locally advanced disease and recurrent disease after surgery in addition to primary metastatic disease. It has been recently recognized that the outcomes of locally advanced disease is different from that of metastatic disease, and in many randomized phase III studies, patients are stratified by 'locally advanced versus metastatic disease' [4–10, 17, 18]. Recurrent disease is not generally distinguished from primary metastatic disease, and these patients are generally categorized together (stage IV) when conducting clinical trials. However, it is still unclear whether the prognosis of recurrent disease is similar to that of primary metastasis. Therefore, we retrospectively investigated the treatment outcomes of patients with recurrent pancreatic cancer after surgery and of those with tumors with primary metastasis, who received gemcitabine monotherapy. The outcomes, response, adverse events and gemcitabine delivery were compared between the 2 groups.

Patients and Methods

Patient Population

We extracted cases with corresponding eligibility criteria from the database of the National Cancer Center Hospital in Tokyo. Patients with recurrent disease after pancreatic resection and those with primary metastatic disease were eligible for this study. All of the enrolled patients had been histologically or cytologically diagnosed as having pancreatic adenocarcinoma and had received gemcitabine monotherapy as first-line chemotherapy between January 1, 2001, and December 31, 2007. Locally advanced unresectable pancreatic cancer (stage III) patients were excluded from the study.

Gemcitabine Treatment

For all patients, an initial 1,000 mg/m^2 dose of gemcitabine was administered intravenously for 30 min on days 1, 8 and 15 of a 28-day cycle until disease progression, an unacceptable adverse event or patient refusal occurred. If patients experienced white blood cell count of <2,000/μl or platelet count of <70,000/μl, gemcitabine administration was omitted on that day and postponed to the next scheduled treatment day. Gemcitabine dose (mg/m^2), treatment durations and the number of injections were reviewed. Dose intensity was calculated by the following formula [19]:

Dose intensity (mg/m^2/week) = Total dose of gemcitabine (mg/m^2)/[(last date of injection – first date of injection) + 7]/7

Tumor responses were evaluated according to RECIST. The disease control rate includes complete response, partial response and stable disease. Adverse events were retrospectively ranked by the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical Analysis

Differences in baseline characteristics, response rate and adverse events between recurrent and metastatic status were detected by Fisher's exact test, and for the numeric data we used the Mann-Whitney U test. The differences in gemcitabine delivery among groups were assessed by t test. Time to treatment failure was defined as the time between the date of starting gemcitabine treatment and the date of recognition of progressive disease, discontinuation due to an adverse event or patient refusal. Overall survival was the duration from starting gemcitabine treatment to death or the last follow-up. Survival curves were estimated by the Kaplan-Meier method.

Univariate analysis was carried out using the Cox proportional hazard model to identify the factors correlating with survival. A significant relation with survival was detected by the multivariate stepwise modeling procedure. In the stepwise analysis, a 0.15 significance level was used for inclusion or exclusion of explanatory variables to determine factors independently affecting survival. For the final model for the Cox regression analysis, we chose a significance level of $p < 0.05$. All statistical analyses were performed using StatView (SAS Inc., Ver. 5.0, Tokyo, Japan).

Results

Patient Characteristics

In total, 452 patients who underwent gemcitabine-based treatment for advanced pancreatic cancer from our database were reviewed and 326 patients were found to be eligible for this analysis (fig. 1). There were 65 recurrent and 261 primary metastatic cancer patients. Baseline characteristics are shown in tables 1 and 2. Compared to metastatic cancer patients, the frequency of liver metastasis was lower in those with recurrences. In addition, patients with recurrences had better Karnofsky performance status (KPS), higher serum albumin, lower white blood cell counts, lower C-reactive protein (CRP) and lower carbohydrate antigen (CA) 19-9 levels at baseline.

Table 1. Baseline characteristics of recurrent and metastatic cancer patients

	Recurrence (n = 65)		Metastasis (n = 261)		p value
	n	%	n	%	
Age					
≤65	32	49.2	144	55.2	0.41
>65	33	50.8	117	44.8	
Gender					
Male	39	60	141	54	0.41
Female	26	40	120	46	
KPS					
70, 80	5	7.7	60	23	<0.005
90, 100	60	92.3	201	77	
Biliary drainage	7	10.8	56	21.5	0.054
Presence of liver metastasis	28	43.1	198	73.9	<0.001
Presence of peritoneal metastasis	13	20	54	20.3	0.99
Presence of lung metastasis	10	15.4	41	15.7	0.99

KPS = Karnofsky performance status.

Treatment Delivery and Response

There were 304 radiographically evaluable patients among the 326. Overall, 38 patients responded (12.5%; 1 complete response, 37 partial responses). In the recurrence group, the response rate was 12.7% (8 of 63 patients), similar to that in the metastasis group (12.0%; 29 of 241 patients, p = 0.83). However, the disease control ratio (complete response + partial response + stable disease) in the recurrence group was significantly higher than that in the metastasis group (82.5 vs. 68.9%, respectively, p = 0.04).

In the recurrence group, the number of gemcitabine administrations and total dose of gemcitabine were higher than in the metastasis group (administrations: median 15.9 vs. 11.8 times, p = 0.012; dosage: 15,318 vs. 11,297 mg, p = 0.021). The median dose intensity of gemcitabine was 576.9 mg/m^2/week in the recurrence group, similar to that in the metastasis group (655.7 mg/m^2/week, p = 0.09).

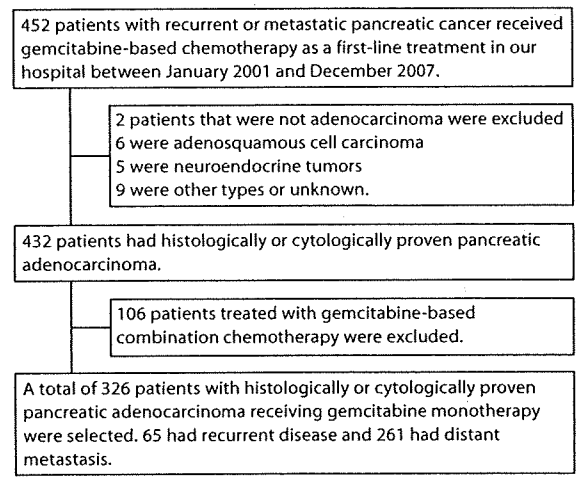

Fig. 1. Flow diagram for identification of eligible patients.

Survival Analysis

In the recurrence group, time to treatment failure was significantly longer than that in the metastatic group (median 138 vs. 77 days, respectively, p = 0.017; fig. 2). The same was true of overall survival, with the recurrence group having a longer survival time than the metastasis group (median 270 vs. 185 days, p = 0.0003; fig. 3). The univariate analysis revealed recurrent or metastatic status to be an important factor influencing survival [hazard ratio (HR) 0.53, p = 0.0002]. Other factors, including KPS (HR 1.73), liver metastasis (HR 0.49), peritoneal metastasis (HR 0.65), white blood cell count (HR 0.63), hemoglobin (HR 1.48), albumin (HR 1.63), alkaline phosphatase (HR 0.49), aspartate aminotransferase (HR 0.69), alanine aminotransferase (HR 0.59), lactate dehy-

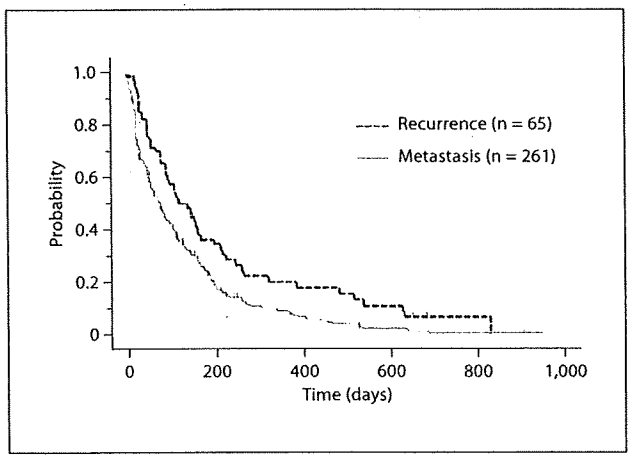

Fig. 2. Times to treatment failure in patients with recurrence and metastasis.

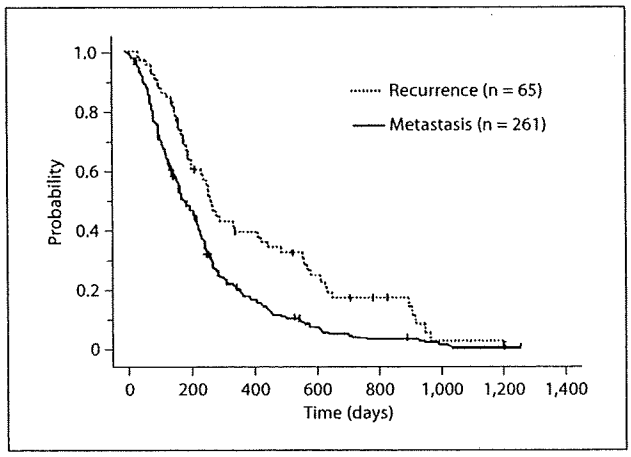

Fig. 3. Overall survival in patients with recurrence and metastasis.

Table 2. Baseline laboratory data of recurrence and metastasis groups

	Recurrence (n = 65)		Metastasis (n = 261)		p value
	median	range	median	range	
WBC, n/μl	5,500	2,700–11,200	6,300	1,800–35,500	0.0002
Hb, g/dl	12	8.4–15.1	12	6.7–16.1	0.66
Albumin, g/dl	3.7	2.2–4.6	3.6	2.4–4.6	0.048
ALP, U/l	327	154–2,751	378	38–3,593	0.43
AST, IU/l	26	13–149	27	11–226	0.89
ALT, IU/l	23	9–141	30	5–305	0.52
LDH, U/l	176	103–626	191	67–2,311	0.72
CRP, mg/dl	0.1	0.1–10.6	0.8	0.1–20.6	<0.001
CA 19-9, U/ml	30	1–52,400	148	1–1,620,000	0.018

WBC = White blood cells; Hb = hemoglobin; ALP = alkaline phosphatase; AST = asparate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein; CA 19-9 = carbohydrate antigen 19-9.

drogenase (HR 0.51), CRP (HR 0.40) and CA 19-9 (HR 0.76), also correlated with survival (table 3). The multivariate analysis after stepwise selection identified KPS (HR 1.43, 95% CI 1.02–2.01), liver metastasis (HR 0.49, 95% CI 0.36–0.67), peritoneal metastasis (HR 0.38, 95% CI 0.27–0.53), alkaline phosphatase (HR 0.59, 95% CI 0.43–0.81), lactose dehydrogenase (HR 0.55, 95% CI 0.42–0.73) and CRP (HR 0.56, 95% CI 0.42–0.75) to be independent prognostic factors, while recurrent or metastatic status was not significant (HR 0.76, 95% CI 0.53–1.09, p = 0.14; table 4).

We also performed a subanalysis of the recurrence pattern only in patients with recurrences (n = 65). The local recurrence only group (n = 12) had somewhat longer survival than the distant only or local and distant recurrence group (n = 53) but the differences did not reach statistical significance (median 564 vs. 269 days, p = 0.67; fig. 4).

Adverse Events

In the recurrence group, the incidence of leukopenia was high compared to that of the metastatic cancer group

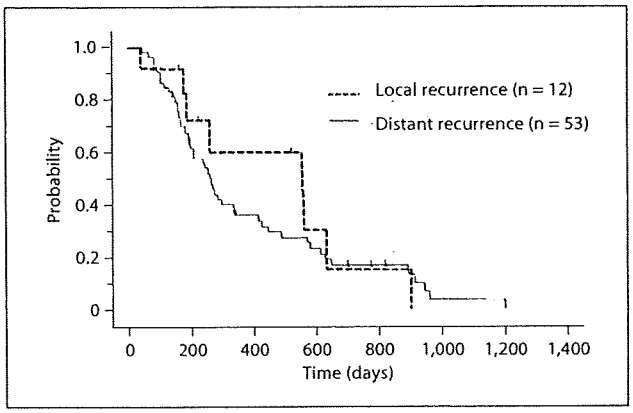

Fig. 4. Overall survival in the recurrence group (local recurrence only and distant metastasis with/without local recurrence).

Table 4. Results of multivariate analysis of survival

	HR	95% CI	p value
Recurrence vs. metastasis	0.76	0.53–1.09	0.14
KPS 70, 80 vs. 90, 100	1.43	1.02–2.01	0.038
Liver metastasis no vs. yes	0.49	0.36–0.67	<0.001
Peritoneal metastasis no vs. yes	0.38	0.27–0.53	<0.001
ALP ≤330 vs. >330	0.59	0.43–0.81	0.001
LDH ≤220 vs. >220	0.55	0.42–0.73	<0.001
CRP ≤1.0 vs. >1.0	0.56	0.42–0.75	0.001

KPS = Karnofsky performance status; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; CRP = C-reactive protein.

Table 3. Results of univariate analysis of survival

	HR	95% CI	p value
Recurrence vs. metastasis	0.53	0.38–0.74	0.0002
Age ≤65 vs. >65	1.27	0.98–1.63	0.07
Male vs. female	1.01	0.79–1.30	0.95
KPS 70, 80 vs. 90, 100	1.73	1.26–2.38	0.008
Biliary drainage no vs. yes	0.98	0.72–1.34	0.91
Liver metastasis no vs. yes	0.49	0.37–0.65	<0.001
Peritoneal metastasis no vs. yes	0.65	0.48–0.89	0.006
Lung metastasis no vs. yes	1.28	0.91–1.81	0.16
WBC ≤6,000 vs. >6,000	0.63	0.49–0.80	0.002
Hb ≤12 vs. >12	1.48	1.15–1.90	0.002
Albumin ≤3.5 vs. >3.5	1.63	1.27–2.10	0.001
ALP ≤330 vs. >330	0.49	0.38–0.63	<0.001
AST ≤35 vs. >35	0.69	0.53–0.89	0.005
ALT ≤35 vs. >35	0.59	0.46–0.76	<0.001
LDH ≤220 vs. >220	0.51	0.39–0.66	<0.001
CRP ≤1.0 vs. >1.0	0.40	0.31–0.52	<0.001
CA 19-9 ≤1,000 vs. >1,000	0.76	0.59–0.98	0.04

KPS = Karnofsky performance status; WBC = white blood cells; Hb = hemoglobin; ALP = alkaline phosphatase; AST = asparate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein; CA = carbohydrate antigen.

Table 5. Adverse events associated with gemcitabine treatment in each category

	Recurrence (n = 65)	Metastasis (n = 261)	p value
Leukopenia			
Grade 1–4	53 (81.5%)	170 (65.1%)	0.008
Grade 3/4	22 (33.8%)	32 (18.8%)	0.003
Neutropenia			
Grade 1–4	47 (72.3%)	169 (64.8%)	0.31
Grade 3/4	22 (33.8%)	94 (36.0%)	0.18
Anemia			
Grade 1–4	58 (89.2%)	225 (86.2%)	0.68
Grade 3/4	7 (10.8%)	22 (8.4%)	0.63
Thrombocytopenia			
Grade 1–4	35 (53.8%)	147 (56.3%)	0.78
Grade 3/4	3 (4.6%)	21 (8.0%)	0.58
Fatigue			
Grade 1–4	30 (46.2%)	135 (51.7%)	0.49
Grade 3/4	0 (0%)	1 (0.4%)	0.99
Anorexia			
Grade 1–4	27 (41.5%)	157 (60.2%)	0.008
Grade 3/4	1 (1.5%)	8 (3.1%)	0.99
Nausea			
Grade 1–4	16 (24.6%)	92 (35.2%)	0.11
Grade 3/4	0 (0%)	1 (0.4%)	0.99

(any grade: p = 0.008; grade 3–4: p = 0.003), although its incidence of neutropenia was similar (p = 0.31). Anorexia of any grade was frequently observed in the metastatic cancer patients (p = 0.008), although other non-hematological events were equally common (table 5). Grade 3 interstitial pneumonitis was observed in 3 metastatic cancer patients. There were 17 patients who died within 30 days after gemcitabine administration and all of them were considered to be cancer-related deaths. Overall, in both groups, gemcitabine monotherapy was well tolerated.

Discussion

This study revealed the relevance of recurrent and metastatic status to survival. Recurrent cancer patients had better survival than primary metastatic cancer patients (median 270 vs. 185 days, p = 0.0003). However, multivariate analysis demonstrated that recurrent or metastatic status was not an independent prognostic factor (HR 0.76, p = 0.14). On multivariate analysis, KPS, liver metastasis, peritoneal metastasis, alkaline phosphatase, lactose dehydrogenase and CRP were found to be important factors relating to survival, and all have previously been reported to be significant prognostic factors for pancreatic cancer [20, 21]. In our study, analysis of patient characteristics revealed that those with recurrent disease tended to have better prognostic factors, such as better KPS and lower CRP, than metastatic cancer patients. This may correlate with tumor burden, which is relatively low when recurrence is found, since patients who undergo resection usually receive close follow-up after surgery. In contrast, in most patients with primary metastasis, pancreatic cancer is diagnosed at an advanced stage after symptom development. Our findings suggest other factors, such as KPS, liver metastasis and CRP, to be more important influences on outcomes than recurrent or metastatic status.

Gemcitabine had a clear survival benefit in pancreatic cancer patients. To our knowledge, 15 phase III trials of systemic chemotherapy for advanced pancreatic cancer have been published [4–18]. All 15 studies included patients with unresectable locally advanced pancreatic cancer. In 8 studies, patients were stratified by locally advanced versus metastatic disease [4–10, 17, 18], and 2 other studies have suggested locally advanced versus metastatic cancer to be a significant prognostic factor in multivariate analysis [11, 12]. On the other hand, no trials have distinguished recurrent from metastatic disease as a prognostic factor. The rates of patients with history of pancreatectomy were described in 8 studies [4, 6–10, 17, 18]. The median percentage of such patients was 11% (range 6.1–20.8%). Of these, only the report by Van Cutsem et al. [4] referred to the relation between pancreatectomy history and prognosis. They examined the effect of tipifarnib given with gemcitabine in 688 patients with advanced pancreatic cancer, including 76 who underwent Whipple resection prior to study entry. The study demonstrated a trend toward better survival in those who had previously undergone surgical resection than in those who had not (median 229 vs. 185 days, HR 0.77, p = 0.09) [4].

In the present study, the response rate in the metastasis group was similar to that in the recurrence group. However, the disease control rate was higher in the recurrence group (82.5 vs. 68.9%, p = 0.04). The relatively low tumor burden in the recurrent cancer group may be one possible explanation for this high disease control rate. In the metastasis group, disease was found to be progressive, with multiple metastases, deterioration of general condition and inadequate organ function. In addition, the primary metastatic disease might tend to have aggressive biology with more rapid growth than the recurrent disease by nature. These factors may relate to difficulty delivering adequate chemotherapy, resulting in a higher progressive disease rate in the metastatic cancer group.

In contrast, 12 of 65 patients in the recurrence group had local recurrence alone. Of these 12 patients, 11 were radiographically evaluable. Ten showed stable disease and 1 achieved partial remission with gemcitabine treatment (data not shown). Therefore, patients with local recurrence alone may contribute to the good disease control rate in the recurrent cancer group. As to treatment delivery, the numbers of gemcitabine administrations and total dose of gemcitabine in the recurrence group were higher than those in the metastasis group (administration: median 15.9 vs. 11.8 times, p = 0.012; dosage: 15,318 vs. 11,297 mg, p = 0.021). The higher disease control rate in the recurrence group may be attributable, at least in part, to this prolonged delivery of gemcitabine since dose intensity did not differ between the 2 groups (576.9 vs. 655.7 mg/m^2/week, p = 0.09). As to adverse events, gemcitabine was well tolerated in both groups, although the rate of grade 3–4 leukopenia was slightly higher in the recurrence group.

In conclusion, we examined differences in clinical outcomes between patients with recurrent versus metastatic unresectable pancreatic cancer. Recurrent cancer patients had a somewhat better outcome, though this was not an independent prognostic factor. Responses to gemcitabine monotherapy were similar, as were drug delivery and toxicity. Although the present study has limitations due to it being a retrospective analysis using an insufficiently large sample size, it appears to be acceptable to treat recurrent and metastatic pancreatic cancer under the same category when conducting clinical trials.

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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 Fitzgeralf (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.

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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 epigastric region was referred to us. Dynamic computed tomography showed a huge, lobulated mass encircling the splenic artery, the splenic vein and the superior mesenteric

Table 1. Profiles of our four patients

Patient no.	Age/sex	UICC-TMN	Stage	Performance status	Surgery	First-line chemotherapy	Second-line chemotherapy	PFS for first-line chemotherapy with GEM	Survival time (days)
1	48/M	T3N0M0	II	0	Pancreatectomy and partial hepatectomy	GEM, 6 cycles SD	S-1, 1 cycle PD	6 months	>794
2	76/M	T4N0M0	III	0	—	GEM, 1 cycle NE	—	NE	412
3	67/M	T3N1M1	IV	0	—	GEM, 2 cycles PD	S-1, 8 cycles PR	2 months	407
4	61/F	T4N0M0	III	0	—	GEM, 6 cycles SD	S-1, 1 cycle PD	6 months	309

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

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/m^2 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/m^2 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

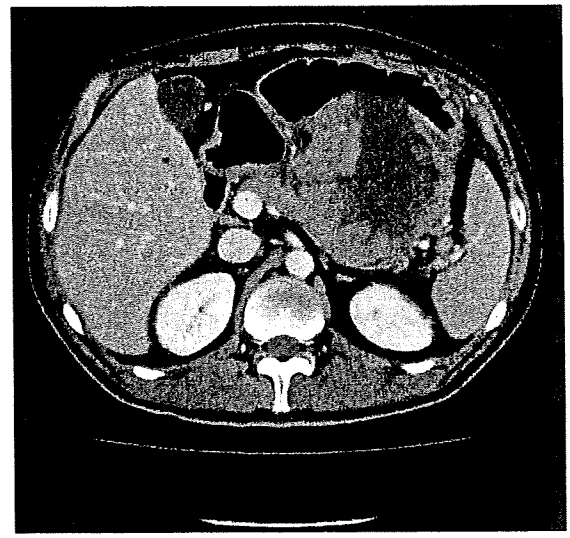

Figure 1. Abdominal computed tomography of Case 1 before treatment. The tumor appeared to be composed of cystic and solid components.

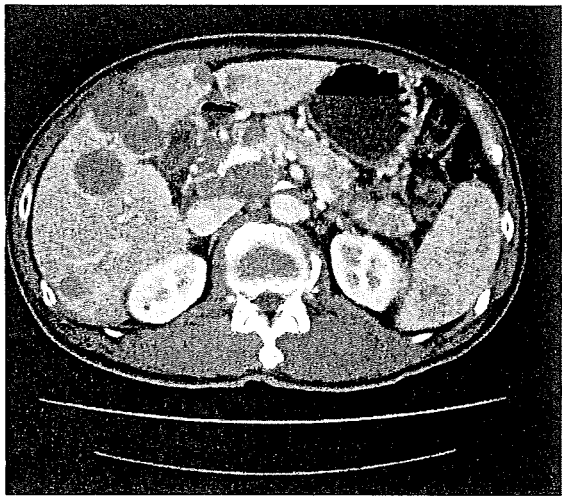

Figure 2. Abdominal computed tomography of Case 2 before treatment. Multiple liver tumors were noted at diagnosis.

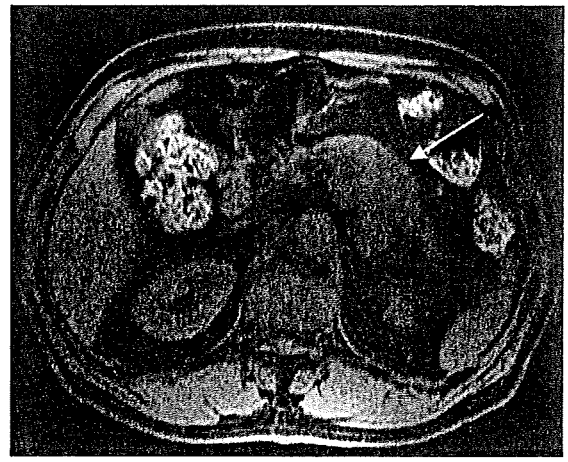

Figure 3. Abdominal magnetic resonance T1-weighted short T1 inversion recovery (STIR) imaging of Case 3 before treatment. This case was not a suitable candidate for intravenous iodine contrast use because of allergy. Tumor is detected in the pancreatic body (arrow) with weak contrast.

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/m^2 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. Therefore, chemotherapy was initiated with gemcitabine administered by intravenous injection over 30 min at the dose of 1000 mg/m^2 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/m^2 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/m^2 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/m^2 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.